IAP Guidebook on Immunization
2018–2019

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Third Edition

Advisory Committee on Vaccines and Immunization Practices,
Indian Academy of Pediatrics

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Foreword

It is a proud privilege for me to write the foreword for the new updated edition of *"ACVIP IAP Guidebook on Immunization 2018–2019".*

Asia in general and the Indian subcontinent in particular is the region where the highest number of children in the world habitat. The health issues, basic health facilities, availability of resources and the vaccine-preventable diseases (VPDs) epidemiology in the region are almost same. Until a few years back, large number of children were partially immunized or unimmunized in many developing countries. But with the availability of vaccines through financial/logistic help from the WHO, UNICEF and GAVI the immunization coverage as well as recommendations are changing. The health care workers (HCWs) from both public and private care system needs to be well informed about the changes in epidemiology and immunization recommendations so as maximum benefit of immunization can be pass on to children.

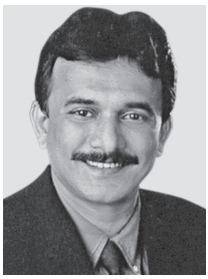
Advisory Committee on Vaccines and Immunization Practices (ACVIP) of Indian Academy of Pediatrics (IAP) regularly draft evidence-based guidelines on pediatric immunization and disseminates it through ACVIP website as well as in the form of IAP Guidebook. This IAP Guidebook is very popular amongst practicing fraternity. Last in 2014, IAP Guidebook was published and hence it was overdue since long to come up with new guidebook with latest recommendations.

As Chair of the ACVIP, and also as President of the Indian Academy of Pediatrics, it gives me great pleasure to present this book to IAP members as a gift from IAP. I am sure that this book will help readers to get well versed with the vaccine science and help them to implement these latest recommendations on immunization in their practice.

My sincere compliments and congratulations to all the members of ACVIP who have put their sincere efforts to draft the guidelines and disseminate the knowledge through this book.

Digant D Shastri
IAP President, 2019

Foreword



Immunization is one of the great triumphs of modern medicine. Its appeal rests in the age old adage 'prevention is better than cure'. Ironically, vaccines are today under attack. The antivaccine movement is growing at an alarming rate. The scientific world is struggling to counter it with a suitable response which is understandable and convincing to lay people.

Fortunately for us, antivaccine lobby is yet to reach Indian shores. No doubt it eventually will. Meanwhile, we have to contend with problems which are unique to the Indian context and to many other underdeveloped countries. Training, accurate information flow and reaching larger populations continues to be the issues needing urgent attention.

Hence, IAP decided to address this matter by bring out a comprehensive advisory on immunization which doctors could reliably refer to. The process began in 2018 with compiling data. Due to the need to address the great many complexities involved, a special body called 'Advisory Committee on Vaccines and Immunization Practices (ACVIP)' deliberated on the current evidences and updates to take a 360 degree view. We had two meetings held by Dr Balasubramanian S in the committee comprising myself, Dr Digant D Shastri, Dr Abhay K Shah, Dr Vijay Kumar Guduru, Dr Harish K Pemde, Dr Pallab Chatterjee and Dr Shivananda S.

The guidelines were published by this team in 2018. The entire IAP community was very happy and relieved that they had an authoritative manual to turn to for their vexing problems regarding vaccines. As all pediatricians like to keep ready reference by their side, we decided to bring out this book which I am sure is a direct outcome of the efforts invested by the ACVIP Team constituted for year 2018–19.

I congratulate and thank all involved in bringing out this book which is one more feather in the cap of IAP. I hope it will be instrumental in the proliferation of safe and effective immunization practices in India.

Santosh T Soans
IAP President, 2018

Preface to the Third Edition

On behalf of the Team ACVIP 2018–2020, we are privileged to submit the new edition of Guidebook from ACVIP.

This guidebook has been edited and rewritten by the present team of ACVIP, maintaining the basic structure of the earlier versions which have been prepared by various stalwarts of vaccinology from all over India.

These guidelines have been prepared based on information from medical literature, local epidemiological data and are essentially aimed at uniform and appropriate vaccination practice amongst members of The Indian Academy of Pediatrics (IAP).

The schedules recommended for various individual vaccines in this guidebook may differ from those adopted by the government agencies based on scientific data as well as practical considerations and ground realities related to the availability of some of the vaccines.

We the members of the Team ACVIP profusely thank the officials of the Central IAP starting from Dr Santosh T Soans, President 2018; Dr Digant D Shastri, President 2019; Dr Bakul Parekh, President 2020; and Dr Remesh Kumar, Honorary Secretary General 2018–2019 and all the Office Bearers and EB Members of IAP 2018–2019 for their confidence in our team and the constant support and guidance.

Team ACVIP 2018–2020

Chairpersons
Dr Santosh T Soans, President, 2018
Dr Digant D Shastri, President, 2019
Dr Bakul Parekh, President, 2020

Convener ACVIP 2018–2019	Dr Balasubramanian S
East Zone Member	Dr Pallab Chatterjee
West Zone Member	Dr Abhay K Shah
North Zone Member	Dr Harish K Pemde
South Zone Member	Dr Shivananda S
Central Zone Member	Dr Vijay Kumar Guduru
Ex-officio	Dr Remesh Kumar (HSG)

Preface to the First Edition

The availability of several vaccines in the private market other than those included in EPI, has mandated the need to formulate guidelines for their use. The IAPCOI recommendations thus go beyond the national immunization program and cater primarily to pediatricians in office practice. The recommendations for vaccines other than those in EPI are formulated after review of available literature and detailed discussion amongst IAPCOI members. Vaccine data specific to India is often not available; however, lack of local information should not be a deterrent against formulating policies that should then be based on data from similar situations in other parts of the world and also on expert opinion. It is likely that such decisions are debatable, however IAPCOI has tried to bring out recommendations in an earnest and unbiased desire to promote what is best for the population that its members cater for. It is also important to understand that immunization is a dynamic subject and recommendations may need to be revised periodically based on available information. The IAPCOI stresses the need to collect local epidemiological data for vaccine preventable diseases so that future recommendations are more robust.

This current edition was considered necessary to discuss vaccines that have recently become available and to update information about earlier vaccines. 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. References have not been given due to space constraints. Brand names have been used only when there is need to highlight relevant variation in different brands so as to avoid confusion. This does not imply endorsement of these vaccines by the IAP. We hope that this updated guide book will continue to serve as a ready reckoner on issues concerning vaccines and immunization in our country.

We gratefully acknowledge the contributions of all committee members and Dr Nitin K Shah.

Tanu Singhal
Convener
IAPCOI
2007–08

YK Amdekar
Chairperson
IAPCOI
2007–08

RK Agarwal
Co-Chairperson
IAPCOI
2007–08
President IAP, 2008

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CHAPTER

Immunization in India: Past, Present, and Future

Shivananda S, Abhay K Shah

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 5 million people have escaped paralysis. Although international agencies such as the WHO and the United Nations International Children's Emergency Fund (UNICEF) and now Global Alliance for Vaccines and Immunization (GAVI) provide extensive support for immunization activities, the success of an immunization program 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-fifth 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 1)**.

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 focuses on mere vaccine coverage.

TABLE 1: Vaccine preventable diseases: India reported cases (year wise).

Diseases	*2018*	*2017*	*2016*	*2015*	*2014*	*2013*	*2012*	*2011*	*2010*	*2009*	*2008*	*2007*	*2006*
Diphtheria	8,788	5,293	3,380	2,365	6,094	3,133	2,525	4,233	3,434	3,529	3,977	3,812	2,834
Japanese encephalitis	1,707	2,043	1,627	1,620	1,657	1,078	_	1,214	555	653	427	4,017	_
Measles	19,474	12,032	17,250	30,168	26,530	8,285	3,305	33,634	31,458	56,188	44,258	41,144	64,185
Mumps	_	_	_	_	_	_	_	_	_	_	_	_	_
Pertussis	13,208	23,766	37,274	25,206	46,706	31,089	44,154	39,091	40,508	60,385	43,697	46,674	30,088
Polio	0	0	0	0	0	0	0	1	44	756	559	874	676
Rubella	2,328	2,748	8,274	3,252	4,870	3,698	1,232	_	_	_	_	_	_
Rubella (CRS)	_	76	25	_	_	_	_	_	_	_	_	_	_
Tetanus (neonatal)	129	295	227	491	492	415	588	734	521	898	876	1,076	625
Tetanus (total)	7,000	4,946	3,781	2,268	5,017	2,814	2,404	2,843	1,756	2,126	2,959	7,491	2,815

Contd...

Contd...

Diseases	*2005*	*2004*	*2003*	*2002*	*2001*	*2000*	*1999*	*1998*	*1997*	*1995*	*1990*	*1985*	*1980*
Diphtheria	5,826	8,465	4,236	5,301	5,472	5,125	1,786	1,378	1,326	2,123	8,425	15,685	39,231
Japanese encephalitis	_	_	_	_	_	_	_	_	_	_	_	_	_
Measles	36,711	55,443	47,147	40,044	51,780	38,835	21,013	33,990	61,004	37,494	89,612	161,216	114,036
Mumps	_	_	_	_	_	_	_	_	_	_	_	_	_
Pertussis	31,122	32,786	33,954	33,289	34,703	31,431	11,264	31,199	21,371	4,073	112,416	184,368	320,109
Polio	66	134	225	1,600	268	265	2,817	4,322	2,275	3,263	10,408	22,570	18,975
Rubella	_	_	_	_	_	_	_	_	_	_	_	_	_
Rubella (CRS)	_	_	_	_	_	_	_	_	_	_	_	_	_
Tetanus (neonatal)	821	1,183	1,720	1,580	1,718	3,287	610	2,049	3,011	1,783	9,313	_	_
Tetanus (total)	2,981	3,883	4,020	12,197	5,764	8,997	2,125	6,705	7,323	_	23,356	37,647	45,948

Polio refers to all polio cases (indigenous or imported), including polio cases caused by vaccine derived polio viruses (VDPV). For disaggregated data please click on this hyperlink: https://extranet.who.int/polis/public/CaseCount.aspx It does not include cases of vaccine-associated paralytic polio (VAPP) and cases of non polio acute flaccid paralysis [AFP]).
** Neonatal Tetanus and Total Tetanus cases equality may be the result from a lack of non-Neonatal Tetanus surveillance system.

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 15 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 institutionalization 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 innovations 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-Guérin (BCG), 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 to increasingly resort to imports. In fact, Government of India had withdrawn indigenous production facilities for oral polio vaccine (OPV) that existed earlier in Coonoor, Tamil Nadu and at Haffkine Institute in Mumbai for trivial reasons. At Coonoor after making several

batches of good quality OPV, one batch of OPV had 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, OPV has been imported in India for last several years. Similarly, decision of production of inactivated polio vaccine (IPV) 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. Though the reported vaccination coverage has always been higher than evaluated coverage, the average vaccination coverage has shown a consistent increase over the last two decades as shown in **Figure 1**. While gains in coverage proved to be rapid throughout the 1980s, taking off from a below 20% coverage to about 60% coverage for some vaccine-preventable diseases (VPDs), subsequent gains have been limited **(Fig. 1)**. Estimates from the 2009 Coverage Evaluation

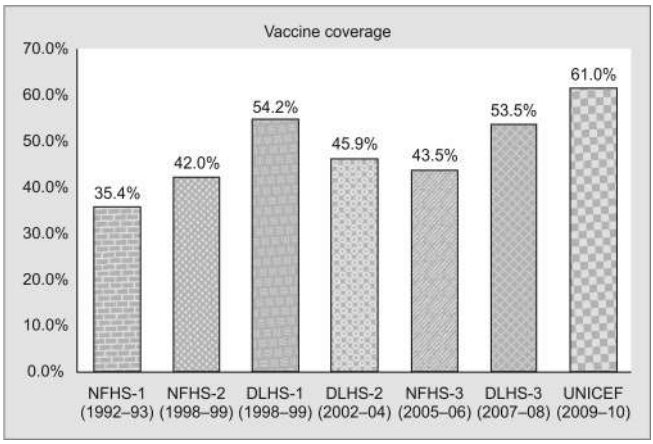


Fig. 1: Trends in vaccination coverage over the last 20 years as shown in different surveys.
(NFHS: National Family Health Survey; DLHS: District Level Health Survey; UNICEF: United Nations International Children's Emergency Fund)
Source: Multi Year Strategic Plan 2013–17, Universal Immunization Program, Department of Family Welfare, Ministry of Health and Family Welfare, Government of India.

Survey (CES 2009) indicate that only 61% of children aged 12–23 months were fully vaccinated (received BCG, measles, and three doses of DPT and polio vaccines), and 7.6% had received no vaccinations at all.[2] Given an annual birth cohort of 26.6 million, and an under-5 year child mortality rate of 59/1,000, this results in over 9.5 million underimmunized children each year.

There is also a tremendous heterogeneity in state and district levels 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, Punjab, and Pondicherry have above 80% coverage **(Table 2)**.[3]

TABLE 2: Percentage of children aged 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	*Full vaccination*	*BCG*	*Three doses of DPT vaccine*	*Three doses of polio vaccine*	*Measles vaccine*
Andhra Pradesh	67.1	97.5	79.0	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	47.0
West Bengal	75.8	96.2	83.6	83.6	82.8

(BCG: Bacillus Calmette-Guérin; DPT: diphtheria, pertussis, and tetanus toxoid; DLHS: District Level Health Survey)

In CES 2009, the reasons for poor immunization coverage have been found to be: did not feel the need (28.2%), not knowing about vaccines (26.3%), not knowing where to go for vaccination (10.8%), time not convenient (8.9%), fear of side effects (8.1%), do not have time (6%), wrong advice by someone (3%), cannot afford cost (1.2%), vaccine not available (6.2%), place not convenient (3.8%), auxiliary nurse midwife (ANM) absent (3.9%), long waiting time (2.1%), place too far (2.1%), services not available (2.1%), and others (11.8%).[2]

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 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 19% in 2005 but zoomed to 49% in 2009.[4]

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. Government of India has included many new vaccines in last decade. This includes birth dose of hepatitis B, pentavalent vaccine, measles, mumps, and rubella (MMR) in place of measles vaccine at 9 months and of late rota virus vaccine and pneumococcal vaccines in selected states in phased manner.

India, along with ten other WHO South East Asia Region member countries, have resolved to eliminate measles and control rubella/congenital rubella syndrome (CRS) by 2020. In this direction, Ministry of Health & Family Welfare has initiated measles-rubella (MR) vaccination campaign in the age group of 9 months to less than 15 years in a phased manner across the nation. The campaign aims to cover approximately 41 crore children. Expanding coverage with these vaccines and introducing new vaccines which are cost effective in the Indian scenario are required. In 1995, following the Global Polio Eradication Initiative of the WHO (1988), India launched Pulse Polio immunization program with Universal Immunization Program which aimed at 100% coverage. Both Oral Polio Vaccine (OPV) and IPV are administered as part of the National Immunization Schedule. While OPV continues to be administered at birth (0 dose), then at 6, 10, and 14 weeks; fractional dose of IPV is administered at 6 and 14 weeks. In due course, OPV will be phased out completely, and only IPV will be administered (either as a standalone vaccine, or as part of a multivalent vaccine). Introduction of monovalent and bivalent OPV into the polio eradication strategy has shown dramatic results with no polio cases being reported since 13 January 2011. Second dose of MR is also introduced at 16–24 months of age. 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 strengthening of an adverse event following immunization (AEFI) monitoring system. Finally setting up a system for monitoring the incidence of vaccine preventable diseases and conducting 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, etc. Several of the above mentioned issues have been addressed by National Vaccine Policy[5] and mechanism such as National Technical Advisory Group on Immunization (NTAGI) is

likely to facilitate evidence-based decisions on new vaccines. Global Vaccine Action Plan (GVAP)[6] signed by 144 member countries of the WHO has also given a call to achieve the decade of vaccines vision by delivering universal access to immunization. The GVAP mission is to improve health by extending by 2020 and beyond the full benefits of immunization to all people, regardless of where they are born, who they are or where they live. It has also called for development and introduction of new and improved vaccines and technologies.

Immunization is considered among the most cost-effective of health investments. 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.[7] There has been improvement in last few years: introduction of newer antigens in UIP (hepatitis B, second dose of measles, Japanese encephalitis, and pentavalent vaccine in many states), framing of National Vaccine Policy, support to indigenous vaccine industry, and acknowledging the need to intensify routine immunization (RI) are steps in right direction.[8] We now need to step up our efforts to strengthen all components of UIP (vaccination schedule, delivery and monitoring, and VPD/AEFI surveillance), overcome all barriers (geographical, politico-social, and technical) and invest heavily in research and development (R&D) to achieve immunization's full potential and a healthier nation.

TIME LINE IN IMMUNIZATION PROGRAM IN INDIA

Universal Immunization Programme is a vaccination program launched by the Government of India in 1985. It became a part of Child Survival and Safe Motherhood Programme in 1992 and is currently one of the key areas under National Rural Health Mission (NRHM) since 2005. The program now consists of vaccination for 12 diseases–tuberculosis, diphtheria, pertussis (whooping cough), tetanus, poliomyelitis, measles, hepatitis B, diarrhea, Japanese encephalitis, rubella, pneumonia (*Haemophilus Influenzae* Type B) and Pneumococcal diseases (*Pneumococcal pneumonia* and meningitis). Hepatitis B and pneumococcal diseases [9] was added to the UIP in 2007 and 2017, respectively.[10,11]

The other additions in UIP through the way are IPV, rotavirus vaccine (RVV), and measles-rubella (MR) vaccine. Four new vaccines

have been introduced into the country's UIP, including injectable polio vaccine, an adult vaccine against Japanese encephalitis and pneumococcal conjugate vaccine (PCV).

Vaccines against rotavirus, rubella, and polio (injectable) will help the country meet its millennium development goals four targets that include reducing child mortality by two-thirds by 2015, besides meeting meet global polio eradication targets. An adult vaccine against Japanese encephalitis will also be introduced in districts with high levels of the disease. The recommendations to introduce these new vaccines have been made after numerous scientific studies and comprehensive deliberations by the NTAGI, the country's apex scientific advisory body on immunization.

Pneumococcal conjugate vaccine protects children against severe forms of pneumococcal disease, such as pneumonia and meningitis. Currently, the vaccine is being rolled out to approximately 21 lakh children in Himachal Pradesh and parts of Bihar and Uttar Pradesh in the first phase. This will be followed by introduction in Madhya Pradesh and Rajasthan next year, and eventually be expanded to the country in a phased manner.

Out of all the causes of diarrhea, rotavirus is a leading cause of diarrhea in children less than 5 years of age. It is estimated that rotavirus cause 872,000 hospitalizations; 3,270,000 outpatient visits and estimated 78,000 deaths annually in India. RVV was introduced in 2016 in a phased manner, beginning with four states initially and later expanded to seven more states making it a total of 11 states by end of 2018, where RVV was available in the country. The vaccine has been further expanded to 17 more states. RVV is now available in 28 states/union territories (UTs), namely, Andhra Pradesh, Haryana, Himachal Pradesh, Jharkhand, Odisha, Assam, Tripura, Rajasthan, Tamil Nadu, Madhya Pradesh, Uttar Pradesh, Manipur, Daman and Diu, Gujarat, Bihar, Sikkim, Arunachal Pradesh, Chhattisgarh, Maharashtra, Dadra and Nagar Haveli, Goa, Chandigarh, Nagaland, Delhi, Mizoram, Punjab, Uttarakhand, and Andaman and Nicobar Islands. The vaccine is expected to be available in all 36 states/UTs by September 2019.

- Since the launch of UIP in 1985, full immunization coverage in India has not surpassed 65% despite all efforts. The Government of India has launched Mission Indradhanush on 25 December

2014 as a special drive to vaccinate all unvaccinated and partially vaccinated children and pregnant women by 2020 under the UIP. This contributed to an increase of 6.7% in full immunization coverage (7.9% in rural areas and 3.1% in urban areas) after the first two phases.[12] *The Intensified Mission Indradhanush (IMI) has been launched by government of India in 2017* to reach each and every child under 2 years of age and all those pregnant women who have been left uncovered under the routine immunization program.

- The target under IMI is to increase the full immunization coverage to 90% by December 2018.[13]
- *Under IMI, greater focus was given on urban areas which was one of the gaps of Mission Indradhanush*.

WAY FORWARD

Immunization has delivered excellent results in reducing morbidity and mortality from childhood infections in the last 50 years. There has been substantial reduction in the incidence of many VPDs. However, there are number of barriers which adversely affect the immunization coverage rates in India. Some of the challenges to immunization include limited capacities of staff, and gaps in key areas such as predicting demand, logistics, and cold chain management, which result in high wastage rates.

India also still lacks a robust system to track VPDs. Vaccination coverage varies considerably from state to state, with the lowest rates in India's large central states. Differences in uptake are geographical, regional, rural-urban, poor-rich, and gender-related. We now need to step up our efforts to strengthen all components of UIP (vaccination schedule, delivery and monitoring, and VPD/AEFI surveillance), overcome all barriers (geographical, politico-social and technical) and invest heavily in R&D to achieve immunization's full potential and a healthier nation.[8]

Some of the key areas which can be addressed are as follows:

- Update microplans to increase access to hard to reach areas, urban, poor, and migratory population
- Strengthen vaccine logistics and cold chain management
- Capacity building
- Improve data management system and tracking mechanisms

- Strengthen the evidence base for improved policy making
- New vaccines introductions
- Immunization campaigning
- Special strategies including Mission Indradhanush
- Innovative communication tools
- Partnership expansion with development partners and private sector
- Partnership with professional bodies like Indian Academy of Pediatrics (IAP), Indian Medical Association (IMA), etc.

REFERENCES

1. WHO (2013). Vaccine-Preventable Diseases: Monitoring System 2013 Global Summary [online]. Available from: http://apps.who.int/immunization_monitoring/globalsummary/countries?countrycriteria%5Bcountry%5D%5B%5D=IND&commit=OK. [Last Accessed October 2019].
2. UNICEF (2010). 2009 Coverage Evaluation Survey: All India Report. New Delhi: The United Nations Children's Fund; 2010 [online]. Available from: http://www.unicef.org/india/ health_5578.htm. [Last Accessed October 2019].
3. International Institute of Population Sciences (IIPS) (2010). District Level Household and Facility Survey (DLHS-3) 2007–08: India. Mumbai: IIPS; 2010 [online]. Available from: http://www.rchiips.org/pdf/INDIA_REPORT_DLHS-3.pdf. [Last Accessed October 2019].
4. Goel S, Dogra V, Gupta SK, et al. Effectiveness of Muskaan Ek Abhiyan (the smile campaign) for strengthening routine immunization in Bihar, India. Indian Pediatr. 2012; 49:103-108.
5. National Vaccine Policy (2011). New Delhi: Ministry of Health and Family Welfare, Government of India; 2011 [online]. Available from: http://mohfw.nic.in/WriteReadData/l892s/1084811197NATIONAL%20VACCINE%20POLICY%20BOOK.pdf. [Last Accessed October 2019].
6. WHO (2013). Global Action Plan 2011–2020. Geneva: World Health Organization; 2013 [online] Available from: http://www.who.int/immunization/global_vaccine_actionplan/GVAP_doc_2011_2020/en/index.html. [Accessed October 2019].
7. World Health Organization (2005). Fact Sheet WHO/288, March 2005 [online]. Available at http://whqlibdoc.who.int/fact_sheet/2005/FS_288.pdf. [Accessed October 2019].
8. Vashishtha VM, Kumar P. 50 years of immunization in India: Progress and future. Indian Pediatr. 2013;50:111-8.

9. PIB (2017). Shri J P Nadda launches Pneumococcal Conjugate Vaccine (PCV) under Universal Immunization Programme (UIP) [online]. Available from: https://pib.gov.in/indexd.aspx [Last Accessed October 2019].
10. "Archived copy" (PDF). Archived from the original (PDF) on March 1, 2013. Retrieved March 9, 2013.
11. Patra N. Universal Immunization Programme In India: The Determinants Of Childhood Immunization. Calcutta: Indian Statistical Institute; 2012. p. 1.
12. Immunization Technical Support Unit. Report of Integrated Child Health and Immunization Survey (INCHIS)-Round 1 and 2. Ministry of Health and Family Welfare, 2014.
13. Ministry of Health and Family Welfare (MOHFW) (2017). Intensified Mission Indradhanush, operational guidelines. MOHFW, 2017 [online]. Available from: https://mohfw.gov.in/sites/default/files/Mission%20Indradhanush%20Guidelines.pdf [Last Accessed October 2019].

2

CHAPTER

General Aspects of Vaccination

2.1 BASIC IMMUNOLOGY

Harish K Pemde

IMMUNOLOGY OF VACCINATION

Innate and Adaptive Immune Responses

Immunity may be broadly classified as innate and adaptive immunity. Innate immunity comprises 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 nonspecific. Adaptive immunity is provided by the B lymphocytes (humoral/antibody-mediated immunity) and T lymphocytes [(cellular/cell-mediated immunity (CMI)]. The innate immune system triggers the development of adaptive immunity by presenting antigens to the B lymphocytes and T lymphocytes. Vaccines that stimulate innate immunity effectively are better immunogens. This can be achieved by live vaccines, adjuvants, toll-like receptor (TLR) agonists, live vectors, and deoxyribonucleic acid (DNA) vaccines. Adaptive immunity takes time to evolve and is pathogen specific **(Table 1 and Fig. 1)**.[1]

HUMORAL VERSUS CELL-MEDIATED IMMUNITY

Humoral immunity is the principal defense mechanism against extracellular microbes and their toxins.[2] B lymphocytes secrete

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 specific immunity

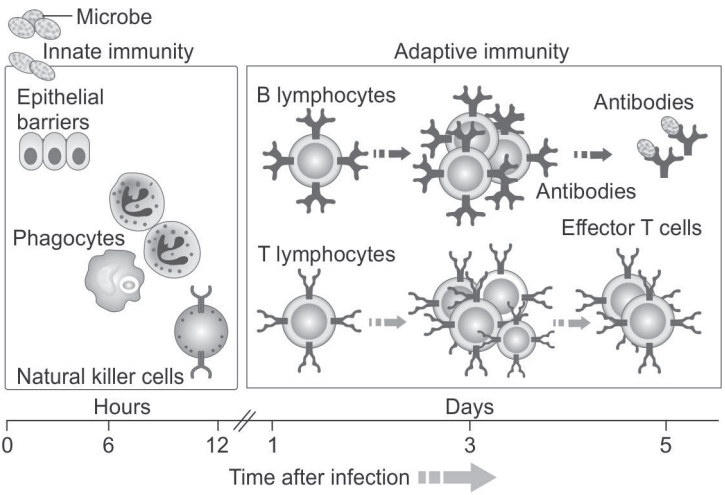


Fig. 1: Innate and adaptive immunity.
Source: Adapted from Vashishtha VM, Kalra A, Thacker N (Eds). FAQ on Vaccines and Immunization Practices. New Delhi: Jaypee Brothers; 2011.

antibodies that act by neutralization, complement activation, or by promoting opsonophagocytosis, which results in early reduction of pathogen load and clearance of extracellular pathogens. Also humoral antibodies prevent colonization, being the first step in pathogenesis by encapsulated organisms like Hib (*Haemophilus influenzae* type b), pneumococcal, meningococcal, and organisms like diphtheria and pertussis. Antibodies are of several different types [immunoglobulin

G (IgG), IgM, IgA, IgD, and IgE] and they differ in their structure, half-life, and site of action and mechanism of action.

Cell-mediated immunity is the principal defense 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. Bacillus Calmette-Guérin (BCG) is the only currently used human vaccine for which there is conclusive evidence that T cells are the main effectors. The T cell responses are more robust, long-lasting, and more cross protective than humoral responses, hence modern vaccinology is being directed in this direction. The inherent T cell-mediated immune regulatory mechanisms prevent any vaccines causing autoimmune diseases.[3]

ACTIVE VERSUS PASSIVE IMMUNITY

Active immunity is acquired through natural infection/immunization and is long lasting as it generally leads to development of memory cells, and when antigen(s) enters the body strong immune response is mounted. Passive immunity is conferred by maternal antibodies or immunoglobulin preparations given parenterally and is short lasting depending on the half-life of immunoglobulins. However, passive immunity provides instant protection required in cases of exposure to, e.g. rabies virus or hepatitis B virus at birth, etc.

TYPES 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 (measles, mumps, and rubella), and chickenpox 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 (PS) antigens are

called unconjugated vaccines. Conjugation of the PS with a protein carrier (glycoconjugates) 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 CMI in currently used vaccines (that have T cell-dependent antigens) is mainly by supporting antibody production. Other important mechanisms by which CMI 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. PS) do not stimulate CMI 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 STEP AFTER IMMUNIZATION

Following injection, the vaccine antigens attract local and systemic dendritic cells, monocytes, and neutrophils. Innate immune responses activate these cells by changing 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 (IM) route which is well vascularized and has a large number of patrolling dendritic cells is preferred over the subcutaneous route. Intradermal route recruits the abundant dendritic cells in the skin and offers the advantage of antigen sparing and early and effective

protection but the geometric mean titers (GMTs) are lower than that achieved with IM and may wane faster. 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 a little immunologic interference. Immunologic interference may occur with multiple live vaccines unless they are given on the same day or at least 4 weeks apart or by different routes. However, rotavirus vaccine and oral polio vaccine (OPV) can be given simultaneously or at any interval before or after any inactivated or live vaccine.

IMMUNE RESPONSES TO VACCINES

Immune Response to Polysaccharide Antigens

Bacterial (*Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae, Salmonella typhi*) 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 (GCs). 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 GCs, bona fide 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 phenomenon, only a single booster of either pneumococcal or meningococcal PS vaccine is recommended even in patients who require lifelong protection.[4,5]

Immune Response to Protein Antigens or T cell-dependent Antigens

Protein antigens which include pure proteins [hepatitis B, hepatitis A, human papillomavirus (HPV), toxoids] or conjugation of PS antigens with a protein carrier (Hib, Meningo, Pneumo, Typhoid) 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 toward follicular dendritic cells (FDCs), initiating the GC reaction. In GC's, B cells receive additional signals from FDCs and follicular T helper cells and undergo massive clonal proliferation, switch from IgM toward 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 GC 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.[3,6]

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 (primary failure). Hence, more than one 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). However, varicella and mumps do not follow this general principle and have waning antibody levels demonstrated therefore need second dose.[2,7]

PRIMARY VERSUS 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.[3]

In secondary immune responses, booster exposure to antigen reactivates immune memory (memory B cells) and results in a rapid (<7 days) increase of IgG antibody titer by a rapid proliferation of memory B cells and their evolution into abundant antibody secreting plasma cells. 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.[3]

DETERMINANTS OF INTENSITY AND DURATION OF IMMUNE RESPONSES

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.

Types of Vaccine

- *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 GCs results into higher antibody responses to protein or glycoconjugate than to PS vaccines. Hence, broadly speaking, live vaccines are superior (exception BCG, OPV) to protein antigens which in turn are superior to PS 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.[3] Thus, less amount of active ingredient per dose is required for an immune response similar to vaccines without adjuvant. However, adjuvants may cause more side effects.

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 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; however, there is a limiting dose for each.

Vaccination Schedule

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

Traditionally, "0-1-6" month schedule (prime and boost) is considered as a more immunogenic schedule than 6-10-14 week or 2-3-5 month or 2-4-6 month schedules for nonlive 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

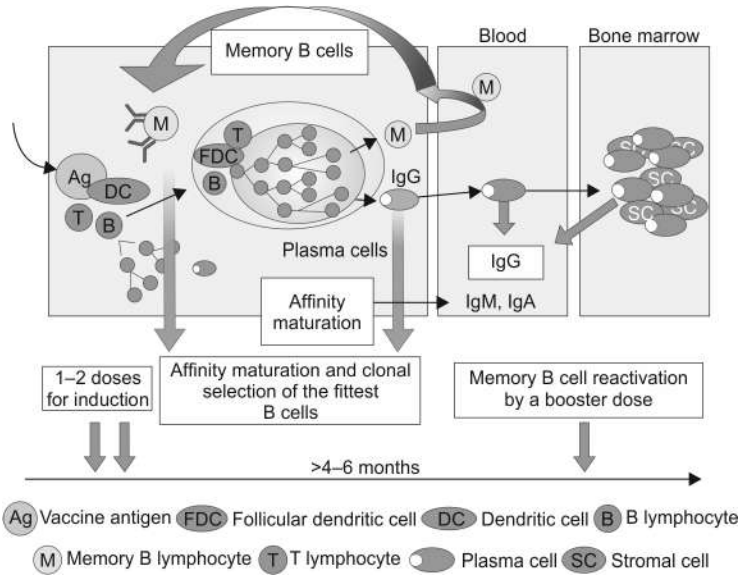


Fig. 2: Schematic presentation of various components of 0-1-6 month immunization schedule at cellular level.
Source: Adapted from Vashishtha VM, Kalra A, Thacker N (Eds). FAQ on Vaccines and Immunization Practices. New Delhi: Jaypee Brothers; 2011.

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 **(Fig. 2)**.

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 4-week minimal interval between primary doses avoids competition between successive waves of primary responses.[2,3]

Other Factors

- *Genetic factors*: The capacity of antigen epitopes to associate to a large panel of major histocompatibility complex (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. T cell responses differ markedly

between individuals and populations because of genetic variability of MHC molecules [human leukocyte antigen A2 (HLA A2)].
- *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.[3]

Secondary Immune Responses

Many factors that determine primary immune responses after immunization also affect secondary immune responses.
- *Live vs inactivated*: Live vaccines generally induce more sustained antibody responses, presumably through prolonged antigen persistence within the host. Secondary responses with inactivated vaccines are highly pronounced (anamnestic response). However, secondary responses are usually blunted with live viral vaccines as pre-existing antibody neutralizes the vaccine virus.
- *Polysaccharide antigens*: Failure to generate GCs limits the induction of memory responses and of high-affinity long-lived plasma cells. Secondary immune response does not occur with PS antigens.
- *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.[3]

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.[8,9]

Immunoglobulin G 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 which is mediated through Th (CD4). 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 postnatal age as maternal antibodies wane.[3,10]

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 2 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 amount 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.[11]

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 causes 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 and 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. However, with the availability of newer vaccines, an immunologically superior schedule of 2, 4, and 6 months may have to be considered for future.

For killed vaccines such as DPT (diphtheria, pertussis, and tetanus), Hib, pneumococcal, and hepatitis 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 reduces (2 doses at 6–12 months followed by a booster dose and 1–2 doses between 12 months and 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.[3]

CORRELATES OF VACCINE-MEDIATED IMMUNITY

A given marker that is measurable, whether the antibody or a cellular component elicited in response to a vaccine that confers protection against a disease is termed a "correlate of protection".[12] Conventionally, due to a relative ease of measurement, it is a specific antibody in the serum of a vaccinee. Measurement of cellular components is difficult, invasive, and highly cost intensive. The correlate can be absolute, e.g. Hib (0.15 μg/mL), hepatitis B (10 mIU/mL) which are directly protective or surrogates (indirect markers), e.g. Varicella (gp Elisa units), ROTA (IgA). Diseases like pertussis and HPV, however, have no established correlates till now. Correlates of protection are important to confirm immunity, compare vaccines, and therefore need to be standardized and replicable.

REFERENCES

1. Vashishtha VM, Kalra A, Thacker N (Eds). FAQ on Vaccines and Immunization Practices. New Delhi: Jaypee Brothers; 2011.
2. Plotkin SA. Vaccination against the major infectious diseases. CR Acad Sci III. 1999;322:943-51.
3. Siegrist CA. Vaccine immunology. In: Plotkin SA, Orenstein W, Offit P (Eds). Vaccines, 5th edition. Saunders Elsevier; 2008.

4. Lee CJ, Lee LH, Lu Cs, et al. Bacterial polysaccharides as vaccine-immunity and chemical characterization. Adv Exp Med Biol. 2001;491:453-71.
5. Kobrynski LJ, Sousa AO, Nahmias AJ, et al. Cutting edge: Antibody production to pneumococcal polysaccharides requires CD1 molecules and CD8+ T cells. J Immunol. 2005;174:1787-90.
6. MacLennan IC, Toellner KM, Cunningham AF, et al. Extrafollicular antibody responses. Immunol Rev. 2003;194:8-18.
7. Comparative trial of live attenuated measles vaccine in Hong Kong by intramuscular and intradermal injection. Bull World Health Organ. 1967;36:375-84.
8. Timens W, Boes A, Rozeboom-Uiterwijk T, et al. Immaturity of the human splenic marginal zone in infancy. Possible contribution to the deficient infant immune response. J Immunol. 1989;143:3200-6.
9. Siegrist CA. Neonatal and early life vaccinology. Vaccine. 2001;19:3331-6.
10. Siegrist CA. Mechanisms by which maternal antibodies influence infant vaccine responses: Review of hypotheses and definition of main determinants. Vaccine. 2003;21:3406-12.
11. Rowe J, Poolman JT, Macaubas C, et al. Enhancement of vaccine-specific cellular immunity in infants by passively acquired maternal antibody. Vaccine. 2004;22:3986-92.
12. Kamat D, Madhur A. Vaccine Immunology. In: Vashishtha VM (Ed). IAP Textbook of Vaccines. New Delhi: Jaypee Brothers; 2013.

2.2 ELEMENTARY EPIDEMIOLOGY

Harish K Pemde

EPIDEMIOLOGY OF VACCINATION

Basics of Epidemiology

Epidemiology is the study of the distribution and determinants of disease frequency in man.[1] 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 (IDs). From vaccinology perspective, there are three reasons to learn epidemiology. They include 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.[2]

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.[3]

FORCE OF TRANSMISSION AND BASIC REPRODUCTIVE NUMBER

The key determinant of incidence and prevalence of infection 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 (Ro)" 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 Ro. Since population is a mix of susceptible and immune persons, one case must attempt to infect more than one person.[4]

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

The magnitude of Ro varies according to location and population. It is strongly influenced by birth rate, population density, and behavioral factors. The magnitude of Ro can be ascertained by cross-sectional surveys. Eradication is difficult when Ro 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, tuberculosis (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, epidemic of Japanese encephalitis in a district or region and 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.[5]

VACCINE CHARACTERISTICS AND DEVELOPMENT

VACCINE IMMUNOGENICITY

This is the ability of a vaccine to induce antibodies. These antibodies may be protective or may not be protective to the vaccine. 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.[6]

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:

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

where, ARU: attack rate in unvaccinated population; ARV: attack rate in vaccinated population; and VE: vaccine efficacy.

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, HERD EFFECT, HERD PROTECTION, AND CONTACT IMMUNITY

The "herd immunity" refers to "the proportion of subjects with immunity in a given population", or in other words, it reflects the "immunity of a population or a community" reflecting the literal meaning of the word.[7] It should not be confused with "herd effect" which is defined as "the reduction of infection or disease in the unimmunized segment as a result of immunizing a proportion of the population". Both "herd immunity" and "herd effect" can be measured either by testing a sample of the population for the presence of the chosen immune parameter, in the former or by quantifying the decline in incidence in the unimmunized segment of a population in which an immunization program is instituted, in the latter. 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 and Hib vaccines have good herd effect.[8]

Conventionally, "herd immunity" theory suggests that, in contagious diseases that are transmitted from individual to individual, chains of infection are likely to be disrupted when a large number of population are immune or less susceptible to the disease. For example, in Finland when coverage with 3 doses inactivated polio vaccine (IPV) reached 51%, the poliomyelitis disappeared from the country. The greater the proportion of individuals who are resistant, the smaller the probability that a susceptible individual will come into contact with an infectious individual. However, it does not apply to diseases such as tetanus (which is infectious, but is not contagious), where the vaccine protects only the vaccinated person from disease.

"Herd immunity" should not be confused with "contact immunity", a related concept wherein a vaccinated individual can "pass on" the vaccine to another individual through contact. Not all vaccines possess this virtue which is mainly the quality of certain live attenuated vaccines that shed very efficiently either through gut or nasal mucosa though still producing "herd effect" and contributing in generation

of "herd immunity". OPV has got this unique quality and provides efficient "contact immunization". Other live oral vaccine like rotavirus vaccines may theoretically also exhibit this phenomenon; however, the evidence is lacking. On the other hand, IPV despite providing "herd immunity" and "herd effect", do not provide "contact immunity". The greater the transmissibility, the higher the contact immunization.

"Herd protection" is another term often used to describe a group of unimmunized individuals that remain protected in a herd by virtue of protection rendered by immunized individuals in a herd or population. However, when this group of individuals moves out of that group/population, they again become susceptible. In this situation, the unvaccinated individuals are indirectly protected by vaccinated individuals, as the latter will not contract and transmit the disease between infected and susceptible individuals.

Herd immunity results from immunization or infection which is transmitted human to human or otherwise. Herd effect results from immunization or other health intervention/program in community as such program(s) reduce the probability of transmission of infection in the community.

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.

REFERENCES

1. Last JM. Dictionary of public health. Am J Prev Med. 2002;23(3):235.
2. Dowdle WR. The principles of disease elimination and eradication. Bull World Health Organ. 1998;76 (Suppl 2):23-5.
3. Park K. Park's Textbook of Preventive and Social Medicine, 21st edition. Jabalpur: Banarsidas Bhanot Publishers; 2011.
4. Dietz K. The estimation of the basic reproduction number for infectious diseases. Stat Methods Med Res. 1993;2(1):23-41.

5. In: Porta M, Greenland S, Last JM (Eds). A Dictionary of Epidemiology, 5th edition. New York: Oxford University Press; 2008.
6. Weinberg GA, Szilagyi PG. Vaccine epidemiology: Efficacy, effectiveness, and the translational research roadmap. J Infect Dis. 2010;201:1607-10.
7. Fine P. Herd immunity: history, theory, practice. Epidemiol Rev. 1993;15(2):265-73.
8. John TJ, Samuel R. Herd immunity and herd effect: New insights and definitions. Eur J Epidemiol. 2000;16:601-6.

2.3 VPD SURVEILLANCE AND IDSurv

Digant D Shastri, Harish K Pemde

BACKGROUND

Disease surveillance is an important component of public health program. The key objectives of an efficient surveillance system include, first to assess burden of a disease in the community, second, to monitor the progress of any ongoing interventions for disease reduction including the impact on disease epidemiology, and finally, early detection of outbreaks in order to initiate investigations and control measures. Surveillance of vaccine-preventable diseases (VPDs) acquires a higher significance than all other surveillance systems like surveillance of noncommunicable illnesses since most of the infectious diseases are now being prevented by highly effective vaccines. The number of effective vaccines is going to go up further in coming time considering the rapid advancement in the field of vaccinology today.

WHY VACCINE-PREVENTABLE DISEASE SURVEILLANCE IS NECESSARY?

The goals of an effective disease surveillance system should serve the following functions:

- To define epidemiology of a disease
- To identify high-risk populations and regions having high transmission of the disease
- To monitor progress of a disease control program
- To specify and monitor molecular epidemiology of an infectious disease including identification of circulating strains of the pathogen responsible for the infectious disease
- To monitor impact of the vaccination program on overall disease epidemiology.

SURVEILLANCE: TERMINOLOGIES

Before we go further and understand the implications of a good VPD surveillance system, we should first understand a few common terminologies employed in describing surveillance.

- Active surveillance, which is done actively by designated persons at any health institutions or community. For example, acute flaccid paralysis (AFP) surveillance done by National Polio Surveillance Project (NPSP).
- Passive surveillance, where suspected or confirmed cases of a disease are reported routinely and passively from identified health facilities, such as Integrated Disease Surveillance Project (IDSP), infectious disease surveillance system (IDSurv), etc.
- Sentinel surveillance, where clinical syndromes after lab confirmation are reported from selected health institutions, such as Rotavirus (Indian National Rotavirus Surveillance Network), Hib-surveillance, etc.
- Population-based surveillance is conducted for selected groups with active diseases in a well-defined area/populations.
- Outbreak surveillance, where notification is done only whenever there is cluster of cases as per predefined norms, such as measles surveillance and diseases reported through IDSP.
- Case-based surveillance where any suspected case is immediately notified for further investigations like AFP and acute encephalitis syndrome (AES) surveillance.
- Zero reporting means reporting even when there is no case found like AFP surveillance.

CURRENT STATUS OF VPD SURVEILLANCE IN INDIA

Vaccine-preventable diseases are still responsible for over 500,000 deaths annually in India.[1] There is lack of disease burden data on many important VPDs in India that results in the perception that the disease is not important public health problem. Further, there is scarcity of diagnostic tools for certain VPDs. Lack of baseline surveillance data also is a bottleneck in introduction of many new vaccines in the National Immunization Program (NIP) and also in monitoring the impact of vaccination provided through Universal Immunization Programme (UIP).[2]

VPD SURVEILLANCE SYSTEMS IN INDIA

Following is the synopsis of available key surveillance systems in India:

- *IDSP (Integrated Disease Surveillance Project)*: Nationwide outbreak surveillance system. Including measles, diphtheria, pertussis, AFP, hepatitis, and AES.

- *CBHI/SBHI (Central and State Bureaus of Health Intelligence)*: Nationwide passive reporting system of suspected cases.
- *Measles—ICMR (Indian Council of Medical Research)*: Selected practitioners and institutions provide clinical samples to NIV-Pune for measles virus isolation and genotyping (Measles NetIndia). A type of case-based surveillance system.
- *AES/JE—NVBDCP (National Vector-borne Disease Control Programme) and ICMR*: Facility-based surveillance for AES in endemic areas. It is run by Government of India under National Vector-borne Diseases Control Programme.

WHO SUPPORTED SURVEILLANCE SYSTEMS

There are three different models for three different VPDs:

1. *AFP and lab surveillance for poliovirus*: Global eradication program.
2. *Fever and rash for measles/rubella*: National mortality reduction target; may be scaled up to a regional elimination goal.
3. *Acute encephalitis syndrome for Japanese encephalitis (JE)*: Control program for endemic districts.

IDSURV—AN INNOVATIVE PROJECT TO REPORT INFECTIOUS DISEASES

Indian Academy of Pediatrics (IAP), in collaboration with its Kutch branch, started an Infectious Disease Surveillance and AEFI (Adverse Event Following Immunization) reporting system for reporting serious AEFI, known as IDSurv.org.[3]

The "standard case definitions" for all the diseases covered under this project were provided.[3] The IAP members were motivated to participate voluntarily to provide information on this website. A provision is there to inform all users whenever a disease outbreak is recorded.

The main objectives of the program were:[3]

- To generate data on burden of key VPDs in India
- To develop an early warning system for pediatric VPDs in India
- To sensitize pediatricians about serious AEFIs and generate data on serious AEFI in India.

Ten key infectious diseases are targeted for surveillance under this project and they include:

1. Acute bacterial meningitis
2. Chickenpox
3. Diphtheria
4. Dengue
5. Enteric fever
6. Measles
7. Mumps
8. Pertussis
9. Pneumonia
10. Hepatitis.

REFERENCES

1. World Health Organization (Regional Office for South-East Asia). [online] Available from http://www.searo.who.int/en/Section1226/Section2715.htm. [Last accessed June, 2013].
2. Vashishtha VM, Kumar P. 50 years of immunization in India: Progress and future. Indian Pediatr. 2013;50(1):111-8.
3. IDsurv. [online] Available from www.idsurv.org. [Last accessed June, 2013].

2.4 PRACTICAL ASPECTS OF IMMUNIZATION

Harish K Pemde

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 Indian Academy of Pediatrics (IAP) 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.

- *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 food-borne 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.
- *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.

- *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.
- *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 (diphtheria, tetanus, and whole-cell pertussis) and DTaP (diphtheria, tetanus, and acellular pertussis) 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.
- Finally, it is important to emphasize 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.[1,2]

INJECTION PROCEDURE

Sterile Technique and Injection Safety

Hands should be washed with soap and water for 2 minutes using WHO's 6-step 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. Autodisable (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 multidose 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. Prefilling 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 labeled, puncture-proof containers located in the same room where the vaccine is administered. Needles should not be recapped before being discarded.[3-5] **Box 1** summarizes a few key recommendations on practical aspect of vaccination of a child.

INJECTION ROUTE, SITE, METHOD, AND NEEDLE LENGTH

With the exception of BCG and sometimes rabies and IPV, all parenteral vaccines are given by either intramuscular (IM) or subcutaneous (SC) route. The SC route is recommended for measles, MMR, varicella, meningococcal polysaccharide, Japanese encephalitis (JE), and Yellow fever vaccines; either SC or IM route may be used for pneumococcal polysaccharide vaccines, such as 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 aluminum 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

BOX 1: General instructions on immunization.

General instructions

- Vaccination at birth means as early as possible within 24–72 hours after birth or at least not later than 1 week after birth
- Whenever multiple vaccinations are to be given simultaneously, they should be given within 24 hours if simultaneous administration is not feasible due to some reasons
- The recommended age in weeks/months/years mean completed weeks/months/years
- Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible
- The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines
- When two or more live parenteral/intranasal vaccines are not administered on the same day, they should be given at least 28 days (4 weeks) apart; this rule does not apply to live oral vaccines
- If given <4 weeks apart, the vaccine given second should be repeated
- The minimum interval between 2 doses of inactivated vaccines is usually 4 weeks (exception rabies)
- Vaccine doses administered up to 4 days before the minimum interval or age can be counted as valid (exception rabies). If the vaccine is administered >5 days before minimum period, it is counted as invalid dose
- Any number of antigens can be given on the same day
- Changing needles between drawing vaccine into the syringe and injecting it into the child is not necessary
- Different vaccines should not be mixed in the same syringe unless specifically licensed and labeled for such use
- Patients should be observed for an allergic reaction (anaphylaxis) for 15–20 minutes after receiving immunization(s)
- When necessary, two vaccines can be given in the same limb (1–2 inches apart) at a single visit
- The anterolateral aspect of the thigh is the preferred site for two simultaneous intramuscular (IM) injections because of its greater muscle mass
- The distance separating the two injections is arbitrary but should be at least 1 inch so that local reactions are unlikely to overlap
- Although most experts recommend "aspiration" by gently pulling back on the syringe before the injection is given, there are no data to document the necessity for this procedure. If blood appears after negative pressure, the needle should be withdrawn and another site should be selected using a new needle
- A previous immunization with a dose that was less than the standard dose or one administered by a nonstandard route should not be counted, and the person should be re-immunized as appropriate for age

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 dry cotton. The injection site should not be rubbed following injection.[6,7]

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 IM injection **(Table 1)**. If a vaccine and an immune globulin preparation are administered simultaneously [e.g. Td/Tdap and tetanus immune globulin (TIg), hepatitis B 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 **(Figs. 1 to 4)**.

TABLE 1: Injection site, type of needle, and technique.

	Site	*Type of needle*	*Comments*
Intramuscular 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 to 10 years)	Deltoid or	22–25 gauge, 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 years onward)	Deltoid or anterolateral thigh	<60 kg 1 inch >60 kg 1.5 inch	

Contd…

Contd…

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

Fig. 1: Intramuscular/subcutaneous site for administration: Anterolateral thigh.

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

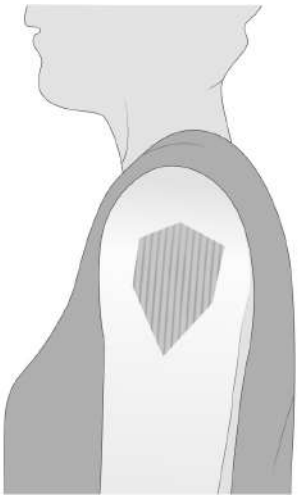


Fig. 2: Intramuscular site for administration: Deltoid muscle at upper arm.

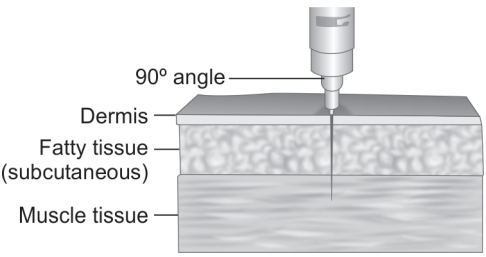


Fig. 3: Intramuscular needle insertion.

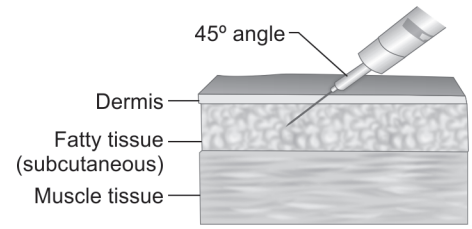


Fig. 4: Subcutaneous needle insertion.

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 at the rate of 15 mg/kg/dose to reduce the discomfort and fever.[7]

CONTRAINDICATIONS AND PRECAUTIONS

Contraindications

A condition in a recipient that greatly increases the chance of a serious adverse reaction.[7] It is a condition in the recipient of the vaccine, not with the vaccine per se. If the vaccine were given in the presence of that condition, the resulting adverse reaction could seriously harm the recipient.

For instance, administering influenza vaccine to a person with a true anaphylactic allergy to egg could cause serious illness or death in the recipient. In general, vaccines should not be administered when a contraindication condition is present.

The most common animal protein allergen is egg protein found in vaccines prepared using embryonated chicken eggs (e.g. yellow fever and influenza vaccines). Ordinarily, a person who can eat eggs or egg products can receive vaccines that contain egg; persons with histories of anaphylactic or anaphylactic-like allergy to eggs or egg proteins should not. Asking persons whether they can eat eggs without adverse effects is a reasonable way to screen for those who might be at risk from receiving yellow fever and influenza vaccines.

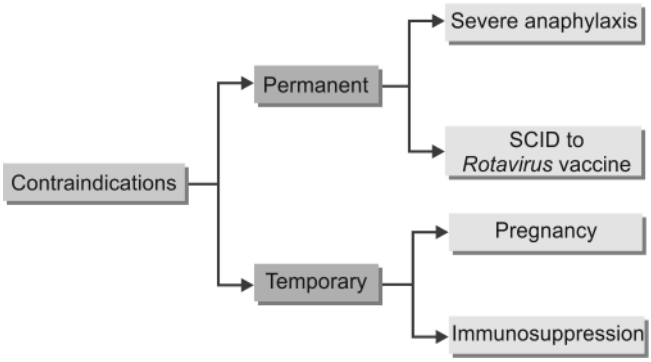
True contraindications are very few. Only three permanent contraindications are:

1. Severe allergic reaction to a vaccine component or following a prior dose of a vaccine
2. Encephalopathy occurring within 7 days of pertussis vaccination
3. Severe combined immunodeficiency (SCID) as a contraindication to rotavirus vaccine **(Flowchart 1)**.

Precautions

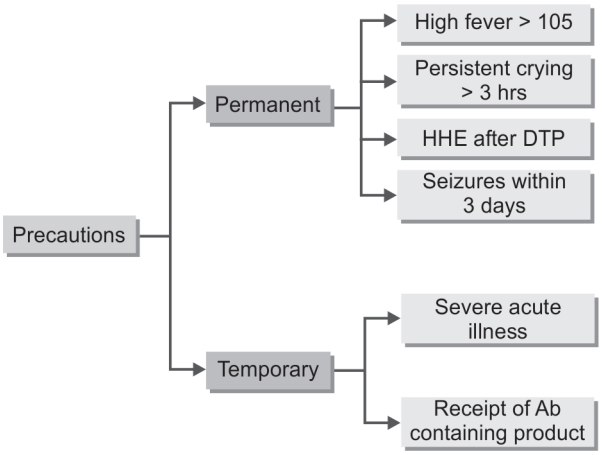
It is similar to a contraindication. A precaution is a condition in a recipient that might increase the chance or severity of a serious

Flowchart 1: Contraindications—permanent and temporary.



(SCID: severe combined immunodeficiency)

Flowchart 2: Precautions—permanent and temporary.



(DTP: diphtheria, tetanus, and pertussis; HHE: hypotonic-hyporesponsive)

adverse reaction, or that might compromise the ability of the vaccine to produce immunity (such as administering measles vaccine to a person with passive immunity to measles from a blood transfusion). Injury could result, but the chance of this happening is less than with a contraindication.[7] In general, vaccines are deferred when a precaution condition is present **(Flowchart 2)**.

BOX 2: Minimum resuscitative equipment.

- Airway, self-inflating resuscitation bag, mask, IV access (intravenous cannula of gauge 22, 24), oxygen cylinder, and oxygen mask with tubes
- Injection adrenaline (1 : 1,000 solution)
- IV hydrocortisone
- Normal saline

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. Record keeping is very important as guidelines issued for reporting of AEFI are also applicable to the private practitioners.[8]

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 counseled about possible side effects, their management, and danger signs before the vaccinee is sent home.[8,9] **Box 2** provides the list of bare minimum equipment and drugs needed to take care of any immediate adverse events following immunization, particularly any hypersensitivity reaction to vaccine.

REFERENCES

1. Kimmel SR, Wolfe RM. Communicating the benefits and risks of vaccines. J Family Practice. 2005;54:S51-57.
2. Healy MC, Pickering LK. How to communicate with vaccine–hesitant parents. Pediatrics. 2011;127:S127-133.
3. Hutin Y, Hauri A, Chiarello L, et al. Best infection control practices for intradermal, subcutaneous, and intramuscular needle injections. Bull World Health Organization. 2003;81:491-500.

4. WHO best practices for injections and related procedures toolkit. (2010) WHO/EHT/10.02 [online] Available from http://whqlibdoc.who.int/publications/ 2010/ 9789241599252_eng.pdf [Last accessed September, 2019].
5. Atkinson WL, Kroger AL, Pickering LK. General immunization practices. In: Plotkin SA, Orenstein WA, Offit PA (Eds). Vaccines, 5th edition. Saunders Elsevier; 2008. pp. 83-109.
6. Nicoll LH, Hesby A. IM injection. An integrative research review and guideline for evidence based practice. Appl Nurs Res. 2000;16:149-62.
7. General Recommendations on Immunization, Recommendations of the Advisory Committee on Immunization Practices (ACIP), MMWR; Recommendations and Reports. 2011;60(2).
8. Ministry of Health and Family Welfare. AEFI Surveillance and Response-Operational Guidelines. (2010) Available from http://www.cdsco.nic.in/AEFI %20 Guidelines% 20 Print %20ready%202010.pdf [Last accessed August, 2019].
9. Rajput M, Sharma L. Informed consent in vaccination in India: Medicolegal aspects. Hum Vaccin. 2011;7:723-37.

2.5 VACCINE STORAGE AND HANDLING

Digant D Shastri

INTRODUCTION

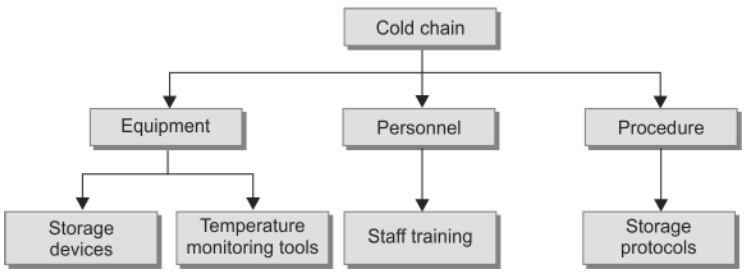
Immunization programs have had a major impact on the health status of the world population, by preventing many cases of infectious disease through immunization. Efficient vaccine storage and handling is a key component of immunization programs. Proper vaccine storage and handling is a shared responsibility from the time the vaccine is manufactured until it is administered. The majority of vaccine storage and handling mistakes are easily avoidable.

Cold chain breaches can occur even in well-designed and well-managed systems as a result of technical malfunctions; but if there are good procedures in place, problems will be detected and effectively managed so that effective protection can be extended to its recipients and vaccine losses can be prevented. Efficient vaccine storage management is an essential quality assurance measure for vaccine service providers.

WHAT IS THE COLD CHAIN?

The "cold chain" is the system of transporting and storing vaccines within recommended temperature from the place of manufacture to the point of administration. It has three main components: (1) personnel, (2) equipment, and (3) procedures **(Flowchart 1).**

Flowchart 1: Cold chain components.



1. Equipment
2. Personnel
3. Procedures.

Above three discussed components combine to ensure proper vaccine transport, storage, and handling. The optimum temperature for refrigerated vaccines is between +2°C and +8°C. For frozen vaccines, the optimum temperature is –15°C or lower. In addition, protection from light is a necessary condition for some vaccines.

IMPORTANCE OF MAINTAINING THE COLD CHAIN

Vaccines and toxoids are made up of proteins, nucleic acids, lipids, and carbohydrates, which may become less effective or even destroyed, when exposed to temperatures outside the recommended range. Cold-sensitive vaccines experience an immediate loss of potency following freezing. Vaccines exposed to temperatures above the recommended temperature range experience some loss of potency with each episode of exposure. Repetitive exposure to heat episodes results in a cumulative loss of potency that is not reversible. 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 with exception of vaccine monitoring tool—vaccine vial monitors (VVMs), which is provided with oral poliomyelitis vaccine (OPV). VVM can indicate the level of heat exposure of individual vials. It will be very difficult to assess the potency of a mishandled vaccine because information on vaccine degradation is sparse; multipoint stability studies on vaccines are difficult to perform and information from manufacturers is not always available **(Table 1)**.

Maintaining the potency of vaccines is important for several reasons:

- Use of ineffective vaccine will lead to vaccine failures, which ultimately leads to reemergence or occurrence of vaccine-preventable disease.
- Vaccines are expensive and such loss of vaccine will cause waste of resource.
- Loss of vaccines may result in short supply of vaccines, which may lead to the cancellation of immunization sessions resulting in lost opportunities to immunize.

TABLE 1: Summary of vaccine sensitivities.

Vaccine	*Exposure to heat/light*	*Exposure to cold*	
Heat- and light-sensitive vaccines			
BCG	Relatively heat stable, but sensitive to light	Not damaged by freezing	+2°C to +8°C
OPV	Heat sensitive	Not damaged by freezing	+2°C to +8°C
Measles	Sensitive to heat and light	Not damaged by freezing	+2°C to +8°C
Freeze-sensitive vaccines			
DPT	Relatively heat stable	Freezes at −3°C	+2°C to +8°C
Hep B	Relatively heat stable	Freezes at −0.5°C	+2°C to +8°C
DT	Relatively heat stable	Freezes at −3°C	+2°C to +8°C
TT	Relatively heat stable	Freezes at −0.5°C	+2°C to +8°C

(BCG: Bacillus Calmette-Guérin; OPV: oral poliomyelitis vaccine; DPT: diphtheria, pertussis and tetanus; DT: diphtheria and tetanus; Hep B: hepatitis B; TT: tetanus toxoid)

- Revaccination of people who have received an ineffective vaccine is professionally uncomfortable and may cause a loss of public confidence in vaccines and/or the healthcare system.
- Proper vaccine storage and management is the responsibility of all those dealing with them right from manufacturer, transporter, stockist, retailers to doctors, and end users.
- Different surveys, studies, and site visits have found that about 17–37% of healthcare providers expose vaccines to improper storage temperatures. Refrigerator temperatures are more commonly kept too cold rather than too warm.

VACCINE STORAGE EQUIPMENT SUPPLIED UNDER THE IMMUNIZATION PROGRAM

Walk-in Freezers

Walk-in freezers (WIF) are used for bulk storage of OPV vaccines and also for preparation and storage of frozen ice packs at state stores. They maintain a temperature of –18°C to –20°C.

Walk-in Coolers

Walk-in-coolers (WIC) are made up of modular and prefabricated physical unclonable function (PUF) insulated panels with floor of either stainless steel panels or modular floor panels with an aluminum chequered plates. These cold rooms are typically controlled between 2°C and 8°C. It has digital light-emitting device/light crystal device (LED/LCD), temperature display, and temperature recorder. It is fitted with an audio-video alarm system to warn of high or low temperature. These are used for bulk storage of vaccines at state and regional stores.

Walk-in coolers/walk-in freezers stores 3 months of requirement of vaccines and 25% buffer stock for the districts they cater.

Deep Freezers

Deep freezers have either top-opening lid or front door. Deep freezers supplied under immunization program have a top-opening lid. The cabinet temperature is maintained between –18°C and –20°C. This is used for storing of OPV at district and also for freezing ice packs.

Ice-lined Refrigerator

These types of refrigerators are top opening. Inside the ice-lined refrigerator (ILR), there is a lining of water containers (ice packs or tubes) fitted all around the walls and held in place by frame. While refrigerator is operating, the water in the containers freezes and if the electricity supply fails, then the ice lining keeps the inside temperature of the refrigerator at a safe level for vaccines. It can keep vaccine safe with as little as 8-hour continuous electricity supply in a 24-hour period.

Hence, it is suitable for use in the area with poor power supply. ILR has two sections—the top and the bottom. The bottom of the refrigerator is the coldest place. OPV and measles vaccine can be placed at the bottom of the ILR. The DPT (diphtheria, pertussis, and tetanus), DT (diphtheria and tetanus), TT (tetanus toxoid), and Hep B (hepatitis B) vaccines should not be kept directly on the floor of the refrigerator as they can freeze and get damaged, and they should be stored in basket along with diluents **(Figs. 1 to 3)**.

Fig. 1: Ice-lined refrigerator.

Fig. 2: Vaccine storage in ice-lined refrigerator.

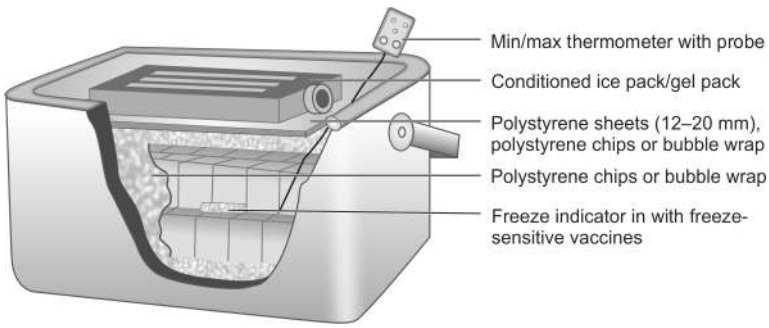


Fig. 3: Vaccine storage in cooler ice-lined refrigerator.

Automatic Voltage Stabilizer

The function of the voltage stabilizer is to control the range of fluctuations in the main voltage of 220 volts (+10 volts). No electrical cold chain equipment should be used or operated without a voltage stabilizer.

Cold Boxes (Coolers)

Cold boxes are big insulated boxes with ice packs. They are mainly used for transportation of vaccines from district store to the primary health center (PHC). In emergency, they can also be used to store vaccines and frozen ice packs. Before placing vaccines in the cold boxes, first put fully frozen ice packs at the bottom and sides of the cold box. The vials of DPT, DT, Hep B, and TT vaccines should not be placed in direct contact with frozen ice packs, place it in cartoon or plastic bag.

Vaccine Carriers

It is used by health workers for carrying vaccines (16–20 vials) to subcenters or to villages. They maintain the cold chain during transport from the PHC for 1-day use in the field. The inside temperature is maintained between +2°C and –8°C with four frozen ice packs for one day (if not opened frequently) **(Table 2)**.

Domestic Refrigerator

Majority of the vaccination service providers in private sector use domestic refrigerator to store the vaccines. The domestic refrigerator is designed and built to store fresh or frozen food and drinks and not for the special storage temperature need of vaccines. They do not have accurate temperature controlling system and hence it can place the safety of vaccines at risk. For vaccine storage the domestic refrigerator has following drawbacks:

- Temperature varies significantly every time the door is opened.
- Temperature rises during defrosting in cycle in cyclic defrost and frost-free refrigerator.
- Cabinet temperature is easily affected by ambient temperature.
- Temperature setting using dial is crude and inaccurate.

TABLE 2: Summary of cold chain equipment used under expanded program on immunization.

Equipment	*Temperature*	*Storage capacity*	*Holdover time*
Electrical			
Deep freezer	−15°C to −25°C	200 ice packs or OPV stock for 3 months	• 43°C for 18 hours • 32°C for 22 hours
ILR	+2°C to + 8°C	BCG, DPT, DT, TT, measles, Hep B vaccine stock for 3 months	• 43°C for 18 hours • 32°C for 22 hours
Nonelectrical			
Cold box (large)	+2°C to + 8°C	All vaccines stored for transport or in case of power failure	• 43°C for 6.5 days • 32°C for 10 hours
Vaccine carrier	+2°C to + 8°C	All vaccines carried for 12 hours	• 43°C for 34 hours • 32°C for 51 hours

(BCG: Bacillus Calmette-Guérin; OPV: oral poliomyelitis vaccine; DPT: diphtheria, pertussis and tetanus; DT: diphtheria and tetanus; Hep B: hepatitis B; TT: tetanus toxoid; ILR: ice-lined refrigerator)

However, if domestic refrigerator is the only alternative to store the vaccines in that it is acceptable to store vaccines provided that the refrigerator and freezer compartments have separate external doors. There are two types of domestic refrigerators—(1) frost-free refrigerator and (2) manual and cyclic defrost refrigerator. The frost-free refrigerators have no heating cycles but have low-level warming cycles and hence it provides more uniform temperatures than manual and cyclic defrost models and may be more suitable for vaccine storage. The manual and cyclic defrost model refrigerator and bar refrigerator (dormitory style) should not be used to store the vaccine as they have wide fluctuations in the temperature in the internal compartment. Safe vaccine storage is possible in domestic refrigerators, if following points are observed:

- Store vaccine in a dedicated refrigerator especially for biologics. Do not store food or drink in vaccine refrigerators.
- The refrigerator compartment temperatures is maintained between 2°C and 8°C and freezer compartment temperatures maintained at or below 5°F (–15°C).
- The door seals are in good condition and are sealing tightly.

- The door closes properly automatically on leaving it free.
- The refrigerator has separate freezer compartment.
- The refrigerator compressor is quiet.
- The refrigerator is free from any coolant or water leak.
- Vaccination clinic staff is well aware about vaccine storage plans.

If the above criteria cannot be met, with that one should go for purpose-built refrigerator for storing the vaccine.

Tips for Better Vaccine Storage in Domestic Refrigerators (Table 3)

- Placement of refrigerator:
  - Refrigerator should be placed away from exposure to direct sunlight and heat, and with restricted accessibility only to the vaccination staff so as to minimize unnecessary door opening and preventing accidental switch off of power supply.
- Recognize individual vaccine refrigerator:
  - Before starting the storage of the vaccines, identify which are the cold and warm areas in the refrigerator?
- Stabilize the temperature of the refrigerator before stocking:
  - The refrigerator temperature needs to be stabilized before starting the use of refrigerator for vaccine storage.
- Monitoring temperatures inside the refrigerators:
  - Monitor internal temperature regularly with thermometer—preferably Celsius digital minimum/maximum thermometer. Place the thermometer in a central location within the storage compartment **(Fig. 4)**.
- Safeguard the power source:
  - Ensure the power source is marked clearly in a way to prevent the refrigerator from being accidentally unplugged or turned off **(Fig. 5)**.

TABLE 3: Periodic maintenance plan for vaccine refrigerator.

Daily	*Weekly*	*Every fortnight*
Check to make sure the doors are closed and sealed	Check for ice buildup in the freezer and defrost, if >0.5 cm frost has accumulated	• Clean the coils and the motor • Defrost and clean the refrigerator and freezer compartments • Adjust the thermostat, if necessary

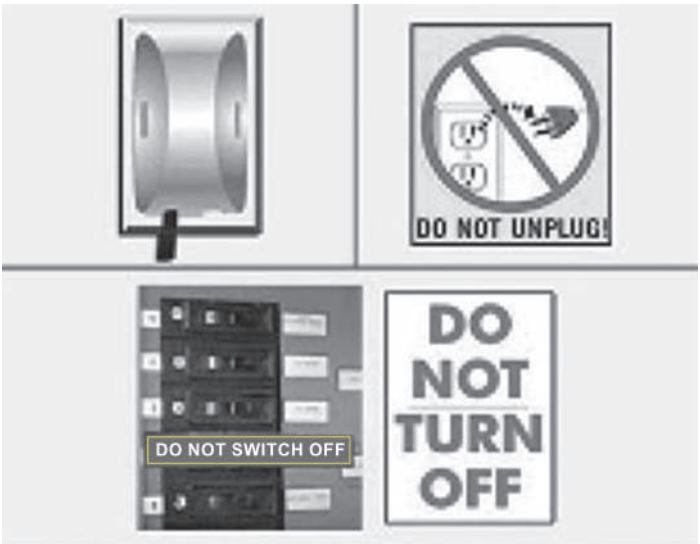


Fig. 5: Safeguard the power source.

Fig. 4: Temperature monitoring.

Fig. 6: Water bottles to increase cool mass.

- Increase cool mass:
  - Place water bottles or ice packs/gel packs in the refrigerator to increase the cool mass; these will assist in stabilizing the temperature in refrigerator compartment and reduces warming periods when the refrigerator is opened. This is also useful, if there is a short-time power cut or refrigerator failure **(Fig. 6)**.
- Ideal storage method:
  - Store vaccines in enclosed plastic-labeled containers or basket. This will allow easy identification of vaccines and minimizes the time spent with the door opened searching for vaccines.
  - Store vaccines in original packing as it can provide some protection from very short-term fluctuations.
  - Do not crowd the vaccines by overfilling the shelves. Allow space between containers and gap of at least 4 cm from all refrigerator walls to allow free air circulation.
  - Never store any vaccine in the door of the refrigerator.
- Place measles, MR, MMR, BCG, OPV, yellow fever, Japanese encephalitis (SA-14-142), meningococcal A conjugate, Rotavac* and/or any other vaccines not damaged by freezing on the top shelf **(Figs. 7 and 8)**.
- Put DTP, DT, Td, TT, Tdap, HepB, DTP+HepB, DTP+HepB+Hib, Hib, PCV, HPV, Rotavirus and/or any other freeze-sensitive vaccines on the middle or lower shelves.

*Rotavac can be stored at –20°C till expiry date. It can be stored upto 6 months at 2 to 8°C.

Fig. 7: Vaccine storage pattern.

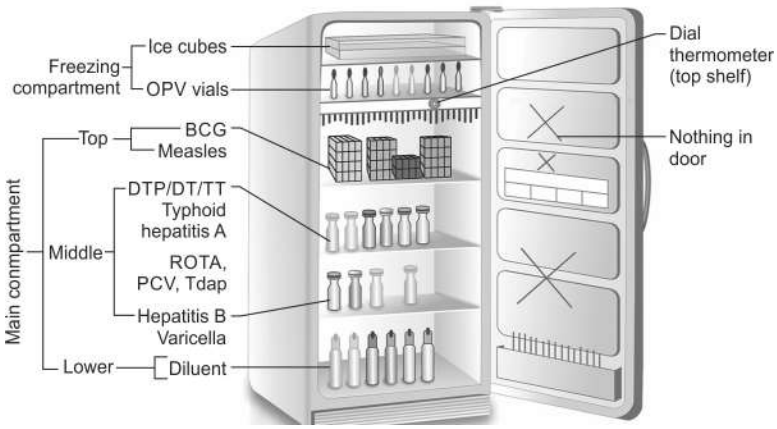


Fig. 8: Storage protocol in domestic fridge.
(OPV: oral poliomyelitis vaccine; BCG: Bacillus Calmette-Guérin; DTP: diphtheria, tetanus, and pertussis; DT: diphtheria and tetanus; TT: tetanus toxoid)

- Store the diluents next to the freeze-dried vaccine with which they are supplied, on the appropriate shelf. If there is not enough space on the shelf, put the diluents on the bottom shelf, clearly labeled so they can be easily identified to their matching vaccine.

The following rules apply for front-opening refrigerators:

- Never put vaccines or diluents in the door shelves. The temperature is too warm for vaccine storage and vaccines are exposed to room temperature each time, the door is opened.

- Never put freeze-sensitive vaccines in contact with, or close to, the evaporator plate in the refrigerator.
- Put water packs or plastic bottles full of colored water in the space below the bottom shelf. This helps to stabilize the temperature, if there is a power cut. Do not use the water packs in vaccine carriers. Never drink the water.
- *Keep the door closed as much as possible*:
  - Reducing door opening helps to keep internal temperatures stable.
  - Vaccine refrigerators should have a sticker to remind staff of avoiding unnecessary door opening.
  - Stick a basic map of vaccine locations outside of the refrigerator door so staff can go "straight" to the vaccine when the door is opened.
  - Do not open the door fully while using, keep it to minimum sufficient for the need.
- *Training and assigning staff*:
  - Good vaccine storage and handling depends on knowledge and habits of the staff.
  - Training ensures that everyone handling vaccines knows how to protect them.
  - Ensure that one person is responsible for adjusting refrigerator controls and the other person is responsible for cold chain management to enable consistency.
- *Maintenance of the vaccine refrigerator*:
  - Report breakdowns immediately and arrange for alternative storage for vaccines while the refrigerator is repaired **(Table 3)**.
  - Defrost refrigerator regularly. This also aids in the efficient functioning of refrigerator.
- *Power failure*:
  - During a power failure of 4 hours or less the refrigerator door should be kept closed.
  - If the backup generator facility is lacking, identify an available unit at another nearby site.
  - If a refrigerator with a backup generator has not been located or is not working, and for power failures more than 4 hours store vaccines in a cooler with conditioned ice packs or gel packs.

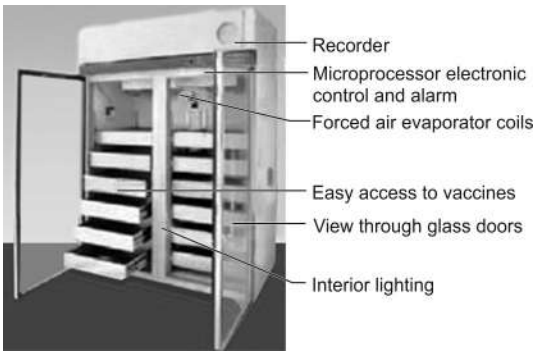


Fig. 9: Purpose-built vaccine refrigerator.

Purpose-built Vaccine Refrigerator

Purpose-built vaccine refrigerator is preferred refrigerator for vaccine storage. It is used by hospitals, pharmacies, and larger general practices. It has following advantages over the domestic refrigerator **(Fig. 9)**:

- Do not require to modify for vaccine storage.
- Programmed to maintain an internal temperature between 2°C and 8°C.
- Cabinet temperature is not affected by ambient temperature and is stable and uniform.
- Evaporator operates at 2°C–8°C, preventing vaccine from freezing.
- Defrost cycle allowing defrosting without rise in cabinet temperature.
- Even distribution of temperature because of ongoing air circulation.
- Have external temperature reading display, maximum/minimum temperature continuous display, and an out-of-range temperature alarm.
- Good temperature recovery—when the fridge is open to access the vaccines.

COLD CHAIN TEMPERATURE MONITORING

Monitoring of temperature is a critical and integral part of any cold chain system. The expensive equipment installed may become meaningless unless a meticulous temperature record documents its proper working. In every vaccine storage equipment, the temperature

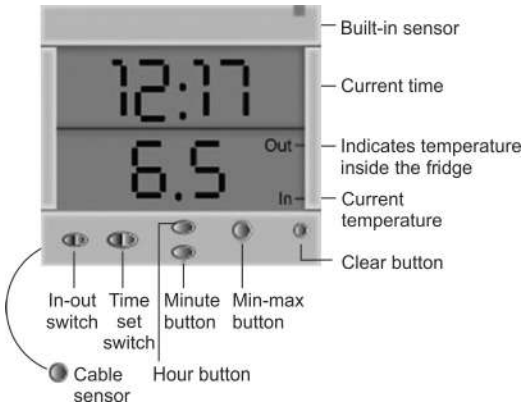


Fig. 10: Minimum/maximum thermometer.

should be monitored. Temperature should be recorded at least two times in a day and plotted on a chart to show high/low excursions. To measure the temperature during storage of vaccines, different type of thermometer is used.

Minimum/Maximum Thermometer (Fig. 10)

It shows the current temperature and the minimum and maximum temperatures achieved. Temperature fluctuations outside the recommended range can also be detected. Available in fluid-filled and digital forms of which digital type with a probe is most effective type. Place the probe directly in contact with a vaccine vial or package. Thermometer must be reset regularly; the thermometer battery must be checked and replaced time to time.

- *Dial thermometer*: They are the most common but not the most accurate. They only indicate the temperature at the time they are read. Temperature fluctuations outside the recommended range may not be detected.
- *Stem (Alcohol) thermometer*: It is more sensitive and accurate compared to dial thermometer as it records temperature from –50°C to +50°C. It can be used in ILR and deep freezers.
- *Digital thermometer*: These are the most accurate constant monitors and also offer alarm to safeguard against damage from refrigerator malfunction. To get accurate reading, place the temperature probe in proper location.

Data Loggers

This temperature chart recording system can record temperatures over a long period of time as well as can provide visual and audio alarms. Loggers use a similar measuring principle to chart as recorders but record the data electronically.

The objective of data logging is to build up a "temperature map" of the vaccine storage areas within the refrigerator to identify the safest areas and the most dangerous areas for vaccine storage, particularly looking for areas where vaccine could freeze.

Each logger is a self-contained miniature computer. Once programmed via computer, loggers are disconnected from the computer, and placed in the vaccine refrigerator in close proximity to the temperature probe. The logger then operates independently on its own battery until the recording is downloaded to the computer.

Vaccine Vial Monitor

A vaccine vial monitor (VVM) is a label containing a heat-sensitive material, which is placed on a vaccine vial to register cumulative heat exposure over time **(Fig. 11)**. A VVM enables the health worker to know whether vaccine has been damaged by exposure to heat. The VVM is a circle with a small square inside it, which is lighter in color than surroundings. The inner square of VVM is made of heat-sensitive material that is lighter in color at the starting point. The combined effect of time and temperature causes the inner square of the VVM to darken gradually. The color change is irreversible. A direct relationship

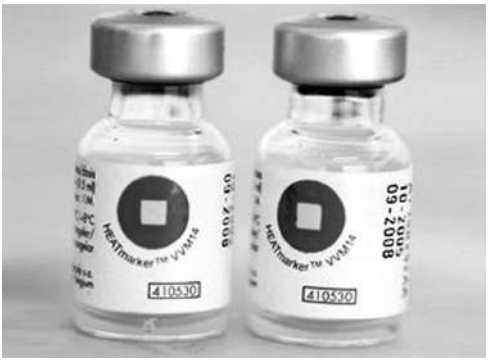


Fig. 11: Vaccine vial monitor.

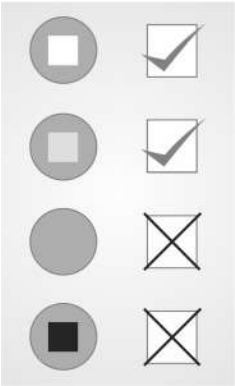


Fig. 12: Decision to use vaccine/s based on vaccine vial monitor (VVM) sensitivity.

exists between rate of color change and temperature. Thus, lower the temperature, slower the color change; and higher the temperature, faster the color change.

Thus, VVM gives information about the heat exposure over a period of time that affects vaccine potency. It does not give information about other factors responsible for vaccine degradation like light. VVMs are not substitutes for expiry dates. If the inner square is lighter than the outer ring, the vaccine can be used, whereas if inner-square matches has darker color than outer ring, then the vaccine should be discarded **(Fig. 12)**.

VACCINE HANDLING PERSONNEL

Designated Vaccine Coordinators Staff

Each vaccination clinic should designate one staff member to be the primary vaccine coordinator and another staff member as a backup in case the primary coordinator is unavailable. The designated person will be responsible for ensuring that all vaccines are handled correctly, that procedures are documented, and that all personnel receive appropriate cold chain training. Designated vaccine coordinators should be fully trained in routine and urgent vaccine storage and handling protocols.

Other Staff

All staff members should be familiar with the policies and procedures for vaccine storage and handling. This especially includes staff members, such as receptionists who accept vaccine shipments. Written policies and procedure documents should be available near the vaccine storage units for easy reference.

Training Personnel

All staff that handle or administer vaccines should be trained in proper vaccine storage and handling practices. All staff should be trained to have an understanding of the importance of cold chain maintenance and basic practices so that they are aware of their responsibilities to the cold chain. Staff who monitor and record vaccine storage unit temperatures should immediately report inappropriate storage conditions (including exposure to inappropriate temperature or light exposures) to the designated vaccine coordinator.

EFFICIENT VACCINE MANAGEMENT PROTOCOLS

Routine Vaccine Storage and Handling Protocols

Routine protocols should include all aspects of day-to-day vaccine management, from ordering vaccines, controlling inventory, handling vaccines, and monitoring storage conditions. It should include following four elements:

1. *Ordering and accepting vaccine deliveries*:
   - Order vaccines to maintain an adequate stock to meet the needs of the vaccination unit.
   - Ensure that the "ordered vaccine stock" is delivered when the vaccination unit is open. Vaccine shipments should be delivered when staff is available to unpack and store.
   - Store vaccines at the recommended temperatures, immediately on arrival, refrigerated vaccines between 2°C and 8°C and frozen vaccines between –50°C and 15°C
   - Maintain a vaccine inventory log including:
     - Vaccine name and number of doses received
     - Date vaccine received
     - Condition of vaccine on arrival
     - Vaccine manufacturer and lot number
     - Vaccine expiration date.

2. Storing and handling vaccines (as discussed above).
3. *Managing inventory*:
   - Rotate vaccine stock so vaccine and diluent with the shortest expiration date is used first.
   - Place vaccine with the longest expiration date behind the vaccine that has short expiry.
   - Remove expired vaccine and diluent from usable stock.
   - Keep vaccine stock well organized.
   - Stick a basic map of vaccine locations outside of the refrigerator door so that staff can go "straight" to the vaccine when the door is opened.
   - Inspect the storage unit daily. A physical inspection helps to ensure that vaccines and thermometers are placed appropriately within the unit.
   - Dispose of all vaccine materials using medical waste disposal procedures.
4. *Managing potentially compromised vaccines*:
   - Identify and isolate all potentially compromised vaccines and diluents
   - Label these vaccines "DO NOT USE" and store separately from uncompromised vaccines and diluents in the recommended temperature range.
   - Contact vaccine manufacturers and/or state immunization program for appropriate actions that should be followed for all potentially compromised vaccines and diluents.

Emergency Vaccine Retrieval and Storage

Various situations like equipment failures, power outages, or natural disasters may compromise vaccine storage conditions. It is important that all the staff involved in the immunization activity is aware of the probable adverse effect of such situations on vaccine storage conditions. Ensure that all staff has appropriate training, so that they understand the urgent vaccine storage and handling protocols and their responsibility in maintaining the cold chain. Emergency vaccine retrieval and storage plan should include the following components:

- Designate an alternate site where vaccines and diluents can be safely stored. While choosing an alternate site, consider availability of types of storage unit(s), temperature monitoring capabilities, and backup generator.

- Obtain and store an adequate packing containers and materials (e.g. frozen or refrigerated gel packs, bubble wrap) in the facility that will be needed to pack vaccines for safe transport.
- Include written directions for packing vaccines and diluents for transport. A calibrated thermometer should be placed in each packing container near the vaccine.
- Incorporate written procedures for managing potentially compromised vaccines.
- Include contact information for vaccine manufacturers and/or the immunization program.

BIBLIOGRAPHY

1. Centers for Disease Control. (1991). Vaccine Management, Recommendations for Handling and Storage of Selected Biologicals. [Online]. Available from: https://wonder.cdc.gov/wonder/prevguid/p0000075/p0000075.asp. [Last accessed October, 2019].
2. DD Shastri. Vaccine storage and handling. In: Parthasarthy A (Ed). IAP Textbook of Pediatrics, 7th Edition. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd.; 2019.
3. Department of Health and Ageing; Australian Government. (2013). National Vaccine Storage Guidelines, "Strive for 5". [Online]. Available from: https://www.health.gov.au/sites/default/files/national-vaccine-storage-guidelines-strive-for-5_0.pdf. [Last accessed October, 2019].
4. Galazka A, Milstien J, Zaffran M. (1998). Thermostability of Vaccines: Global Programme for Vaccines and Immunization. [Online]. Available from https://apps.who.int/iris/bitstream/handle/10665/64980/WHO_GPV_98.07.pdf?sequence=1&isAllowed=y. [Last accessed October, 2019].
5. Gupta SK, Shastri DD. Cold chain and vaccine storage. In: Shah NK, Agrawal R, Sukumaran TU, Vashishtha VM (Eds). IAP Textbook of Vaccines, 1st edition. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd; 2014. pp. 89-99.
6. Ketan B, Jariwala V, Kirit S. Target-5: Guide to Vaccine Storage and Handling, 1st Edition. Gujarat: IAP Surat publication; 2006.
7. Shastri DD. Vaccine storage and handling. In: Parthasarathy A (Ed). IAP Textbook of Pediatrics Infectious Diseases, 1st edition. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd.; 2013. pp. 493-501.
8. Shastri DD. Vaccine storage and handling. In: Parthasarthy A (Ed). IAP Textbook of Pediatrics, 5th edition. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd; 2013. pp. 1-5.
9. World Health Organization. (2002). Getting started with VVMs. VVM for all, Technical Session on Vaccine Vial Monitors, [Online]. Available from: http://vaccineresources.org/files/Getting_started_with_VVMs.pdf. [Last accessed October, 2019].
10. World Health Organization. Immunization in Practice (WHO/EPI/PHW/84.01 to 84.07).

2.6 ADVERSE EVENTS FOLLOWING IMMUNIZATION

Harish K Pemde, Dipak Polpakara

Vaccines are among the safest medicines to use and these are considered very effective tool for preventing infectious diseases. Like any other drug, no vaccine is 100% effective or 100% safe 100% of time.[1] As with other drugs, adverse events can occur with vaccines too. In addition to the vaccines themselves, the process of administration of vaccines is a potential source of an adverse event following immunization.

An adverse events following immunization (AEFI) surveillance system is usually a passive system to enable spontaneous reporting of all adverse events. It is a part of the National Regulatory Authority (NRA) for vaccines. The primary purpose of spontaneous AEFI reporting is to monitor the known adverse events associated with vaccine use, and to identify the new adverse events, i.e. safety signals after a product is marketed.[2] India is a major vaccine producing and exporting nation supplying 70% of UN vaccine requirements. A functional NRA is a prerequisite for supplying vaccines to UN agencies.[3] The Operational Guidelines for Surveillance and Response to AEFI (2015) provides guidance for the AEFI surveillance system in India.[4]

ADVERSE EVENTS FOLLOWING IMMUNIZATION

An AEFI is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine, i.e. might have not been caused by vaccine ingredients or the process of vaccination or immunization but have a temporal relationship with administration of vaccine **(Table 1)**. It can be any unfavorable or unintended sign, abnormal laboratory finding, symptom, or disease.[5] Sometimes, mass use of vaccines can cause anxiety in community and even such responses can be considered as AEFI.

CAUSE-SPECIFIC TYPES OF ADVERSE EVENT FOLLOWING IMMUNIZATION

- *Vaccine product-related reaction*: An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent

properties of the vaccine product (or ingredients), e.g. extensive limb swelling following DTP vaccination. In this scenario, vaccine might have been used correctly without compromising with manufacturing process, transport, or storage. Thus, absolutely correct use of vaccine may also cause this type of AEFI. In most cases, such events are usually not serious in nature.

- *Vaccine quality defect-related reaction*: An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product including its administration device as provided by the manufacturer, e.g. failure by the manufacturer to completely inactivate a lot of IPV leads to cases of paralytic polio.
- *Immunization error-related reaction*: An AEFI that is caused by inappropriate vaccine handling, prescribing, or administration and thus by its nature is preventable, e.g. transmission of infection by contaminated multidose vial.
- *Immunization anxiety-related reaction*: An AEFI arising from anxiety about the immunization, e.g. vasovagal syncope in an adolescent following vaccination. The anxiety may spread to community too, at times.
- *Coincidental event*: An AEFI that is caused by something other than the vaccine product, immunization error, or immunization anxiety, e.g. fever after vaccination (temporal association) and malarial parasite isolated from blood **(Table 1)**.

TYPES OF ADVERSE EVENTS FOLLOWING IMMUNIZATIONS BASED ON SEVERITY

- *Serious AEFI*: An AEFI is considered serious if it (1) results in death, hospitalization, or persistent or significant disability/incapacity, (2) occurs in clusters, (3) causes parental/community concern, or (4) results in congenital anomaly/birth defect.
- *Severe AEFI*: Severe AEFIs are minor AEFIs with increased intensity/severity, e.g. high grade fever following pentavalent vaccination or post-DPT swelling extending beyond nearest joint. The patient may not be hospitalized and will not have sequelae.
- *Minor AEFI*: Minor AEFIs can be local reactions (pain, swelling, and redness) or systemic reactions (fever > 38°C, irritability,

TABLE 1: Adverse events following immunization in commonly used vaccines.

Vaccine	*Reaction*	*Onset interval*	*Frequency per doses given*
BCG	Fatal dissemination of BCG infection	1–12 months	0.19–1.56/ 1,000,000
OPV	Vaccine associated paralytic poliomyelitis (VAPP)	4–30 days	2–4/1,000,000
DTwP	Prolonged crying and seizure	0–24 hours	< 1/100
	HHE	0–24 hours	< 1/1,000–2/1,000
Measles	Febrile seizures	6–12 days	1/3,000
	Thrombocytopenia	15–35 days	1/30,000
	Anaphylaxis	1 hour	1/100,000
Rotavirus	Intussusception	3–14 days	1–2/100 000

(HHE: hypotonic-hyporesponsive episode; BCG: Bacille Calmette–Guérin; OPV; oral polio vaccine; DTwP: diptheria tetanus-pertussis)
Source: AEFI Surveillance and Response Operational Guidelines by Ministry of Health and Family Welfare, Government of India. 2015.

malaise, etc.), which can be managed with antipyretics and anti-inflammatory and resolves within 2–3 days.

PROCESS OF REPORTING ADVERSE EVENTS FOLLOWING IMMUNIZATIONS

Most vaccinations in India are given through the government system through outreach sessions by auxiliary nurse midwives (ANMs) and sessions in health facilities. To make reporting simple and to get as many cases reported, health workers and medical personnel are asked to notify serious and severe AEFIs immediately to the nearest primary health center (PHC) medical officer (MO) or the District Immunization Officer (DIO). Private practitioners are also encouraged to notify AEFIs similarly to the DIO. The MO at the PHC then reports the case in the case reporting format (CRF) within 24 hours to the DIO who has another 24 hours to verify the case and send it to the State Immunization/EPI (Expanded Program of Immunization) Officer and the Immunization Division, Ministry of Health and Family Welfare (MOHFW) simultaneously. The CRF gives only the most basic details

of the affected person, vaccines and session details, and status of the patient (brief clinical summary) at the time of filling the format.

INVESTIGATING ADVERSE EVENTS FOLLOWING IMMUNIZATIONS

As soon as the AEFI is reported, case investigation begins. The preliminary case investigation format (PCIF) acts as a checklist and records the details of the investigations done with relation to the case. The investigation involves verifying personal details, vaccine and program details, a clinical examination, interviews with the treating physicians, caregivers, service providers, volunteers, etc. to understand the sequence of events. An epidemiological investigation is also conducted. The cold chain and vaccine transportation conditions are studied. Hospital records, laboratory test reports, and other relevant documents are collected. In case of death, postmortem is recommended. Verbal autopsies formats have been designed specifically for finding the cause of AEFI deaths. These forms should be used whenever a death is alleged to be associated with vaccine. These, along with the filled PCIF are submitted simultaneously to the state and the national level within 10 days of notification. Whenever required, experts of the District/State AEFI Committees are requested to participate in the investigation.

ADVERSE EVENTS FOLLOWING IMMUNIZATIONS COMMITTEES

Adverse events following immunization committees have been formed in all districts, states, and at the national level. The responsibilities of the AEFI committees are to strengthen AEFI reporting at all levels, ensure maintenance of national policy and standards, ensure prompt and thorough investigation of serious/severe AEFI, carry out periodic review of AEFI for trends of nonserious AEFIs reported through the Health Management Information System (HMIS)/routine immunization reporting, respond to the media and community concerns to allay fears regarding vaccine safety, ensure high standards of AEFI surveillance to ensure that no serious AEFI are missed, and recommend changes to the immunization program

for ensuring vaccine safety. All AEFI committees at all levels meet at least once a quarter.

The District AEFI Committee, when it meets, discusses all the case reports and records, summarizes the findings of the investigation in the final case investigation form (FCIF) and gives its opinion on the probable diagnosis. The FCIF is sent to the State AEFI Committee and the immunization division within 100 days of notification. At the state level, the causality assessment experts of the State AEFI Committee discusses all the reports available, gives a diagnosis, and classifies the case as per WHO classification. A proportion of cases causally assessed by the states are further causally assessed by the National AEFI Committee.

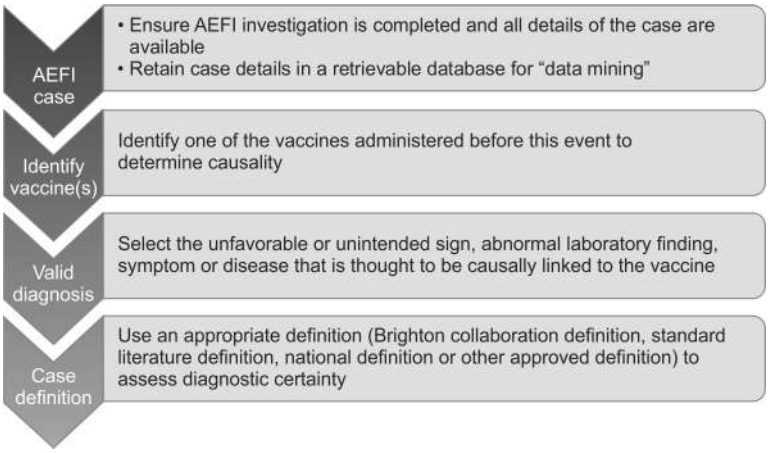
CAUSALITY ASSESSMENT

Causality assessment is the systematic evaluation of the information obtained about an AEFI to determine the likelihood of the event having been caused by the vaccines received. The causality assessment is conducted at state and national levels by trained experts in the AEFI committees within a month of receipt of all records and reports of the AEFI case. The criteria for causality in the causality assessment process includes proof of temporal relationship, biological plausibility, strength of association, consistency of association, specificity, definitive proof that the vaccine caused the event, consideration of alternate explanations, and prior evidence that the vaccine in question could cause a similar event.

Step 1: Eligibility for Causality Assessment

Eligibility for causality assessment considers whether the event occurred following vaccination, all records, and reports of case investigation are available including a diagnosis and the suspect vaccine is identified. Another requirement is the availability of definitions for the event identified (Brighton' or other standard literature or national definition or other approved definition). This is a critical step to identify the event as a diagnosis if possible, or a well-defined abnormal symptom or laboratory test finding. A valid diagnosis is the backbone of AEFI causality assessment and must be arrived at before doing the causality assessment. This can be a disease/symptom/sign/lab finding **(Flowchart 1)**.

Flowchart 1: Eligibility for causality assessment.



Once all information is available, a causality assessment question is proposed in the following manner:

Create your question on causality here

Has the _____ vaccine/vaccination caused _____ (The event for review in step 2—valid diagnosis)

Keeping this question in mind, a checklist is filled which collects information and evidence relevant for causality assessment from the available reports and records.

The Causality Assessment Checklist

It is shown in **Table 2**.

The information collected in the above checklist is further processed through an algorithm for decision making and conclusion related to causality.

The Causality Assessment Algorithm

The **Flowchart 2** leads to classification of cause(s) of AEFI in the following categories:

A. Consistent causal association to immunization:
   A1. Vaccine product-related reaction (as per published literature)
   A2. Vaccine quality-defect related reaction

TABLE 2: Causality assessment checklist.

I. Is there strong evidence for other causes?	*Y N UK NA*	*Remarks*
1. In this patient, does the medical history, clinical examination and/or investigations, confirm another cause for the event?	☐☐☐☐	
II. Is there a known causal association with the vaccine or vaccination?		
Vaccine product		
1. Is there evidence in published peer-reviewed literature that this vaccine may cause such an event if administered correctly?	☐☐☐☐	
2. Is there a biological plausibility that this vaccine could cause such an event?	☐☐☐☐	
3. In this patient, did a specific test demonstrate the causal role of the vaccine?	☐☐☐☐	
Vaccine quality		
4. Could the vaccine given to this patient have a quality defect or is substandard or falsified?	☐☐☐☐	
Immunization error		
5. In this patient, was there an error in prescribing or nonadherence to recommendations for use of the vaccine (e.g. use beyond the expiry date, wrong recipient, etc.)?	☐☐☐☐	
6. In this patient, was the vaccine (or diluent) administered in an unsterile manner?	☐☐☐☐	
7. In this patient, was the vaccine's physical condition (e.g. color, turbidity, presence of foreign substances, etc.) abnormal when administered?	☐☐☐☐	
8. When this patient was vaccinated, was there an error in vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling, etc.)?	☐☐☐☐	
9. In this patient, was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session, etc.)?	☐☐☐☐	
10. In this patient, was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size, etc.)?	☐☐☐☐	

Contd...

Contd...

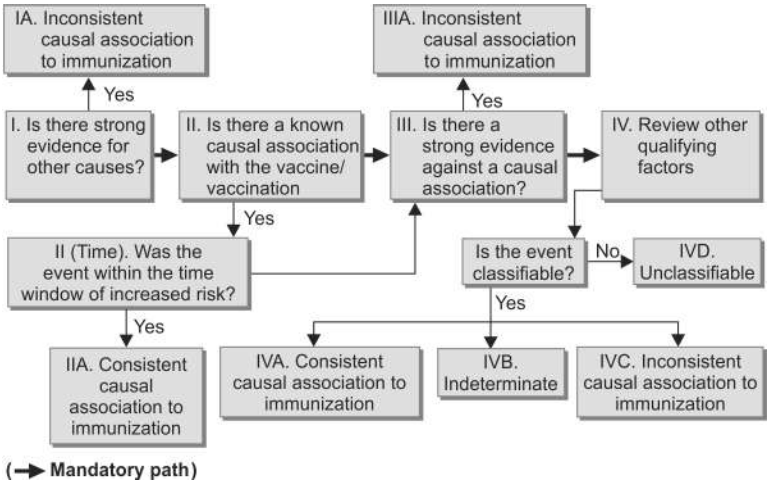
Immunization anxiety (Immunization Triggered Stress Response - ITSR)		
11. In this patient, could this event be a stress response triggered by immunization (e.g. acute stress response, vasovagal reaction, hyperventilation or anxiety)?	☐☐☐☐	
II (time). If "yes" to any question in II, was the event within the time window of increased risk?		
12. In this patient, did the event occur within a plausible time window after vaccine administration?	☐☐☐☐	
III. Is there strong evidence against a causal association?		
1. Is there a body of published evidence (systematic reviews, GACVS reviews, Cochrane reviews, etc.) against a causal association between the vaccine and the event?	☐☐☐☐	
IV. Other qualifying factors for classification		
1. In this patient did such an event occur in the past after administration of a similar vaccine?	☐☐☐☐	
2. In this patient did such an event occur in the past independent of vaccination?	☐☐☐☐	
3. Could the current event have occurred in this patient without vaccination (background rate)?	☐☐☐☐	
4. Did this patient have an illness, pre-existing condition or risk factor that could have contributed to the event?	☐☐☐☐	
5. Was this patient taking any medication prior to the vaccination?	☐☐☐☐	
6. Was this patient exposed to a potential factor (other than vaccine) prior to the event (e.g. allergen, drug, herbal product, etc.)?	☐☐☐☐	

(Y: Yes; N: No; UK: Unknown; NA: Note applicable; GACVS: Global Advisory Committee on Vaccine Safety)

A3. Immunization error-related reaction
A4. Immunization anxiety-related reaction.

B. Indeterminate:
B1. Temporal relationship is consistent but there is insufficient definitive evidence for the vaccine causing the event (may be a new vaccine-linked event—a signal which requires further analysis/studies)

Flowchart 2: Causality assessment algorithm.



B2. Qualifying factors result in conflicting trends of consistency and inconsistency with causal association to immunization

C. Inconsistent causal association to immunization—coincidental

D. Unclassifiable (in which the specific additional information required for classification is asked for)

Causality Assessment Classification

This is shown in **Figure 1**.

The causality assessment can also be done using a WHO software (http://gvsi-aefi-tools.org/). This is an easy to learn software and can be used even on a single adverse event. A screen shot of the first window of this software is given in **Figure 2**.

Steps after Causality Assessment

After causality assessment, the results need to be shared with all stakeholders for taking relevant action **(Table 3)**. In case of vaccine product-related reactions, these events are reviewed to see whether these events are occurring at a rate higher than expected. In such cases, the regulator needs to be informed. For vaccine quality-defect related reactions, further analysis is needed to find out if a particular vaccine brand or lot is involved and the regulator and manufacturer needs to

	A. Consistent with causal association to immunization	B. Indeterminate	C. Inconsistent with causal association to immunization
Adequate information available	A1. Vaccine product-related reaction (As per published literature) A2. Vaccine quality defect-related reaction A3. Immunization error-related reaction A4. Immunization anxiety-related reaction (ITSR**)	B1. *Temporal relationship is consistent but there is insufficient definitive evidence for vaccine causing event (may be new vaccine-linked event) B2. Reviewing factors result in conflicting trends of consistency and inconsistency with causal association to immunization	C. Coincidental • Underlying or emerging condition(s), or conditions caused by exposure to something other than vaccine
Adequate information not available	**Unclassifiable** Specify the additional information required for classification:		

*B1: This is a potential signal and may be considered for investigation
** Immunization Triggered Stress Response

Fig. 1: Causality assessment classification.

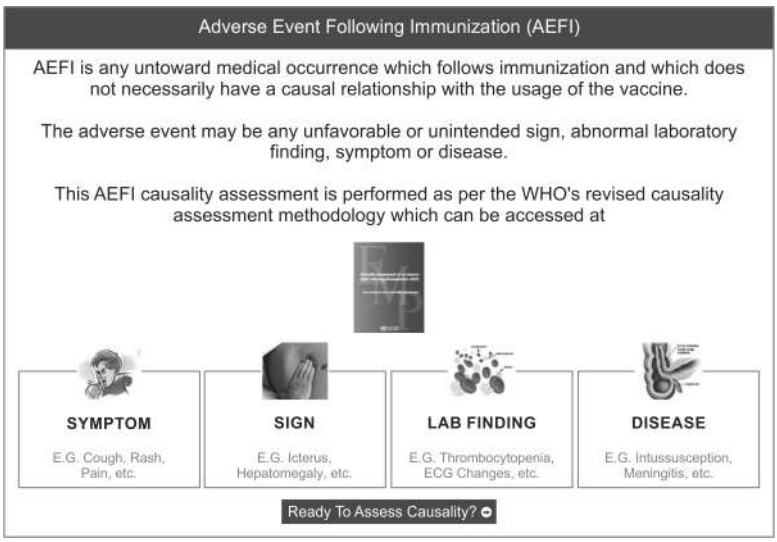


Fig. 2: WHO software for causality assessment.

TABLE 3: Follow-up action after causality assessment.

Type of AEFI	*Follow-up action*
Vaccine-related reaction	If a higher reaction rate than expected is observed from a specific vaccine or lot, inform the immunization division who can update drug regulators to consider: • Withdrawing that lot • Changing manufacturing specifications or quality control • Obtaining vaccine from a different manufacturer.
Immunization-related errors	Correcting the cause of the error. This may mean one or more of the following: • Change in logistics for supplying vaccine • Change in procedures at the health facility • Training of health workers • Intensified supervision. Whatever action is taken, it is important to review it at a later date to check that the immunization-related errors have been corrected.
Coincidental	The main objective is to present the evidence showing that there is no indication that the AEFI is a vaccine-related reaction or an immunization-related error and that the most likely explanation is a coincidental event. This communication can be challenging when there is widespread belief that the event was caused by immunization. Sometimes, it may be useful to enlist further expert investigation to convince/ensure that the event truly was coincidental. The potential for coincidental events to harm the immunization program through false attribution is immense.

Source: AEFI Surveillance and Response Operational Guidelines by Ministry of Health and Family Welfare, Government of India. 2015.[7]

be informed. Training and capacity building including intensification of supervision and monitoring is required for immunization error-related reactions. When immunization anxiety-related reactions are identified, it should be ensured that the immunizations take place in a nonstressful environment. All cases in the indeterminate category in B1 should be maintained in a database and reviewed to identify a signal suggesting a new potential causal association of vaccine with a new adverse reaction (sign/symptom/abnormal laboratory test). Cases in B2 are followed up for additional information which can help in making a decision to classify into vaccine/vaccination related or coincidental. Confirmation of classification of coincidental

cases is conveyed to the informer and the patient and relatives. For unclassifiable cases, the specific missing information to help in classifying is to be asked for from the districts. Other actions which can be undertaken include changes in policies and guidelines, research in indicated areas, and communication activities.

Involvement of Healthcare Service Providers

Often healthcare professionals, relying on experience and intuition, are the first to suspect a medical product problem and bring it to the attention of public health and regulatory officials.[6] AEFIs are to be reported following all vaccines used for preventive use including vaccines given in private sector, travel vaccines, etc. Other than reporting, pediatricians and other clinicians can be members of the AEFI committees and contribute to investigations and causality assessments. Representatives of professional bodies such as IAP and Indian Medical Association (IMA) as AEFI Committee Members can also help in assisting the immunization program manager to give correct messages to the media in times of crisis. Medical colleges and large hospitals have huge catchment areas and can contribute to AEFI surveillance by reporting AEFI cases to the immunization program manager.

MANAGEMENT OF ANAPHYLAXIS

Although anaphylactic reactions are rare after vaccination, their immediate onset and life-threatening nature require that all personnel and facilities providing vaccinations have procedures in place for anaphylaxis management. All vaccination providers should be familiar with the office emergency plan and be currently certified in cardiopulmonary resuscitation. Anaphylaxis usually begins within minutes of vaccine administration.[6] Rapid recognition and initiation of treatment is required to prevent possible progression to cardiovascular collapse. If flushing, facial edema, urticaria, itching, swelling of the mouth or throat, wheezing, dyspnea, or other signs or symptoms of anaphylaxis occur, the patient should be placed in a recumbent position with the legs elevated if possible.[6] Administration of epinephrine is the management of choice. Additional drugs also

BOX 1: Emergency management of anaphylaxis.
Administer epinephrine (1:1,000 solution) 0.01 mL/kg/dose (maximum 0.5 mL) intramuscular in anterolateral thigh
Set up IV access
Lay patient flat and elevate legs if tolerated. Give high flow oxygen and airway/ventilation if needed
If hypotensive, set up additional wide bore access and give IV normal saline 20 mL/kg under pressure over 1–2 minutes
IM adrenaline may be repeated after 3–5 minutes if required
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
(IM: intramuscular; IV: intravenous)

might be indicated **(Box 1)**. Maintenance of the airway and oxygen administration might be necessary. After the patient is stabilized, arrangements should be made for immediate transfer to an emergency facility for additional evaluation and treatment.

HOW TO REPORT ADVERSE EVENTS FOLLOWING IMMUNIZATIONS FROM PRIVATE SECTOR?

The majority of children in India receive immunization through public health facilities. However, it is estimated that approximately 10–20% of total immunization is provided through private sector and by pediatricians.[7] Moreover, the vaccines not part of the Universal Immunization Programme (UIP) in India are provided by the private sector only. There is an evolving AEFI surveillance system in India for UIP vaccines from government sector; however, the reporting from private sector is limited so far. It is important that AEFI from this sector are also reported and investigated, as per the laid down national guidelines, which are applicable to private sector also. Additionally, the AEFI reporting from private sector will provide vital information on the safety of new and underutilized vaccines in India. Once a serious AEFI happens in the private sector at a clinic of pediatricians, in the rural area, she/he should immediately inform medical officer in-charge of nearest PHC or other health facility. In the urban area,

either she/he can inform medical officer-in-charge of nearest urban health center or to the DIO. By all channels, the information should reach DIO as soon as possible.[2]

The private practitioners (including pediatricians) should use the "First Information Report" (FIR) form for reporting serious AEFI cases to the district officials. Once an AEFI is reported from private sector, the DIO and district AEFI committee members would then investigate the reported AEFI case. The pediatricians should help the investigation team in collection of all the related information.[2]

Online AEFI Reporting Platform for Private Practitioners

Indian Academy of Pediatrics, through its ACVIP has resolved to collaborate with the National AEFI program by suggesting the following measures:

Integrate IAP disease surveillance project (IDSURV) with:

- AEFI reporting for a web-based and integrated voice recording (IVR) reporting. (www.idsurv.org)
- The IDSURV program will automatically send information to the concerned DIO/state immunization officer.

This "public–private partnership" (PPP) has been enthusiastically received by Ministry of Health, Government of India for prompt implementation. However, if this system has to be effective, there should be an assurance from the Government that the investigation will focus on system failures rather than on individual punitive action.

REFERENCES

1. World Health Organization. Surveillance of Adverse Events Following Immunization, Field guide for managers of immunization programs. Geneva: World Health Organization; 1997.
2. Chitkara AJ, Thacker N, Vashishtha VM, et al. Adverse event following immunization (AEFI) surveillance in India, position paper of Indian Academy of Pediatrics, 2013. Indian Pediatr. 2013;50:739-41.
3. Chen RT, Rastogi SC, Mullen JR, et al. The vaccine adverse event reporting system (VAERS). Vaccine. 1994;12:542–50.
4. Government of India. Adverse Events Following Immunization: Surveillance and Response Operational Guidelines. New Delhi: Ministry of Health and Family Welfare, Government of India; 2010.

5. Government of India. Adverse Events Following Immunization: Surveillance and Response Standard Operating Procedures. New Delhi: Ministry of Health and Family Welfare, Government of India; 2010.
6. General Recommendations on Immunization, Recommendations of the Advisory Committee on Immunization Practices (ACIP), MMWR; Recommendations and Reports / Vol. 60 / No. 2 January 28, 2011.
7. Government of India. Multi Year Strategic Plan (MYP) for UIP of India 2005–10. New Delhi: Ministry of Health and Family Welfare, Government of India; 2010.

2.7 SCHEDULING OF VACCINES

Pallab Chatterjee

Main objectives of scheduling of vaccines are to achieve maximum effectiveness using recommended vaccines for a country while minimizing the number of health care system interactions. Epidemiological, immunological, and programmatic aspects are taken into account while scheduling vaccines. In past two decades, many new vaccines have been developed, vaccination schedule is undergoing rapid changes, and has become more complex.[1] Traditionally, public sector in developing countries is slow to incorporate newer vaccines as compared to private sector after the vaccine is licensed for use. Cost-effectiveness, safety, and effectiveness for a given region are important issues for introduction of newer vaccines. As such, vaccination schedule in public sector has lesser number of vaccines as compared to those developed by private sector. It often becomes a matter of debate what is the best schedule, but the knowledge of principles that go behind making each schedule will help pediatricians to build an informed opinion.

RATIONALE FOR IMMUNIZATION

Immunized individual gets protection from disease after exposure or infection with organism against which vaccine has been given. When many children in a community are immunized, even unimmunized people get protection from disease due to reduction in transmission of infection, which is known as herd immunity. Thus, disease control or elimination requires the induction of protective immunity in a sufficient proportion of population that would restrict the spread of disease and even eradication as happened with smallpox.

IDEAL IMMUNIZATION SCHEDULE

An ideal immunization schedule is dictated by various considerations foremost being appropriate immunologic response to vaccines and epidemiologic consideration of the VPDs. An optimal and not necessarily best immunological response may be considered

appropriate for effective protection at the earliest in a situation where risk of contracting infection at an early age is high. Immunization schedule at individual level and community level often varies considerably as safety and cost-effectiveness are taken into consideration. For public sector programs, usually it is cost first, efficacy next followed by safety. However, at individual level, it is safety first, efficacy next followed by cost. An ideal immunization schedule depends on the following considerations.[2]

- *Immunological*: Minimum age at which vaccine elicits immune response, number of doses required, and spacing of doses (interval between primary series and boosters if multiple doses are required).
- *Epidemiological*: Susceptibility for infection and disease. Disease severity and mortality
- *Programmatic*: Opportunity to deliver with other scheduled interventions

MINIMUM AGE AT WHICH THE FIRST DOSE OF VACCINE SHOULD BE GIVEN

The minimum age at which a vaccine should be given is dependent on factors like disease epidemiology, immunological responsiveness, and maternal antibodies:

- *Disease epidemiology*: Protective immune response must be achieved prior to the most vulnerable age. Most vulnerable age may depend on the disease burden in a country, earlier when the burden is high and vice versa.
- *Immunological responsiveness*: There is limitation of antibody responses in early life due to the limited and delayed induction of GCs in which antigen specific B cells proliferate and differentiate. Therefore, later the age better is the immunological response.
- *Maternal antibodies*: Maternal antibodies may exert their inhibitory influence on immune responses up to 1 year of age.
- *Booster doses*: Immunological principle—after initial immunization, a booster dose is intended to increase immunity against that antigen back to protective levels.

PRINCIPLES OF ANTIBODY VACCINE INTERACTIONS

Inactivated antigens are generally not affected by circulating antibody, so they can be administered before, after, or at the same time as the antibody. Simultaneous administration of antibody (in the form of immune globulin) and vaccine is recommended for postexposure prophylaxis of certain diseases, such as hepatitis B, rabies, and tetanus.

Live vaccines must replicate in order to cause an immune response. Antibody against injected live vaccine antigen may interfere with replication. If a live injectable vaccine [measles-mumps-rubella (MMR), varicella, or combination measles-mumps-rubella-varicella (MMRV)] must be given around the time that antibody is given, the two must be separated by enough time so that the antibody does not interfere with viral replication. If the live vaccine is given first, it is necessary to wait at least 2 weeks (i.e. an incubation period) before giving the antibody. If the antibody is given before a dose of MMR or varicella vaccine, it is necessary to wait until the antibody has waned (degraded) before giving the vaccine to reduce the chance of interference by the antibody. The necessary interval between an antibody-containing product and MMR or varicella-containing vaccine (except zoster vaccine) depends on the concentration of antibody in the product, but is always 3 months or longer.

COMBINATION VACCINES

As more effective vaccines are being developed, the question of the number of needle pricks to which the young infants are subjected to becomes important. More vaccines may also lead to more visits to physicians. Combination vaccines represent one solution to the issue of increased number of injections during a single visit. Among the traditional vaccines, DPT combination was a standard for a long time, so was MMR. Logical additions to diphtheria, pertussis, and tetanus (DPT) were *Haemophilus influenzae* type B (Hib), injectable polio, and hepatitis B. The preservation of efficacy will need to be continually seen by trials and monitored by surveillance as more such combinations are on the horizon.

FACTORS THAT AFFECT THE INCLUSION OF A NEW VACCINE IN THE NATIONAL IMMUNIZATION PROGRAM

- Disease (burden, severity, mortality, national security, risk of importation, competing priorities)
- Recipient (age, cohort size, politics)
- Vaccine (local production, availability, cost, efficacy, safety, other vaccines).

In countries still having a high burden of natural disease, disease prevention and controlling the morbidity and mortality is the most important objective, therefore, vaccine with highest effectiveness is chosen for inclusion in the national program; whereas, in a country with a low burden of natural disease, the main concerns are low or no side effects of a new vaccine which will decide acceptance of the vaccine. Therefore, a vaccine with a high safety level can only be included in the immunization schedule.

CATCH-UP IMMUNIZATION

Missed immunization does not require restarting of the entire series or addition of doses to the series for any vaccine in the recommended schedule. Two or more inactivated vaccines can be given simultaneously or at any interval between doses without affecting the immune response. An inactive vaccine can similarly be given simultaneously or at any interval with a live vaccine. However, two live (intranasal/injectable) vaccines should either be given simultaneously or at least 4 weeks apart. If a dose of DTP, IPV, Hib, pneumococcal conjugate, hepatitis A, hepatitis B, human papilloma virus (HPV), measles, mumps, rubella (MMR), or varicella vaccine is missed, subsequent immunization should be given at the next visit as if the usual interval had elapsed. For Rota vaccine, same principle can be followed, though upper age limit of last dose should be maintained. Minimal interval recommendation should be followed for administration of all doses.

ADOLESCENT IMMUNIZATION

Tdap and HPV are vaccines prescribed for adolescent immunization in India by IAP.[3] Meningococcal conjugate vaccine is recommended for adolescents in the United States.

WHO RECOMMENDATIONS

The World Health Organization monitors vaccination schedules across the world, noting what vaccines are included in each country's program, the coverage rates achieved, and various auditing measures.[4] WHO gives broad guidelines to help different countries prepare their vaccination schedules according to their epidemiological needs and cost-effectiveness. Summary of WHO position papers on Recommendations for Routine Immunization are regularly updated.[5] WHO further subclassifies the vaccines as: (a) recommendations for all individuals (BCG, hepatitis B, DPT, polio, Hib, PCV, rotavirus, measles, rubella, HPV); (b) recommendations for individuals residing in certain regions [Japanese encephalitis (JE), yellow fever, tick borne encephalitis]; (c) recommendations for individuals in some high-risk populations (typhoid, cholera, meningococcal, hepatitis A, rabies); and (d) recommendations for individuals receiving vaccinations from immunization programs with certain characteristics (mumps, influenza) **(Tables 1 and 2)**.

TABLE 1: Vaccination schedule under routine immunization in India, 2017.

Vaccine	*When to give*	*Dose*	*Route*	*Site*
For pregnant women				
Td-1	Early in pregnancy	0.5 mL	Intramuscular	Upper arm
Td-2	4 weeks after TT-1*	0.5 mL	Intramuscular	Upper arm
Td-Booster	If received two TT doses in a pregnancy within the last 3 years	0.5 mL	Intramuscular	Upper arm
For infants				
BCG	At birth or as early as possible till 1 year of age	0.1 mL (0.05 mL until month of age)	Intradermal	Left upper arm
Hepatitis B birth dose	At birth or as early as possible within 24 hours	0.5 mL	Intramuscular	Anterolateral side of midthigh
OPV zero dose	At birth or as early as possible within the first 15 days	2 drops	Oral	Oral

Contd...

Contd...

Vaccine	*When to give*	*Dose*	*Route*	*Site*
OPV 1,2, and 3	At 6 weeks, 10 weeks, and 14 weeks	2 drops	Oral	Oral
Pentavalent 1,2, and 3		0.5 mL	Intramuscular	Anterolateral side of midthigh
Fractional IPV	At 6 and 14 weeks	0.1 mL	Intradermal	Upper arm—right
Rotavirus (In selected districts)	At 6 weeks, 10 weeks, and 14 weeks	5 drops	Oral	Oral
Pneumococcal conjugate vaccine (in selected districts)	At 6 weeks and 14 weeks At 9 completed months—booster	0.5 mL	Intramuscular	Anterolateral side of midthigh—right
Measles rubella 1st dose	9 completed months–12 months (give up to 5 years if not received at 9–12 months age)	0.5 mL	Subcutaneous	Right upper arm
JE 1st dose†	9 completed months	0.5 mL	Subcutaneous	Left upper arm
For children and adolescents				
DPT booster	16–24 months	0.5 mL	Intramuscular	Anterolateral side of midthigh
OPV booster	16–24 months	2 drops	Oral	Oral
Measles Rubella 2nd dose	16–24 Months	0.5 mL	Subcutaneous	Right upper arm
Rubella‡	Adolescent girls	0.5 mL	Subcutaneous	Right upper arm
JE 2nd dose	16–24 months with DPT/OPV booster	0.5 ml	Subcutaneous	Left upper arm
DPT booster 2	5–7 years	0.5 mL	Intramuscular	Upper arm
Td	10 years and 16 years	0.5 mL	Intramuscular	Upper arm
Vitamin A§				

*Give Td-2 or booster doses before 36 weeks of pregnancy. However, give these even if more than 36 weeks have passed. Give Td to a woman in labor, if she has not previously received Td.

†JE vaccine (SA 14-14-2) is given in select endemic districts, after the campaign is over in that district.

‡Rubella vaccine will be given as part of measles second dose

§The second to ninth doses of vitamin A can be administered to children 1–5 years old during biannual rounds, in collaboration with Integrated Child Development Services (ICDS).

(DPT: diphtheria, pertussis, and tetanus; IPV: inactivated polio vaccine; JE: Japanese encephalitis; OPV: oral polio vaccine)

TABLE 2: IAP Immunization Schedule 2018–19.

	Birth	*6 weeks*	*10 weeks*	*14 weeks*	*6 months*	*9 months*	*12 months*	*13 months*	*15 months*	*16–18 months*	*2–3 years*	*4–6 years*	*9–14 years*	*15–18 years*
BCG	BCG													
Hepatitis B	HB1	HB 2	HB 3	HB* 4										
Polio	OPV O	IPV** 1	IPV** 2	IPV** 3						IPV*** B1				
DTwP/DTaP		DTP 1	DTP 2	DTP 3						DTP B1		DTP B2		
HiB		HiB 1	HiB 2	HiB 3						HiB B1				
Pneumococcal		PCV 1	PCV 2	PCV 3					PCV B1				PCV	
Rotavirus		Rota 1	Rota 2	Rota 3****										
MMR						MMR 1			MMR 2			MMR3/ MMRV		
Varicella									Varicella 1			Varicella 2		
Hepatitis A							Hep A1			Hep A2*****				
Typhoid					TCV									
Influenza							Influenza (yearly)******							
Meningococcal						MCV 1	MCV 2				MCV			
JE							JE 1	JE 2						

Contd...

Contd...

	Birth	*6 weeks*	*10 weeks*	*14 weeks*	*6 months*	*9 months*	*12 months*	*13 months*	*15 months*	*16–18 months*	*2–3 years*	*4–6 years*	*9–14 years*	*15–18 years*
Tdap													Tdap	Td
HPV													HPV 1 and 2	HPV 1, 2, 3
Cholera									Cholera 1 and 2					
		Range of recommended age for all children							Range of recommended age for catch-up immunization					
		Range of recommended age for high-risk children/area							Not recommended					

* Fourth dose of hepatitis B permissible for combination vaccines only
** In case IPV is not available or feasible, the child should be offered bOPV (3 doses). In such cases, give two fractional doses of IPV at 6 weeks and 14 weeks
*** b-OPV, if IPV booster (standalone or combination) not feasible
**** Third dose not required for RV1. Catcth-up up to 1 year of age in UIP schedule
***** Live attenuated hepatitis A vaccine: single dose only
****** Begin influenza vaccination after 6 months of age, about 2–4 weeks before season; give 2 doses at the interval of 4 weeks during first year and then single dose yearly till 5 years of age
Meningococcal vaccine (MCV): 9 months through 23 months—2 doses, at least 3 months apart; 2 years through 55 years—single dose only
Japanese Encephalitis (JE): For individuals living in endemic areas and for travelers to JE endemic areas provided their expected stay is for a minimum period of 4 weeks
HPV: 2 doses at 6 months interval 9–14 years age; 3 doses (at 0, 1–2 and 6 months) 15 years or older and immunocompromised
Cholera vaccine: Two doses 2 weeks apart for >1 year old; for individuals living in high endemic areas and travelling to areas where risk of transmission is very high
TCV: typhoid conjugate vaccine; HPV: human papilloma virus

REFERENCES

1. History of Vaccine Schedule. (2010) Children's Hospital of Philadelphia. [online] Available from http:/ / www.chop.edu /service /vaccine-education- center/vaccine-schedule/ history-of-vaccine-schedule.html [Last accessed August, 2019].
2. Choudhury P. Scheduling of vaccine. In: Vashishtha VM, Agarwal R, Sukumaran T (Eds). IAP Text Book of Vaccines, Indian Academy of Pediatrics. New Delhi: Jaypee Brothers; 2013.
3. Indian Academy of Pediatrics Committee on Immunization (IAPCOI). Consensus recommendation on Immunization and IAP Immunization Timetable 2012. Indian Pediatr. 2012;49:560.
4. WHO vaccine-preventable diseases: Monitoring system. 2013 global summary. Available from http://apps.who.int/immunization_ monitoring/ globalsummary/schedules. [Last accessed November, 2013]
5. World Health Organisation (2013). Updated 1st August 2013. [online] Available from http://www.who.int/immunization/policy/ Immunization_routine_ table1.pdf. [Last accessed November, 2013].

3

CHAPTER

Licensed Vaccines

3.1 BACILLUS CALMETTE–GUÉRIN VACCINE

Shivananda S

EPIDEMIOLOGY

Mycobacterium tuberculosis is the causative agent of human tuberculosis (TB). Other species which can also cause disease in humans include *M. bovis*, *M. africanum*, *M. canettii*, *M. caprae*, *M. microti*, and *M. pinnipedii*.

Tuberculosis occurs most commonly in children less than 5 years. While pulmonary TB (PTB) is the predominant form of TB in children, extrapulmonary TB is also common (around 30–40% of cases).

Children, who develop TB disease, usually do so within 1 year following infection, and childhood TB is therefore, an indicator of ongoing transmission of *M. tuberculosis* in the community.[1]

Infants and young children (especially <2 years) are at risk of developing severe disseminated disease associated with a high rate of mortality. In infants, the time between infection and disease can be shorter than in older children and the presentation may be more acute, resembling severe recurrent or persistent pneumonia where in PTB is suspected, if there is no response to usual antibiotics.

Adolescents are at increased risk of TB, in whom sputum positive adult type of pulmonary disease is known. They may be the source of transmission to others.

Globally, 1.7 billion people are estimated to be infected with *M. tuberculosis* and 5–15% of these individuals will develop active TB during their lifetime.

In 2016, an estimated 10.4 million people developed active disease, about 1 million were children. Ten percent of them are human immunodeficiency virus (HIV) positive. In 2016, an estimated 253,000 children died of TB and 52,000 of them are HIV-infected children. Globally, there were 600,000 new cases in 2016 with resistance to rifampicin of which 490,000 had multidrug-resistant TB (MDR-TB). Only 22% of them were enrolled and were started on MDR-TB treatment and an estimated 6.2% of those with MDR-TB had extensively drug-resistant TB (XDR-TB). XDR-TB patients had a treatment success rate of 30% in 2016.[2] Tuberculosis continues to spread mainly in poor, crowded, and poorly ventilated settings. HIV infection and malnutrition are complementary factors.

Tuberculosis is preventable and curable but the majority of cases are not diagnosed, 40% of the estimated 1 million children with TB were notified to national TB programs. Diagnosis is difficult in children as cough and sputum production is also less common and disease is paucibacillary. In the first year of primary infection, 40–60% of children are at risk of developing a progressive disease such as meningitis and miliary TB.[3,4]

PREVENTION

The United Nations (UN) sustainable development goals include ending TB epidemics by 2030 (Goal 3). To reach this goal in 2015, the World Health Organization (WHO) member states endorsed the End-TB Strategy, which aims to reduce the number of TB deaths by 95% by 2035 compared to that of 2015, suggested three strategies:[5]

1. Pillar 1, on integrated patient-centered care and prevention, focuses on early detection and treatment for all TB patients and prevention. One of the components of this pillar is vaccination against TB.
2. Pillar 2 focuses on policies and supportive systems to strengthen health and social sectors in order to prevent and end TB.
3. Pillar 3 calls for intensified research and innovation.

Bacillus Calmette–Guérin (BCG) vaccination of infants, at birth or as soon as possible after birth, is one of the key components of pillar 1 of the End-TB Strategy. It has been estimated that high global coverage (90%) and widespread use of BCG in routine infant vaccination programs could prevent over 115,000 TB deaths per birth cohort in the first 15 years of life.

VACCINE

Bacillus Calmette–Guérin vaccine is one of the oldest vaccines first used in humans in 1921. BCG vaccine is derived from the bovine tuberculosis strain.[6] 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 Vaccine Laboratory, Guindy, Tamil Nadu till recently.

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, amber-colored ampoules or 2 mL vials with normal saline as diluent. The vaccine is light sensitive and deteriorates on exposure to ultraviolet rays. In lyophilized form, it can be stored at 2–80°C for up to 12 months without losing its potency. 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 2–8°C, protected from light, and discarded within 4–6 hours of reconstitution. WHO recommends that all BCG vaccines used in immunization programs adhere to WHO standards. BCG is currently the only available TB vaccine. Even though BCG has demonstrated significant effectiveness, protection has not been consistent against all forms of TB and in all age groups. BCG is not effective when used as post-exposure prophylaxis.[1,7] Several new TB candidate vaccines are in development, some of which are in advanced clinical trials. Some are designed to be used for booster vaccination following neonatal BCG vaccination.

Vaccine Characteristics

Bacillus Calmette–Guérin vaccine is usually administered by intradermal injection. Correct vaccine administration technique by a trained health worker is important to ensure correct dosage and optimal BCG vaccine efficacy and safety. Correct intradermal administration can be verified by a wheal of 5 mm formation. BCG vaccine should be injected in a clean, healthy area of skin. The vaccine should be given preferably in the lateral aspect of the upper arm. 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.

There are no details related to efficacy/effectiveness and safety for other anatomic sites of administration. BCG vaccination usually causes a scar at the site of injection due to local inflammatory processes. Approximately, 10% of vaccine recipients do not develop a scar and that does not mean that protection has not been achieved.

The standard dose of reconstituted vaccine is 0.05 mL upto 1 month age, thereafter 0.1 mL for infants aged 1 year. BCG vaccine is not available in combination with other vaccines.

Immunogenicity, Efficacy, and Effectiveness

Bacillus Calmette–Guérin induces cell-mediated immunity: Considerable difference has been observed about the efficacy and effectiveness of the vaccine between studies and populations. An extensive systematic review and meta-analysis of 18 randomized controlled trials (RCTs) compared the incidence of PTB in BCG-vaccinated and unvaccinated participants, and examined vaccine efficacy.

Among those vaccinated as neonates, protection against PTB was 59% (RR 0.41, 95% CI: 0.29–0.58).

In studies where BCG was given in childhood and with stringent tuberculin skin test (TST) screening, protection against PTB was 74% (RR 0.26, 95% CI: 0.18–0.37). In trials without stringent TST screening, the average protection against PTB was reduced.[6]

In a systematic review and meta-analysis of 12 cohort studies, protection against PTB was found to range from 44% to 99% in 11 studies, with no protection at all in one published report.[4,5] Protection was found to vary by age, with neonatal vaccination providing 82% protection against PTB (RR 0.18, 95% CI: 0.15–0.21). In school-age TST-negative children, BCG was 64% protective against PTB (RR 0.36, 95% CI: 0.30–0.42).[6]

The same review also evaluated 8 case-control studies, which revealed 54% neonatal BCG vaccine effectiveness (VE) from 7 studies (OR 0.46, 95% CI: 0.40–0.52), but found only one case control study in older children, which reported minimal protection. Regarding BCG vaccine efficacy and effectiveness against meningeal and miliary tuberculosis, evidence from RCTs and case control studies and evidence from a meta-analysis of 6 RCTs indicated a high degree of vaccine efficacy, reducing severe TB in vaccinated individuals by 85% (RR 0.15, 95% CI: 0.08–0.31). Protection was highest for those immunized during the neonatal period, with 90% reduction of severe TB (RR 0.10, 95% CI: 0.01–0.77).[7,8]

A systematic review and meta-analysis of 14 case-control studies examined BCG against meningitis and miliary TB.[4,6] The study revealed that the incidence of TB meningitis was reduced by 73% (95% CI: 67–87%), with higher protection in the Latin American studies (VE 87%, 95% CI: 78–92%) compared to Asian settings (VE 69%, 95% CI: 60–76%). Incidence of miliary TB was reduced by 77% (95% CI: 58–87%) as reported in 4 of the studies in Asia and Latin America. These studies support previous evidence that BCG vaccination confers a high degree of protection against severe forms of TB.

Duration of Protection and Revaccination

A systematic review concluded that protection after primary infant BCG vaccination could last for up to 15 years in some populations.[8,9] Longer duration of protection was found in persons who had a negative TST result prior to vaccination, and in those who had received neonatal BCG vaccination.

Safety

About 95% of BCG vaccine recipients experience a reaction at the injection site characterized by a papule which may progress to become

ulcerated, with healing after 2–5 months leaving a superficial scar. This is considered normal.

Adverse events following immunization (AEFI): They are dependent on a number of factors including the strain used in the vaccine, number of viable bacilli in the batch, and variation in injection technique. Severe AEFI include local reactions such as injection site abscess, severe ulceration or suppurative lymphadenitis usually caused by inadvertent injection of the vaccine subdermally.[9] Disseminated BCG diseases that may occur between 1.56 and 4.29 cases per million doses and has a high-case fatality rate. BCG disease also varies with the strain and can have an incidence of up to 1% of infants and HIV-infected children. BCG vaccine-related complications may occur distal to the site of inoculation in the skin, intestines, bones (osteitis) or bone marrow (osteomyelitis) >12 months after vaccination. BCG immune reconstitution inflammatory syndrome (IRIS) also occurs in association with HIV infection. Other noted BCG syndromes have included uveitis and skin lesions such as lupus vulgaris.

A recent RCT in Denmark noted a regional lymphadenitis rate of 6.1 (95% CI: 3.3–10) per 1,000 vaccinated. All children, even those with suppuration, recovered without sequelae within 4–6 months with conservative treatment. However, in some circumstances aspiration or surgery may be required for treatment of such conditions.[10-12]

Disseminated BCG disease is seen mainly in persons with primary immunodeficiencies (and family outbreaks may occur, if this complication is not recognized before all are given BCG) or HIV infection.

It has been observed that children who were HIV-infected at birth and vaccinated with BCG at birth, and who later developed AIDS, were at increased risk of developing disseminated BCG disease.[2] Although BCG is a safe vaccine in immune-competent infants, severe AEFI can occur in HIV-infected infants.

Preterm infants and low birth weight infants: BCG vaccination at birth in healthy preterm infants born after 32–36 weeks of gestation was found to be safe and effective.

Co-administration of Vaccines

There is evidence that BCG vaccine can be safely coadministered with diphtheria-pertussis-tetanus (DTP), polio, hepatitis B, *Haemophilus*

influenzae type b (Hib) and measles and rubella vaccines. There is no evidence to suggest reduced immunogenicity, and no safety concerns have been reported.

WHO Position

Universal Vaccination Strategy at Birth

In countries or settings with a high incidence of TB, a single dose of BCG vaccine should be given to all healthy neonates at birth, for prevention of TB and leprosy. If BCG vaccine cannot be given at birth, it should be given at the earliest opportunity thereafter and should not be delayed, in order to protect the child before exposure to infection occurs. Coadministration of BCG with the hepatitis B birth dose is safe and strongly recommended. In order to avoid missed opportunities for neonatal vaccination, BCG multi-dose vials should be opened and used despite of any wastage of unused vaccine.[13-15]

Vaccination of Older Age Groups

Bacillus Calmette–Guérin vaccination of unvaccinated, TST-negative school children may provide long-term protection (Up to 20 years or longer). BCG vaccination of older age groups is recommended for the following:

- Unvaccinated TST- or interferon-gamma release assay (IGRA)-negative older children, adolescents, and adults from settings with high incidence of TB and/or high leprosy burden.
- Unvaccinated TST- or IGRA-negative older children, adolescents, and adults moving from low to high TB incidence or leprosy burden settings.
- Unvaccinated TST- or IGRA-negative persons at risk of occupational exposure in low- and high-TB incidence areas (e.g., healthcare workers, laboratory workers, medical students, prison workers, other individuals with occupational exposure).[3]

Vaccination of Special Populations, Contraindications, and Precautions

Bacillus Calmette–Guérin vaccination is contraindicated for individuals known to be allergic to any component of the vaccine.

Pregnant and Lactating Women

As a precaution, in the absence of adequate evidence on safety, BCG vaccination is not recommended during pregnancy. BCG vaccines may be administered to lactating women.

Immunocompromised and HIV-infected Persons

Children who are HIV-infected when vaccinated with BCG at birth are at increased risk of developing disseminated BCG disease. However, if HIV-infected individuals, including children receiving antiretroviral therapy (ART), are clinically well and immunologically stable; (CD 4% > 25% for children aged 5 years) they should also be vaccinated with BCG.

Neonates born to women of unknown HIV status should be vaccinated as the benefits of BCG vaccination outweigh the risks.

Neonates of unknown-HIV status born to HIV-infected women should be vaccinated, if they have no clinical evidence suggestive of HIV infection, regardless of whether the mother is receiving ART.

Young unvaccinated children traveling to high-TB incidence countries, particularly those likely to have repeated travel during childhood, should be vaccinated.

Neonates born to mothers with pulmonary TB (PTB): Asymptomatic neonates born to mothers with bacteriologically confirmed PTB should receive preventive treatment, if TB disease has been excluded, and should be regularly followed to verify absence of TB. If an infant remains asymptomatic and has no immunological evidence of TB at the end of preventive treatment, and is also HIV-negative, BCG vaccination should be provided using a normal infant dose.

REFERENCES

1. Marais BJ, Gie RP, Schaaf HS, et al. The clinical epidemiology of childhood pulmonary tuberculosis: a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis. 2004;8(3):278-85.
2. World Health Organization (WHO). (2017). Global TB Report 2017 [online] Available from: http://www.who.int/tb/publications/global_report/en/. [Last accessed September, 2019].
3. Plotkin S, Orenstein W, Offit P, Edwards KM. Tuberculosis (and Leprosy). Plotkin's Vaccines, 7th edition. USA: Elsevier; 2017.
4. World Health Organization (WHO). (2017). Compendium of WHO guidelines and associated standards: ensuring optimum delivery of the

cascade of care for patients with tuberculosis 2017 [online]. Available from http://apps.who.int/iris/bitstream/10665/259180/1/9789241512572-eng.pdf. [Last accessed September, 2019].
5. World Health Organization (WHO). (2015). The End TB Strategy. [online]. Available from: http://www.who.int/tb/strategy/endtb/en/. [Last accessed September, 2019].
6. World Health Organization (WHO). (2017). Recommendations to assure the quality, safety and efficacy of BCG vaccines. [online]. Available from: http://who.int/biologicals/areas/vaccines/TRS_979_Annex_3.pdf?ua=1. [Last accessed September, 2019].
7. Hesseling AC, Johnson LF, Jaspan H, et al. Disseminated bacille Calmette–Guérin disease in HIV-infected South African infants. Bull World Health Organ. 2009;87(7):505-11.
8. Mangtani P, Abubakar I, Ariti C, et al. Protection by BCG vaccine against tuberculosis: A systematic review of randomized controlled trials. Clin Infect Dis. 2014;58(4):470-80.
9. Abubakar I, Pimpin L, Ariti C, et al. Systematic review and metaanalysis of the current evidence on the duration of protection by bacillus Calmette–Guérin vaccination against tuberculosis. Health Technol Assess. 2013;17(37):1-372.
10. Azzopardi P, Bennett CM, Graham SM, et al. Bacille Calmette-Guérin vaccine-related disease in HIV-infected children: a systematic review. Int J Tuberc Lung Dis. 2009;13(11):1331-44.
11. Nissen TN, Birk, NM, Kjærgaardb, et al. Adverse reactions to the Bacillus Calmette-Guérin (BCG) vaccine in new-born infants—an evaluation of the Danish strain 1331 SSI in a randomized clinical trial. Vaccine. 2016;34(22):2477-82.
12. Alrabiaah AA, Alsubaie SS, Bukhari EI, et al. Outbreak of Bacille Calmette-Guérin-related lymphadenitis in Saudi children at a university hospital after a change in the strain of vaccine. Ann Saudi Med. 2012;32(1):4-8.
13. World Health Organization (WHO). (2018). Evidence to recommendation table: Need for vaccination at birth vs at 6 weeks. [online]. Available from: http://www.who.int/immunization/policy/position_papers/bcg_vaccination_birth_vs_6weeks.pdf. [Last accessed September, 2019].
14. World Health Organization (WHO). (2018). Evidence to recommendation table: BCG efficacy against TB. [online]. Available from: http://www.who.int/entity/immunization/policy/position_papers/bcg_efficacy_tb.pdf. [Last accessed September, 2019].
15. World Health Organization (WHO). (2018). Evidence to recommendation table: Need for revaccination. [online]. Available from: http://www.who.int/entity/immunization/policy/position_papers/bcg_evidence_recommendation_table_revaccination.pdf. [Last accessed September, 2019].

3.2 POLIO VACCINES

Shivananda S

February 2012 is a most remarkable and significant in the history of polio for India which celebrated a full year without a child paralyzed by indigenous wild poliovirus (WPV). The success was possible due to the (a) ability of the program to reach all children repeatedly, (b) the use of a new bivalent-oral polio vaccine (bOPV), (c) sustained political commitment and accountability, (d) societal support, and (e) the availability and mobilization of resources needed to complete the job. The country remains polio-free today.[1]

EPIDEMIOLOGY

Poliomyelitis is an acute infection by three poliovirus serotypes types 1, 2, or 3, and was the leading cause of permanent disability in children in the past. Almost all the children used to be infected by feco-orally or oro-orally, 0.5% of the infected developing disability. Most epidemic and endemic cases of poliomyelitis are caused by poliovirus type 1, followed by type 3.

In 1988, more than 125 countries had WPV transmission with 350,000 of paralytic polio cases, motivated World Health Assembly (WHA) to take a decision to eradicate poliomyelitis by the year 2000 and the Global Polio Eradication Initiative (GPEI) was established.

Since then sustained use of polio vaccines was given an impetus leading onto a precipitous fall of paralytic poliomyelitis cases by 99% in 2015. As of November 2019 only 2 countries—Afghanistan (20) and Pakistan (82) remain endemic. 106 cases of cVDPV2 have been reported from Africa, Nigeria, DRC, Pakistan.

The last case of poliomyelitis caused by naturally circulating WPV type 2 (WPV2) was recorded in India in 1999. Global eradication of WPV2 was certified in 2015. No case due to WPV type 3 (WPV3) has been detected globally since 10 November 2012 in Nigeria.

VIRUS

Polioviruses are single-stranded ribonucleic acid (RNA) enteroviruses of the *Picornaviridae* family. Polioviruses share most of their biochemical and biophysical properties with other enteroviruses, and are resistant to inactivation by many common detergents and disinfectants, including soaps, but are rapidly inactivated by ultraviolet light. Viral infectivity is stable for months at +4°C and for several days at +30°C.

DIAGNOSIS

World Health Organization (WHO) guidelines relay on acute flaccid paralysis (AFP) cases below 15 years to identify the cases polio.

All cases of AFP are investigated and clinically examined, and stools samples are collected and subjected to virological investigations including molecular polymerase chain reaction (PCR) done to differentiate WPV, circulating vaccine-derived poliovirus (cVDPV), and in addition, all discordant poliovirus isolates are partially sequenced to determine their origin and relatedness to other isolates. According to the laboratory results and review by national polio expert committees, cases are further classified as confirmed, polio-compatible, or polio-negative.

NATURAL IMMUNITY

Normal children infected by polioviruses develop immunity through humoral (circulating antibody) and mucosal [secretory immunoglobulin A (IgA)] immune responses. The presence in blood of neutralizing antibody against polioviruses indicates protective immunity; detectable antibody is an excellent correlate of protection against paralytic disease.[2]

Mucosal immunity decreases the replication and viral shedding and acts as a potential barrier to its transmission.

VACCINES

Inactivated polio vaccine (IPV), first developed and licensed in 1955, is given by injection and is available only in trivalent form containing

the three virus serotypes PV1, PV2, and PV3. OPV as a monovalent (mOPV) vaccine was initially licensed in 1961 followed by a trivalent version (tOPV) in 1963. Bivalent OPV (bOPV containing types 1 and 3 Sabin viruses) has been licensed and used in some settings since December 2009. Following the planned global switch from tOPV to bOPV in April 2016, tOPV will no longer be available and will be replaced by bOPV. Thereafter, mOPV2 will be stockpiled for emergency.[2,3]

Oral Polio Vaccine

Vaccine Characteristics

Oral polio vaccine (OPV) is composed of live attenuated polioviruses derived of their parent WPV strains by passage in nonhuman cells to obtain the three vaccine strains (Sabin 1, 2, and 3). Attenuation reduces its neurovirulence and transmissibility. There are several licensed formulations of OPV: (i) mOPV1, mOPV2 or mOPV3; (ii) bOPV containing types 1 and 3; and (iii) tOPV containing types 1, 2, and 3.

Seroconversion with mOPV1 approximately threefold higher than that of the type 1 component of tOPV. Massive use of mOPV1 resulted in the virtual elimination of poliovirus type 1 in the most difficult to control districts in western Uttar Pradesh, India. The mOPV3 has been used selectively in areas with imported or endemic circulation of poliovirus type 3. mOPV2 may be needed for potential applications in controlling an outbreak of type 2 cVDPV before and after cessation of OPV. A clinical trial in India confirmed that the immunogenicity of bOPV was superior to types 1 and 3 compared with tOPV. The main advantage of bOPV is that it enhances individual and population immunity simultaneously for poliovirus types 1 and 3, without any serious loss in immunogenicity compared with the mOPVs. Between 2009 and 2014, more than 5 billion doses of bOPV were used in campaigns by the GPEI.

WPW2 was eradicated in 1999 and to reduce the repercussions of neurovirulent cVDPV2 and vaccine-associated paralytic poliomyelitis (VAPP), in 2016 Strategic Advisory Group of Experts (SAGE) recommended the cessation of use of type 2 OPV switch from to tOPV to bOPV after this mOPV2 will be utilized for outbreaks

response, e.g. following an emergence of cVDPV2 or WPV2 and will be stock piled.

Oral polio vaccine is administered as two drops (~0.1 mL), directly into the mouth. It is highly heat-sensitive and must be kept frozen for long-term storage or, after thawing, at temperatures between +2°C and +8°C for a maximum of 6 months. Vaccine vial monitors give a visual indication of whether the vaccine has been kept at the correct temperature conditions.

Safety

The main safety issues of OPV are VAPP and cVDPV which used to occur with tOPV which is not available now and with bOPV safety issue profile is better because most of these events, more than 50%, were due to Sabin 2 virus.

Vaccine-associated Paralytic

A review by national expert committee is necessary and follow up is needed to identify VAPP, as it clinically resembles paralytic polio by WPV. The incidence of VAPP is around 2–4 per million births per year and epidemiologically different in different countries. In industrialized countries, VAPP occurs mainly in early infancy associated with the first dose of OPV and decreases sharply (>10-fold) with subsequent OPV doses. In lower-income countries, which experience relatively lower rates of vaccine seroconversion, this decline is more gradual and VAPP may occur with second or subsequent doses of OPV, with the age distribution concentrated among children aged 1–4 years.[4,5] The contributing factors to this difference are: (1) lower immune responsiveness to OPV, and (2) higher prevalence of maternally-derived antibody in populations in low-income settings. The risk of VAPP is one case per 2.9 million doses of OPV for children receiving the first doses of OPV, the risk was estimated as one case per 1.4 million children vaccinated. The risk of VAPP is highest after the first dose of OPV. Recipients of a first dose and their contacts had a 6.6-fold higher risk of VAPP than did recipients of subsequent doses and their contacts. The risk of VAPP however is lesser in India due to 1, neonatal OPV administration maternal antibodies would play protective role in

preventing VAPP and initiating immunization schedule by 6 weeks. A recent review reported that the majority of recipient VAPP cases were associated with type 3 poliovirus (42%), followed by type 2 (26%), type 1 (20%), and mixtures of more than one virus (15%).

Vaccine-derived Polio Virus

The attenuated viruses in live OPV vaccines may reacquire neurovirulence and transmission capacity through replication and genetic divergence effect by >1% genetic divergence [or >10 nucleotide (nt) changes] for PV1 and PV3 and >0.6% (or >6 nt changes) for PV2 90% of reported cVDPV are due to type 2 polio virus.

Key risk factors for cVDPV emergence and spread are: (1) development of immunity gaps arising from low-OPV coverage, (2) prior elimination of the corresponding WPV serotype, (3) emphasis on use of mOPV and bOPV in national immunization days (NIDs) and Subnational Immunization Days, leading to increasing susceptibility to type 2 in the population, and (4) insensitive AFP surveillance.

Oral polio vaccine is contraindicated. OPV should not be given to a child who is a member of a family in which there are immunocompromised persons to avoid the possibilities of vaccine spread.

These viruses are further subdivided into three categories: (1) cVDPVs, when evidence of person-to-person transmission in the community exists; (2) immunodeficiency-associated VDPVs (iVDPVs), which are isolated from people with primary B-cell or combined immunodeficiency disorders years or more; and (3) ambiguous VDPVs (aVDPVs), which are either clinical isolates from persons with no known immunodeficiency, or sewage isolates of unknown origin.[14] If the circulation of cVDPV continue to circulate for >6 months following detection which represent programmatic failures to contain the cVDPV then they are known persistent cVDPVs.

In July 2015, the GPEI revised the definition of cVDPV to enhance its sensitivity.[6] In the new guidelines, cVDPVs are defined as genetically linked VDPVs isolated from: (i) at least two individuals—not necessarily AFP cases—who are not household contacts; (ii) one individual and one or more environmental surveillance (ES) samples; or (iii) at least two ES samples if they were collected at more than one distinct ES collection site (no overlapping of catchment

areas), or from one site, if collection was more than 2 months apart, cVDPVs have lost their attenuating characters, hence they can cause paralysis in affected persons as well as transmissibility can replicate at normal body temperature; the reasons for cVDPVs outbreaks are low immunization coverage in the community and poor sanitation.

In 2014, a total of 56 cases of paralytic poliomyelitis caused by cVDPVs were reported from five countries; in 55 of the cases the virus was serotype 2 and in one it was serotype 1. Nigeria reported the largest number of cases (30). In 2015, as of 15 December, seven countries reported a total of 24 cases of paralytic poliomyelitis caused by cVDPVs, most of which were serotype.

Immunogenicity and Effectiveness

Until recently tOPV was the vaccine of choice by GPEI and demonstrated its effectiveness in eradicating WPW2 from the world poliomyelitis cases were declined sharply.

The ability of OPV to infect contacts of vaccine recipients (i.e. contact spread) and "indirectly vaccinate" these contacts against poliomyelitis is considered by many to be another advantage of OPV compared with IPV.

By 4–6 weeks after the OPV is given vaccine viral shedding takes place from the gut and upper respiratory tract and this also occur in nonvaccinated contacts thereby transmission of vaccine virus and herd intestinal immunity occurs in the community. This shedding will stop with subsequent administration of OPV by 6–8 weeks. In high-income countries, seroconversion rates in children following administration of three doses of tOPV approach 100% for all three poliovirus types. However, in some developing countries, the same three-dose course of tOPV in children was found to induce detectable antibodies in only 73%, 90%, and 70% to poliovirus type 1, 2, and 3, respectively.[2,9] In lower-income settings, the response to OPV appears to vary, e.g. in Northern India seroconversion rates were relatively as low as 17–34%.[7,8] The reduced antibody response to OPV in children in low-income settings probably due to complex interactions between the host, e.g. levels of maternal antibody, poor intestinal immunity in malnourished children, diarrhea at the time of vaccination, household exposure to other OPV recipients, zinc deficiency, the vaccine and its delivery, and the environment (e.g.

prevalence of other enteric infectious agents). Also type 2 vaccine virus interferes with immunological responses to vaccine virus types 1 and 3; consequently type 2 virus induces seroconversion preferentially, and children require multiple doses of OPV in order to respond to all three serotypes.

A dose of OPV administered at birth, or as soon as possible after birth, can significantly improve the seroconversion rates after subsequent doses and induce mucosal protection before enteric pathogens can interfere with the immune response, giving the first OPV dose at a time when the infant is still protected by maternally-derived antibodies may also prevent VAPP.

Studies from India demonstrated that the birth dose increases the levels of poliovirus neutralizing antibodies and seroconversion rates achieved after completion of the routine vaccination schedule.[9]

Mucosal Immunity

Intestinal mucosal immunity, primarily mediated by locally produced secretory IgA after live poliovirus exposure, is measured primarily by resistance to poliovirus replication and excretion in the pharynx and intestine after challenge with mOPV or tOPV.[4] In developing countries with inadequate hygiene and great potential for fecal–oral spread of enteric viruses, the clear increase in mucosal (intestinal) immunity induced by OPV over IPV would seem to offer a major advantage to OPV in reducing the circulation of polio-viruses. A recent study in India indicated that IPV compared to OPV can more effectively boost mucosal immunity in infants and children with a history of multiple doses of OPV.

Persistence of Mucosal Immunity

No data are available from developing countries about the duration of mucosal immunity for polioviruses. Several studies have assessed resistance to oral challenge by vaccine viruses years after the initial administration of OPV. One study reported that children were completely resistant to intestinal infection 10 years after vaccination, unless prechallenge serum antibodies were 1:8 or lower.

Duration of Protection

After induction of active immunity either by vaccination or exposure to poliovirus, usually measured by circulating antibody titer, protection

is life-long and protective immunity will not decrease even the antibody titers decline over time and may fall below detectable levels. Seroconversion is a reliable correlate of immunity against paralytic disease.

Coadministration with Other Vaccines

Oral polio vaccine is usually administered concurrently with other vaccines including Bacillus Calmette–Guérin (BCG), diphtheria, pertussis, and tetanus (DPT), hepatitis B, measles, Hib, pneumococcal conjugate vaccine (PCV) conjugate, and/or rotavirus vaccines. No interference with regard to effectiveness or increased incidence with rota vaccine even though there is a less immunological interference with first dose.

Immunocompromised Persons

In a small proportion of individuals with a primary immunodeficiency disease, OPV immunization can lead to persistent iVDPV infections, with chronic shedding of iVDPVs that show regained neurovirulence, human immunodeficiency virus (HIV) infection does not appear to be a risk factor for VAPP or paralytic poliomyelitis caused by WPV.

Inactivated Polio Vaccine

Vaccine Characteristics

Inactivated polio vaccine is made from selected WPV strains—Mahoney or Brunhilde (type 1), MEF-1 (type 2), and Saukett (type 3)—or from Sabin strains, and are now grown in Vero cell culture or in human diploid cells. IPV manufacturing relies on inactivation of cell culture-derived polioviruses with formaldehyde, in a final formulation containing sufficient antigen units for each serotype. IPV may contain formaldehyde, as well as traces of streptomycin, neomycin or polymyxin B. Some formulations of IPV contain 2-phenoxyethanol (0.5%) as a preservative for multi-dose vials. IPV formulations do not contain thiomersal, which is incompatible with IPV antigenicity. The vaccine should be refrigerated to preserve potency but not frozen as this could diminish potency. Available as 10-dose and 5-dose IPV vials can be used up to 28 days after opening IPV is also available as combination vaccine.

Safety of Inactivated Polio Vaccine

Inactivated polio vaccine is very safe, whether given alone or in combination with other vaccines. There may be transient minor local erythema (0.5–1%), induration (3–11%), and tenderness (14–29%).

Immunogenicity, Efficacy, and Effectiveness

Inactivated polio vaccine has been shown to be highly effective in eliciting humoral antibody responses to poliovirus in both high-income and low-income settings. The immunogenicity of IPV schedules depends on the age at administration and number of doses antigenic properties, interval age at last dose between the doses, and due to interference by maternal antibodies. A study of immunogenicity of a three-dose schedule in Puerto Rico found seroconversion rates of 85.8%, 86.2%, and 96.9% for serotypes 1, 2, and 3, respectively on a 6, 10, 14 week schedule, compared with 99.6%, 100%, and 99.1% on a 2, 4, 6 month schedule.[11] At completion of the two-dose immunization series, seroprotection rates ranged from 89% to 100% for poliovirus type 1, from 92% to 100% for poliovirus type 2, and from 70% to 100% for poliovirus type 3. Seroprotection rates after three doses are clearly higher than after two, particularly when the schedule is 2–4–6 months. However, schedules of 3–4–5 and 2–3–4 months also give good responses, although lower than after 2–4–6 months, particularly with regard to geometric mean titers (GMTs).

The humoral immunogenicity of conventional inactivated poliovirus vaccines (cIPV) in an Expanded Programme of Immunization (EPI) schedule appears to be superior to the use of OPV in such schedules in developing countries. After two or three doses in the first 6 months of life, antibody levels fall although the vaccinees usually retain seroprotective titers until the first booster is given during the second year of life, and this third or fourth injection gives a marked anamnestic response with booster dose.

Neonatal

In infants who received cIPV within the first 2 weeks of life, 100%, 100%, and 97.9% had neutralizing antibodies at titers greater than or equal to 1:8 against poliovirus types 1, 2, and 3, respectively, 1 month after the dose given at 2 months of age versus 96%, 100%, and 71% of infants who had not received prior cIPV.

Jain and colleagues documented the immunogenicity of a cIPV-only schedule given at 0, 6, and 10 weeks of age in Indian neonates and was able to demonstrate better seroconversion (80% seroconverted against all three poliovirus types) with this schedule than with an EPI schedule using OPV (at 6, 10, and 14 weeks of age) preceded by cIPV or OPV at birth (72% and 72% seroconverted against all three poliovirus types, respectively). Thus, all these data do show that cIPV at birth appears to prime the immune system, and these data are aligned with results from cIPV-followed-by-OPV sequential schedule trials.[10]

Inactivated polio vaccine is less effective than OPV in inducing intestinal mucosal immunity in previously unvaccinated individuals. Children given IPV then challenged with OPV become infected and shed OPV in their feces.

Preterm infants all develop neutralizing antibodies after three doses of cIPV, although titers might be lower than in term infants, particularly if the infants are chronically ill.

Intradermal Inactivated Polio Vaccine

Fractional doses of IPV 1/5 of a full dose reduces the cost and allows immunization of a larger number of persons with a given vaccine supply. Studies have generally demonstrated that a single fractional dose of IPV (one-fifth of the full dose) gives lower seroconversion rates than a full dose but after two doses, the rates are similar to those after two full doses. The median antibody titers induced by the two fractional doses, although high, were lower than with the two full doses. In studies in Cuba (4 and 8 months) and in Bangladesh (6 and 14 weeks)[12], two doses of fractional-dose IPV induced seroconversion rates of 98% and 81% to type 2 poliovirus, respectively. The results indicate that two fractional doses of IPV provide higher seroconversion rates than a single full dose, as shown in Cuba (63% when given at age of 4 months) and in Bangladesh (39% when given at age of 6 weeks). This approach, using two fractional doses instead of one full dose, increases the immunogenicity of IPV and can extend coverage study in India by Jacob John in 1990 using the modern cIPV demonstrated that one-fifth of the intramuscular dose is immunogenic in humans when delivered intradermally (ID). Several trials have shown that two

consecutive doses of fractional (ID) IPV compared well to one dose of full [intramuscularly (IM)] dose of IPV in infants regardless of whether they received tOPV or bOPV. Type 2 seroconversion, antibody levels, and priming were similar, if not better, after two fractional IPV doses each one-fifth of a full dose. These data will help the countries to propose this alternate use of IPV as a way to maximize the available, but too limited, quantities of IPV.

Coadministration of OPV and IPV or Sequential Use of IPV and OPV

IPV Followed by OPV

Sequential administration of IPV followed by OPV reduces or prevents VAPP while maintaining the high levels of intestinal mucosal immunity conferred by OPV. Sequential schedules of IPV followed by two or more doses of OPV have been used or studied in several countries including Israel, Oman, Pakistan, UK, and USA. Such schedules reduce the number of doses of IPV and optimize both the humoral and gut immunity to reduce the VAPP among vaccines and contacts oral mucosal immunity among IPV recipients and prevent the spread of vaccine virus.[4]

Continued use of OPV will induce effective intestinal immunity, thereby enhancing community resistance to transmission of imported WPV.

A key advantage of a sequential regimen of cIPV preceding OPV is to address the VAPP risk as it has been now well-documented that starting polio immunization with cIPV can eliminate the occurrence of the VAPP associated with the first doses of OPV.

This has proven to be a very successful strategy in the United States and in Hungary. From 1992 to 2006, Hungary switched from three annual mOPV campaigns to sequential schedule of one dose of cIPV-followed-by-tOPV and saw a complete cessation of VAPP.

Concurrent IPV and OPV

In developing country settings, the concurrent administration of tOPV and IPV has induced uniformly high antibody responses to all three poliovirus types, as evidenced from the studies from Thailand and

Pakistan.[13] A single dose of IPV will effectively close immunity gaps to poliovirus type 2 (and types 1 and 3) in previously tOPV-vaccinated children. Two recent studies in India found that single dose of IPV in infants and children with a history of multiple doses of OPV, boosted intestinal mucosal immunity, and prevalence of excretion reduced by 38–76%. Sequential schedule, IPV at 2 months followed by two doses of bOPV at 4 and 6 months, results in seroconversion rates of >98% to poliovirus type 1, >80% to type 2, and >98% to type 3, respectively, indicating high immunogenicity with this schedule.

OPV Followed by IPV

A recent study in India assessed a schedule with bOPV-, bOPV -bOPV -bOPV + IPV at birth, 6 and 10 weeks, and bOPV + IPV at 14 weeks. This schedule, four doses of bOPV and one dose of IPV, resulted in excellent seroconversion rates (>99% to poliovirus type 1, 69–78% to type 2, and >98% to type 3).

Mucosal Immunity/Protection

A study in India in 6–9-month-old infants who had previously received multiple doses of tOPV and mOPV1 were given a single dose of cIPV. Nearly 100% of children who were seronegative to types 2 and 3 at the time of the dose seroconverted. In addition, the dose of cIPV was associated with a marked boost in intestinal immunity as documented by decreased fecal shedding following an OPV challenge.

cIPV vaccinees could excrete poliovirus in stools and in nasopharyngeal secretions after challenge, which was seen as an important disadvantage versus OPV. Subsequent observations made it clear that cIPV-induced nasopharyngeal immunity could limit the virus shedding from this site after challenge.

No data are available on the long-term persistence of circulating antibodies and waning of intestinal immunity conferred by a single IPV dose to be administered per WHO recommendations (e.g. OPV at 6, 10, and 14 weeks along with IPV at 14 weeks) whereas it has been shown that intestinal immunity conferred by OPV can wane. With the switch from tOPV to bOPV1 and 3, the single dose of IPV will be the only exposure children on this schedule have to the type 2 antigen.

By the end of 2016, IPV-containing vaccines are routinely recommended for infant vaccinations against poliomyelitis and approximately 180 countries are using IPV. By 2018, all the countries will be using IPV.

Jacob John evaluated the performance of cIPV to boost humoral (and also intestinal) immunity in 1–4-year-old Indian infants who had received previous doses of tOPV. This supplemental dose of cIPV had excellent immunogenicity and led to higher increases in antibodies to all three polio types than did the bOPV challenge dose administered for intestinal immunity. Evaluation studies show that one dose of cIPV administered in OPV-primed subjects is able to boost humoral much better than one additional OPV dose. Results obtained with the most recent trials where OPV priming was done with bOPV, seem to suggest that a cross (heterotypic)-priming is induced by bOPV and that a one-dose cIPV boost is able to achieve substantial humoral and intestinal responses against type 2 poliovirus. These observations do confirm the wisdom of the current position recommended by the WHO in the scope of the polio endgame strategy.

WHO recently amended strategy stated that "The national choice of vaccines and vaccination schedules during the preeradication period must include OPV or IPV, or a combination of both, and should be based on assessments of the probabilities and consequences of wild poliovirus importation. It is clear that after eradication of the circulation of polioviruses, the use of OPV will have to stop".

Countries where poor sanitation and overcrowding facilitate the fecal–oral spread of virus, OPV is critical. Because OPV induces higher levels of intestinal immunity than IPV. Inactivated polio vaccine has an important role because it induces high levels of individual immunity with lesser doses than OPV and overcomes the problems of OPV by bypassing the intestines, which can impede OPV seroconversion in developing countries. IPV also boosts intestinal and humoral immunity in prior OPV vaccinees who have not seroconverted, particularly against type 2 after bOPV1 and 3 administration. Thus, IPV following OPV can improve protection against the current circulating wild virus types because it improves on both the systemic and mucosal immunity induced by OPV. IPV also has a major role to play in preventing VAPP and emergence and transmission of vaccine-derived polioviruses (VDPVs).

It is not possible to say when IPV usage will cease. The last GPEI Strategic Plan 2013–18 stated that "risks associated with eventual bOPV cessation may be similar to those associated with OPV2 cessation. It is recommended that countries have to continue administering at least one dose of IPV in their immunization programs for at least 5 years after bOPV cessation.

WORLD HEALTH ORGANIZATION POSITION

Vaccination with OPV plus IPV

For all countries using OPV in the national immunization program, WHO continues to recommend the inclusion of at least one dose of IPV in the vaccination schedule. The primary purpose of this IPV dose is to induce an immunity base that could be rapidly boosted if there is an outbreak of polio due to poliovirus type 2 after the introduction of bOPV2. The inclusion of IPV may reduce risks of VAPP and also boost both humoral and mucosal immunity against poliovirus types 1 and 3 in vaccine recipients. For polio-endemic countries and countries at high risk for importation and subsequent spread of poliovirus, WHO recommends a bOPV birth dose (zero dose) followed by a primary series of three bOPV doses and at least one IPV dose. The zero dose of bOPV should be administered at birth or as early as possible within 7 days.

Schedule could be three bOPV doses plus one IPV dose initiated from the age of 6 weeks with a minimum interval of 4 weeks between the bOPV doses. One dose of IPV should be given at 14 weeks of age or later (when maternal antibodies have diminished and immunogenicity is significantly higher).

Schedule bOPV-bOPV, -bOPV + IPV or Birth 6–10–14 weeks

Due to shortage of IPV instead of using single dose of IPV which seroconverts lower level than two fractional doses can be used along with bOPV with a schedule birth.

bOPV-bOPV+fIPV, -bOPV, -bOPV+fIPV Birth 6–10–14 weeks

This is a dose-sparing and results in better immunogenicity than a single full dose of IPV. To ensure early protection, a schedule of

fractional intradermal doses administered at 6 and 14 weeks may be considered.

Countries with insufficient routine vaccination coverage and which rely on supplementary immunization activities (SIAs) to increase population immunity should continue the SIAs using bOPV until routine coverage improves or until the globally-coordinated withdrawal of bOPV.

Inactivated Polio Vaccine Only Schedule

An IPV-only schedule may be considered in countries with sustained high vaccination coverage and very low risk of both WPV importation and transmission. In situations where combination vaccines are used, a primary series of three doses of IPV should be administered beginning 6 weeks at 4 weeks interval along with booster dose at 15–18 months.

Sequential IPV–OPV Schedule

Countries with high vaccination coverage (e.g. 90–95%) and low importation risk (neighboring countries and major population movement an IPV–bOPV sequential schedule can be used when VAPP is a significant concern. For sequential IPV–bOPV schedules, WHO recommends that IPV be given at 2 months of age (e.g. a three-dose IPV–bOPV–bOPV schedule), or at 2 months and 3–4 months of age (e.g. a four-dose IPV–IPV–OPV–OPV schedule).

To mitigate the risk of undetected transmission, WHO recommends that endemic countries and countries with a high risk of WPV importation should not switch to an IPV-only or a sequential IPV–bOPV schedule at this time. The 3 bOPV + 1 IPV schedule as currently recommended should be adopted and SIAs should continue to support intensive efforts to eliminate poliovirus transmission.

National Immunization Days

Objective is to reduce the widespread transmission of wild polio in the endemic countries. The NIDs are conducted twice annually for a period of 1–3 days when one dose of OPV is administered to all children <5 years of age, regardless of prior vaccination history. A second dose is repeated similarly after 4–6 weeks. The NIDs usually

take place during the low transmission season for both the polio and enteroviruses—the optimal period to interrupt the few remaining chains of poliovirus transmission.

The NIDs are necessary in developing countries to rapidly increase immunity levels in the population to achieve and surpass herd immunity threshold levels for poliomyelitis and, hence, rapidly interrupt the transmission of polioviruses.

Oral polio vaccine administered in campaigns also seems to be more immunogenic compared with OPV administered in the routine program.

- National immunization days are conducted during the low poliovirus transmission season because this is the period when the fewest chains of poliovirus transmission are maintained.
- National immunization days are conducted during the low transmission season for other enteroviruses that may interfere with poliovirus seroconversion.
- The cold chain can be better maintained for these short campaigns.
- Massive use of OPV probably also results in intensive secondary spread of shed virus.

Children residing in polio-endemic countries using NIDs may receive 13–14 doses of OPV by the time they reach their fifth birthday.[13]

India—nearly 160 million children are immunized in a single round credited as the largest mass campaigner in the world ever conducted.

Mopping-up Campaigns

Mopping-up campaigns usually target children younger than 5 years of age where in two doses of OPV given with an interval of 4–6 weeks. These campaigns include house-to-house administration of OPV with an objective to eliminate the last potential or known reservoirs of WPV circulation, critical component to achieve interruption of the final chains of poliovirus transmission in all polio-endemic areas.

IMPACT OF POLIO ERADICATION PROGRAM

Across the world there is a decrease in the number of reported poliomyelitis cases globally from 35,251 (estimated to be approximately 350,000 cases) in 1988 (when the polio eradication target was adopted) to 359 in 2014, a decrease of more than 99% cases in the world. Only

three countries in the world Pakistan, Afghanistan, and Nigeria have reported cases lastly in 2016; India has been declared as polio free from 2012.

- Wild polio virus 2 last detected in UP, India in October 2009.
- Wild polio virus 3 last detected in Nigeria in November 2012.
- 102 cases of WPV1 reported from Pakistan and Afghanistan.

Surveillance

Surveillance is critical to monitor and guide the polio eradicating programs to and finally to certification of polio-free status. AFP surveillance systems have been established in all polio-endemic countries.

Two activities are involved: (1) AFP surveillance, and (2) virological studies of polio viruses. To improve the sensitiveness of the program all cases resembling acute polio paralysis are investigated. On the basis of the experience of each population, a rate of at least one case of nonpolio AFP per 100,000 populations younger than 15 years of age would be expected annually and achievement of such a rate would indicate adequate surveillance. In 2005, the Advisory Committee on Poliomyelitis Eradication recommended that the nonpolio AFP rate in polio-endemic countries should be at least 2/100,000 persons younger than 15 years of age.

A global network of 145 formally accredited laboratories has been established to process all stool specimens collected from AFP cases worldwide for virologic investigations.

Obstacles to Eradication

All the countries are committed for the Global Polio Eradication Program (GPEP) in the world committed with political will and utilizing the resources.

Accessibility and security of the health workers is the major concerns in the countries where last cases of wild polio are reported.

The Polio Eradication and Endgame Strategic Plan 2013–2018

World Health Assembly initiated the GPEI in 1988 to reduce the global incidence of polio. Since then more than 99% polio cases and the number of countries with endemic polio are reduced from 125

to 3. More than 10 million people are walking today who otherwise would have been paralyzed.[1] At the beginning of 2013, polio—a highly infectious viral disease that causes swift and irreversible paralysis—was a distant memory in most of the world.

On 26 May 2012, the WHA declared ending polio a "programmatic emergency for global public health". Emphasizing the India's success using available tools and technology, the threat to the global community of ongoing poliovirus transmission in the last three endemic countries—Afghanistan, Nigeria, and Pakistan—and the growing knowledge about and risk of cVDPVs, which can cause outbreaks of paralytic disease, the WHA called on the WHO Director-General to develop and finalize a comprehensive polio endgame strategy.[5] The Polio Eradication and Endgame Strategic Plan 2013–2018 (the Plan) was developed to capitalize on this new opportunity to end all polio disease.

Four Main Objectives ***(Fig. 1)***

1. Stop all WPV transmission by the end of 2014 and new cVDPV outbreaks within 120 days of confirmation of the first case.

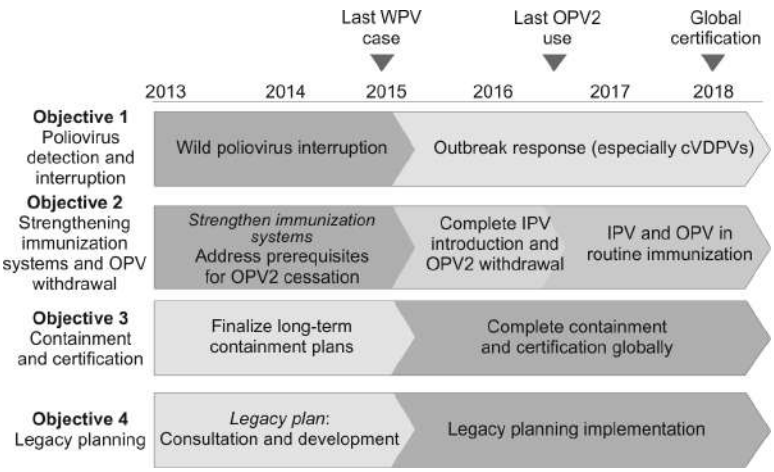


Fig. 1: Four main objectives. This figure shows that with full funding, the objectives can be pursued in parallel, with working target dates established for the completion of each.
(WPV: wild poliovirus; OPV: oral polio vaccine; IPV: inactivated polio vaccine; cVDPV: circulating vaccine-derived poliovirus)

2. Hasten the interruption of all poliovirus transmission and help strengthen immunization systems.
3. Certify all regions of the world polio-free and ensure that all poliovirus stocks are safely contained.
4. Ensure that a polio-free world is permanent and that the investment in polio eradication provides public health dividends for years to come.

Immunization Systems Strengthening and OPV Withdrawal: This objective seeks to hasten the interruption of all poliovirus transmission and help build a stronger system for the delivery of other lifesaving vaccines. This objective engages all 145 countries that currently use OPV in their routine immunization programs, as well as the GAVI Alliance and immunization partners. Success in eliminating cVDPVs depends on the eventual withdrawal of all OPV, beginning with the withdrawal of the type 2 component of trivalent OPV (tOPV). Introducing at least one dose of affordable IPV into the routine immunization schedule globally and then replacing the trivalent OPV with bivalent OPV in all OPV-using countries—setting the stage for eventually ending bOPV use in 2019–2020.

REFERENCES

1. Polio Global Eradication Initiative (2018). Polio Eradication and Endgame Strategic Plan 2013–2018. [online] Available from: http://www.polioeradication.org/resourcelibrary/strategyandwork.aspx. [Last Accessed October 2019].
2. Bernier R. Some observations on poliomyelitis lameness surveys. Rev Infect Dis. 1984;6(Suppl 2):S371-5.
3. Sutter RW et al. Poliovirus vaccine-live. In: Plotkin SA, Orenstein WA, Offit PA. Vaccines, 6th edition. Philadelphia: Elsevier-Saunders, pp. 598-645.
4. Platt LR, Estívariz CF, Sutter RW. Vaccine-associated paralytic poliomyelitis: a review of the epidemiology and estimation of the global burden. J Infect Dis. 2014;210(Suppl 1):S380-9.
5. Kohler KA, Banerjee K, Gary Hlady W, et al. Vaccine-associated paralytic poliomyelitis in India during 1999: decreased risk despite massive use of oral polio vaccine. Bull World Health Organ. 2002;80(3):210-6.
6. Global Polio Eradication Initiative (2015). Reporting and classification of vaccine derived polioviruses [online] Available from: http://www.polioeradication.org/Portals/0/Document/Resources/VDPV_ReportingClassification.pdf. [Last Accessed October 2019].

7. Estívariz CF, Jafari H, Sutter RW, et al. Immunogenicity of poliovirus vaccines administered at age 6-9 months in Moradabad District, India: A randomized controlled phase 3 trial. Lancet Inf Dis. 2012;12:128-35.
8. John TJ. Immunisation against polioviruses in developing countries. Rev Med Virol. 1993;3:149-60.
9. Bhaskaram P, Nair KM, Hemalatha P, et al. Systemic and mucosal immune response to polio vaccination with additional dose in newborn period. J Trop Paediatrics. 1997;43(4):232-4.
10. John TJ, Jain H, Ravishankar K, et al. Monovalent type 1 oral poliovirus vaccine among infants in India: report of two randomized double-blind controlled clinical trials. Vaccine. 2011;29(34):5793-801.
11. Dayan GH, Thorley M, Yamamura Y, et al. Serologic response to inactivated polio vaccine: a randomized clinical trial comparing 2 vaccination schedules in Puerto Rico. J Inf Dis. 2007;195:12-20.
12. Anand A, Zaman K, Estívariz CF, et al. Early priming with inactivated poliovirus vaccine (IPV) and intradermal fractional dose IPV administered by a microneedle device: A randomized controlled trial. Vaccine. 2015;33(48):6816-22.
13. du Chatelet IP, Merchant AT, Fisher-Hoch S, et al. Serological response and poliovirus excretion following different combined oral and inactivated poliovirus vaccines immunization schedules. Vaccine. 2003;21:1710-8.
14. Sutter RW, Bahl S, Deshpande JM, et al. Immunogenicity of a new routine vaccination schedule for global poliomyelitis prevention: an open-label, randomised controlled trial. Lancet. 2015;386:2413-21.

3.3 HEPATITIS B VACCINE

Shivananda S

BACKGROUND

Hepatitis is the main manifestation of viral infection in humans is caused by only five virus species: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV). Together these viruses caused 1.34 million deaths in 2015.[1] All of the hepatitis viruses cause acute hepatitis; HBV frequently cause chronic hepatitis. Chronic hepatitis can lead to cirrhosis which may progress to hepatocellular carcinoma (HCC), the most common type of primary liver cancer. In India, 2–4% of individuals are chronic carriers of HBV that place us in intermediate endemicity.[2] Infection with HBV may occur perinatally (vertical transmission), during early childhood (the so-called horizontal spread), through sexual contact, or nosocomially. Chronic HBV infection in India is acquired in childhood, presumably before 5 years of age, through horizontal transmission. 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. According to a recent study, the seropositivity of hepatitis B was found to be 2.9% amongst pregnant women in India.[3] The risk of infection in a child born to a hepatitis B positive mother ranges from 10% to 85% depending on the mother's hepatitis B e antigen (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 up to 25% of chronic carriers will die of chronic liver disease as adults. HBV genotypes A and D are prevalent in India, which are similar to the HBV genotypes in the West.[1] Infection with HBV is one of the most important causes of chronic hepatitis, cirrhosis of liver, and HCC. These outcomes are all preventable by early childhood immunization. It is for this reason that the World Health Organization (WHO) has recommended universal hepatitis B vaccination.[4]

VACCINES

Safe and effective vaccines against hepatitis B have been available since 1982. The active substance in the hepatitis B vaccine is the viral surface protein HBsAg (hepatitis B surface antigen). The plasma-derived hepatitis 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 aluminum salts and preserved with thimerosal (thimerosal-free vaccines are also available) since 1986. Hepatitis B vaccine is available as single- and multidose vials and should be stored at 2–8°C. The vaccine should not be frozen; frozen vaccine should be discarded. A WHO review of published and manufacturers' data, based on *in vivo* and in vitro testing to assess the thermostability of monovalent hepatitis B vaccines, suggests that hepatitis B vaccines are relatively heat-stable.[5] Hepatitis B vaccines are available as monovalent formulations for birth doses or for vaccination of older persons at risk, and in combination with other vaccines for infant vaccination, including diphtheria-tetanus-pertussis (DTP), *Haemophilus influenzae* type b (Hib), and inactivated polio vaccine (IPV).[4]

Immunogenicity, Efficacy and Effectiveness

The protective efficacy of hepatitis B vaccination is related to the induction of antibody to hepatitis B surface antigen (anti-HBs) antibodies, but also involves the induction of memory T-cells. An anti-HBs concentration of 10 mIU/mL measured 1–3 months after administration of the last dose of the primary vaccination series is considered a reliable correlate of protection against infection.[6] The primary three-dose vaccine series induces protective antibody concentrations in >95% of healthy infants, children, and young adults.[4]

Dosage and Administration

The dose in children and adolescents (aged less than 18 years) is 0.5 mL/10 μg and in those 18 years and older is 1 mL/20 μg. It should be injected intramuscularly in the deltoid/anterolateral thigh.

Injections should be avoided due to low gluteal immunogenicity. The vaccine is extremely safe and well tolerated.

Immunization Schedules

Infants

The primary three-dose hepatitis B vaccination series for monovalent vaccines, consists of one monovalent birth dose followed by either two doses of monovalent or hepatitis B-containing combination vaccine administered during the same visits as the first and third doses of DTP-containing vaccines. Alternatively, four doses of hepatitis B vaccine may be given for programmatic reasons (e.g. one monovalent birth dose followed by three monovalent or hepatitis B-containing combination vaccine doses) administered during the same visits as the three doses of DTP-containing vaccines.[4] The additional dose is not harmful. Delay in administration of the birth dose to infants of chronically infected mothers increases the risk of perinatal HBV transmission.

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.[4] 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 comorbidities. Antibody titers greater than 10 mIU/mL signify a response and are considered protective.[6] Nonresponders should be tested for hepatitis B carrier status. If found to be negative, the same three-dose schedule should be repeated. Almost all respond to a three-dose revaccination schedule.

Although the 0-1-6 schedule is the preferred schedule, hepatitis B vaccine schedules are very flexible and there are multiple options for adding the vaccine to existing national immunization schedules without requiring additional visits for immunization. These include:

- Birth, 6, and 14 weeks
- Birth, 6 weeks, 6 months
- Birth, 6 weeks, 10 weeks, 14 weeks.

As of now, from the data available, none of the above schedules needs a booster. However, data are limited regarding long-term protection for schedules with shorter intervals. Schedules with a birth dose are necessary in all areas of high and moderate endemicity to prevent perinatal transmission.

Duration of Protection

The standard three-dose hepatitis B vaccine series consists of two priming doses administered 1 month apart and a third doses administered 6 months after the first dose. This schedule results in very high antibody concentrations. Increasing the interval between the first and second dose of hepatitis B vaccine has a little effect on immunogenicity or final antibody concentration, whereas longer intervals between the last two doses result in higher final antibody concentrations. The higher the peak of anti-HBs concentrations following immunization, the longer it usually takes for antibody levels to decline to ≤10 mIU/mL.[6]

Several studies have documented the long-term protective efficacy of this schedule in preventing HBsAg-carrier status or clinical HBV-disease even when the anti-HBs concentrations decline to ≤10 mIU/mL over time. Even an absent anamnestic response following booster vaccination may not necessarily signify susceptibility to HBV in such individuals. Furthermore, observational studies have shown the effectiveness of a primary series of hepatitis B vaccine in preventing infection up to 22 years postvaccination of infants.[5] However, hepatitis 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. An anamnestic response would occur, with the titers going up, should there occur contact with the virus again in future.

Need of Boosters

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 comorbidities such as chronic renal disease, levels should be checked periodically and booster vaccination given whenever levels drop to below protective levels.

Coadministration

Hepatitis B vaccines do not interfere with the immune response to any other vaccine and vice versa. The immune responses and safety of hepatitis B-containing combination vaccines are comparable to those observed when the vaccines are administered separately.[5]

HEPATITIS B IMMUNOGLOBULIN

Hepatitis B immunoglobulin (HBIg) provides passive immunity and is indicated along with hepatitis B vaccine in management of perinatal/occupational/sexual exposures to hepatitis B in susceptible individuals.[5] The dose of HBIg in adults is 0.06 mL/kg and in neonates/infants 0.5 mL. HBIg should be stored at 2–8°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 nonresponders to hepatitis B vaccination (genetic reasons/immunocompromised status). In this situation, two doses of HBIg 1 month apart are indicated. A few intravenous preparations of HBIg (like Hepatect CP) are also available in the market; however, they are not adequately evaluated for their efficacy.

Recommendations for Use

Individual Use

The committee has recommended the following schedule: the first dose should be administered at birth within 24 hours and three more doses along with combination vaccines at 6-10-14 weeks. The existing schedule of 0–6 weeks–14 weeks may also be used in catching up schedule. However, the hepatitis B vaccine may be given through

other schedules as described above, considering the programmatic implications and logistic issues.

The committee stresses the significance and need of a birth dose. The birth dose can reduce perinatal transmission by 18–40%.

Hepatitis B vaccination is recommended for all children worldwide. Reaching all children with at least three doses of hepatitis B vaccine should be the standard for all national immunization programs. Importantly, all national programs should include a monovalent hepatitis B vaccine birth dose.[4]

Delay in the administration of the first dose beyond the 7th day of life has been shown to be associated with higher rates of HBsAg acquisition in later childhood. The WHO position paper of 2009 clearly states that "since perinatal or early postnatal transmission is an important cause of chronic infections globally, the first dose of hepatitis B vaccine should be given as soon as possible (<24 hours) after birth even in low-endemicity countries".[4]

Catch-up Vaccination

Hepatitis B vaccine as a 0-1-6 schedule should be offered to all children/adolescents who have not been previously vaccinated with hepatitis B vaccine. This is to address problems related to horizontal mode of transmission of the virus. Prevaccination 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. Prevaccination 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 hepatitis B are discussed separately.

Prevaccination and Postvaccination Testing

Prevaccination serological testing is not advisable as routine practice. The WHO HBV testing guidelines recommend offering focused testing to individuals from populations most affected by HBV infection.[5] Routine postvaccination testing for immunity is not necessary, but it is recommended for high-risk individuals whose

subsequent clinical management depends on knowledge of their immune status.

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, hepatitis B vaccine can be given in the 0–6 weeks–6 months schedule. If the mother's HBsAg status is not known, it is important that hepatitis B vaccination should begin within a few hours of birth so that perinatal transmission can be prevented.

If the mother is HBsAg positive (and especially HBeAg positive), the baby should be given HBIg along with hepatitis B vaccine within 12 hours of birth, using two separate syringes and separate sites for injection. The dose of HBIg is 0.5 mL intramuscular. HBIg may be given up to 7 days of birth but the efficacy of HBIg after 48 hours is not known. Three more doses of Hepatitis B vaccine should be administered at 6–10–14 weeks as part of combination vaccine. If HBIg is not available (or is unaffordable), hepatitis B vaccine may be given at 0, 1 and 2 months with an additional dose between 9 months and 12 months. The efficacy of prophylaxis with both HBIg and hepatitis B vaccine is 85–95% and that with hepatitis B vaccine alone (first 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/nonresponders.[7]

IMMUNIZATION OF PRETERM INFANTS

Preterm infants and low-birth weight infants with birth weight less than 2,000 grams have a decreased response to hepatitis B vaccines administered before the age of 1 month. However, by the chronological age of 1 month, preterm babies irrespective of their initial birth weight and gestational age are likely to respond as adequately as full-term infants.[4,5,7]

Recommendations for Preterm Infants

- *Greater than 2,000 g*: As for full-term infants.
- Less than 2,000 g:

- *Mother HBsAg negative*: Dose 1 at 30 days of age, dose 2 and 3 as per schedule adopted for full-term infants.
- *Mother HBsAg positive*: Hepatitis B vaccine + HBIg (within 12 hours of birth), continue vaccine series with three more doses beginning at 4–6 weeks of age as per schedule for full-term infants. Immunize with four doses, do not count birth dose as part of vaccine series.[8] Check anti-HBs and HBsAg 1 month after completion of vaccine series.

PATIENTS WITH CHRONIC RENAL FAILURE

Patients suffering from chronic renal failure are at particular risk of infection with HBV, since they may need hemodialysis. These patients have been offered schedules that include more than three doses of the standard vaccine, or vaccine containing a higher dose of HBsAg (e.g. double the usual adult dose) on each occasion, or both.[5]

HEALTHCARE WORKERS[8]

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, healthcare 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 months schedule. An accelerated schedule may be required as dose 1 of the series at any visit, dose 2 at least 4 weeks after dose 1 and dose 3 at least 8 weeks after dose 2 and at least 16 weeks after dose 1.

POSTEXPOSURE PROPHYLAXIS TO PREVENT HEPATITIS B VIRUS INFECTION IN EXPOSED HEALTHCARE PERSONNEL

Healthcare personnel (HCP) are defined as persons (including nonmedical employees, students, medical personnel, public-safety workers, or volunteers) whose occupational activities involve contact with patients or with blood or other body fluids from patients in a healthcare, laboratory, or public-safety setting.[7] Hepatitis B vaccine

should be offered to all HCP who have a reasonable expectation of being exposed to blood and body fluids on the job. It is preferable that medical students and trainees be offered the vaccine, as exposure is more common during the training period.

All HCP, including trainees, who have direct patient contact or who draw, test, or handle blood specimens should have postvaccination testing for anti-HBs. Postvaccination testing should be done 1–2 months after the last dose of vaccine. For immunocompetent HCP, periodic testing or periodic boosting is not needed.

An exposure that might place HCP at risk for HBV infection includes percutaneous injuries (e.g. a needle stick or cut with a sharp object) or contact of mucous membrane or nonintact skin with blood, tissue, or other body fluids that are potentially infectious.[9]

In addition, HBV has been demonstrated to survive in dried blood at room temperature on environmental surfaces for at least 1 week. The potential for HBV transmission through contact with environmental surfaces is well established. The risk of HBV infection in the exposed HCP is primarily related to the degree of contact with blood in the work place and also to the hepatitis B e antigen (HBeAg) status of the source person.

Following a percutaneous or mucosal exposure to blood, three factors need to be considered when deciding the nature of postexposure prophylaxis (PEP). These include:

- HBsAg status of the source
- Vaccination status of the exposed HCP
- Vaccination response status of the HCP.

The PEP recommendations are given in **Table 1**.

PUBLIC HEALTH PERSPECTIVES

Hepatitis B vaccination is great public health significance. Though the Government of India (GOI) initiated hepatitis B vaccination since 2002, the IAP ACVIP (Indian Academy of Pediatrics Advisory Committee on Vaccines and Immunization Practices) believes that all infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours. In countries where there is high disease endemicity and where HBV is mainly spread from

TABLE 1: Recommendations for postexposure prophylaxis after percutaneous or mucosal exposure to HBV in HCP.

*Vaccination and antibody response status of exposed persons**	*Treatment*		
	Source is HBsAg positive	*Source is HBsAg negative*	*Source is unknown on not tested*
Unvaccinated	HBIg† × I and begin a hepatitis B vaccine series	Begin a hepatitis B vaccine series	If the source is suspected to be high risk, refer to the column "Source is HBsAg positive." If not, begin a hepatitis B vaccine series
Fully vaccinated and known responder‡	No treatment	No treatment	No treatment
Vaccinated with 3 doses and known nonresponder‡	HBIg† × I and begin a hepatitis B revaccination series§	No treatment	If the source is suspected to be high risk, refer to the column "Source is HBsAg positive." If not, begin a hepatitis B revaccination series
Vaccinated with six doses and known nonresponder[3]	HBIg†,‖ × 2	No treatment	Treat based on known or suspected risk of source
Fully vaccinated with three doses but antibody titer unknown	Test for anti-HBs.¶ If adequate,‡ no treatment. If inadequate, HBIg† × I and hepatitis B vaccine booster.	No treatment	If the source is suspected to be high risk, refer to the column "Source is HBsAg positive." If not, test for anti-HBs.¶ If adequate,‡ no treatment, If inadequate, give vaccine booster and check anti-HBs in 1–2 months

* Persons known to have had HBV infection in the past or who are chronically infected do not require HBIg or vaccine.
† Hepatitis B immune globulin (0.06 mL/kg) administered IM.
‡ Adequate response is anti-HBs of at least 10 mIU/mL after vaccination.
§ Revaccination = additional three-dose series of hepatitis B vaccine administered after the primary series.
‖ First dose as soon as possible after exposure and the second dose 1 month later.
¶ Testing should be done as soon as possible after exposure.
(anti-HBs: antibody to hepatitis B surface antigen; HBIg: hepatitis B immunoglobulin; HBV: hepatitis B virus; HCP: healthcare personnel; IM: intramuscular)
Source: Adapted from "Updated U.S. PHS Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis," MMWR. 2001;50(RR-11):8.

mother to infant at birth or from child to child during early childhood, providing the first dose at birth is particularly important, but even in countries where there is intermediate endemicity or low endemicity an important proportion of chronic infections are acquired through early transmission.[3] Delivery of hepatitis B vaccine within 24 hours of birth should be a performance indicator for all immunization programs, and reporting and monitoring systems should be strengthened to improve the quality of data on the birth dose.

HEPATITIS B (HEP B) VACCINE

Routine vaccination:

- Administer monovalent hepatitis B vaccine to all newborns within 24 hours of birth.
- Administration of a total of three doses of hepatitis B vaccine is permissible when a combination vaccine containing hepatitis B is administered at 6–10–14 weeks after the birth dose.
- Infants who did not receive a birth dose should receive three doses of a hepatitis B containing vaccine starting as soon as feasible.
- The ideal minimum interval between dose 1 and dose 2 is 4 weeks, and between dose 2 and 3 is 8 weeks. Ideally, the final (third or fourth) dose in the hepatitis B vaccine series should be administered no earlier than age 24 weeks and at least 16 weeks after the first dose, whichever is later.
- Hepatitis B vaccine may also be given in any of the following schedules: birth, 1 and 6 months, birth, 6 and 14 weeks; birth, 6, 10 and 14 weeks, etc. All schedules are protective.

Catch-up vaccination:

- Administer the three-dose series to those not previously vaccinated.
- In catch-up vaccination, use 0, 1, and 6 months schedule.

REFERENCES

1. Global Hepatitis Report, World Health Organization, Geneva: 2017. Available from http://apps.who.int/iris/bitstream/10665/255016/1/9789241565455-eng. pdf?ua=1, [Accessed May 2017].
2. Acharya SK, Madan K, Dattagupta S, et al. Viral hepatitis in India. Natl Med J India. 2006;19:203-17.
3. Mehta KD, Antala S, Mistry M, et al. Seropositivity of hepatitis B, hepatitis C, syphilis, and HIV in antenatal women in India. J Infect Dev Ctries. 2013;7:832-7.
4. Hepatitis B vaccines. WHO Position Paper. Weekly Epidemiological Record, No 27. 2017.

5. Damme PV, Ward J, Shouval D, et al. Hepatitis B vaccines. In: Plotkin SA, Orenstein WA, Offit PA (Eds). Vaccines, 6th edition, Philadelphia: Saunders Elsevier; 2016.
6. Jack AD, Hall AJ, Maine N, et al. What level of hepatitis B antibody is protective? J Infect Dis. 1999,179:489-92.
7. CDC. Immunization of Health-Care Personnel; Recommendations of the Advisory Committee on Immunization Practices, MMWR. 2011; 60(7):1-4.
8. Centers for Disease Control and Prevention. A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2005;54:RR-16. Available from http://www.cdc.gov/mmwr/PDF/rr/rr5416.pdf. [Accessed October 2019].
9. WHO prequalified vaccines. Available https://extranet.who.int/gavi/PQ_Web/, Available from: www.cdc.gov/mmwr/pdf/rr/rr6007.pdf [Accessed May 2017].

3.4 DIPHTHERIA, TETANUS AND PERTUSSIS VACCINES

Pallab Chatterjee

BACKGROUND

The morbidity and mortality due to diphtheria, tetanus, and pertussis (DTP) have reduced significantly in India since introduction of the whole-cell vaccines in Expanded Program for Immunization (EPI). However, coverage with three doses of the whole-cell vaccine, diphtheria, tetanus and whole cell pertussis (DTwP) vaccine has increased over the years to 91% for DTwP1 to 88% for DTwP3.[1] The need of completing the schedule and boosters should be stressed upon by the pediatrician.

EPIDEMIOLOGY

Diphtheria

The use of DTP vaccines has had significant impact at the burden of diphtheria. However, the disease is still persisting in a few states and published reports of the disease do exist in Indian literature indicating outbreaks, secular trends and a shifting epidemiology over the years.[2-4] The reported incidence for diphtheria has been 2,599 cases and 176 deaths in 2016, and has increased to 5,293 cases, which accounted for one-third of the global incidence (16,435 cases) and 148 deaths in 2017.[5] But underreporting is highly likely. The corresponding figures for the year 1980, 1990, and 2000 were 39,231, 8,425, and 5,125, respectively.[6] Diphtheria, however, remains endemic in countries in Africa, Latin America, Asia, the Middle East, and parts of Europe, where childhood immunization with diphtheria toxoid-containing vaccines is suboptimal.

Pertussis

In India, the incidence of pertussis declined sharply after launch of Universal Immunisation Programme (UIP). Prior to UIP, India reported 200,932 cases and 106 deaths in the year 1970 with a mortality rate of <0.001%. During the year 1987, the reported incidence was about 163,000 cases which came down to 39,091 in 2011 to 23,779 in 2017

reflecting a decline of more than 75%.[6] Among different states, MP, Jharkhand, Assam, UP, WB, and D&N Haveli reported the maximum cases in 2017, of which only 6 deaths were reported.[5] However, a large number of cases go unreported, and many nonpertussis cases are reported and clubbed under the head of "whooping-cough" cases. The actual number may be high considering the low coverage with primary and booster doses of DTP vaccine in the country. The data on pertussis disease and infection in adolescents and adults is sorely lacking. Further, there is no data on *Bordetella pertussis* infection rates in the community that may be responsible for appearance of typical pertussis disease in infants and children.[7]

Tetanus

The incidence of tetanus in India has also declined sharply from 45,948 cases in 1980 and 23,356 cases in 1990 to only 4,702 cases in 2017.[6] But the worrying part is persistence of neonatal tetanus, though there has been a decline from 588 cases in 2012 to 295 cases with 9 deaths in 2017.[5]

DIPHTHERIA, TETANUS, AND PERTUSSIS VACCINES

Diphtheria, Tetanus, and Whole Cell Pertussis Vaccines

Popularly known as triple antigen, DTwP is composed of tetanus and diphtheria toxoids as well as killed whole-cell pertussis (wP) bacilli adsorbed on insoluble aluminum salts which act as adjuvants. The content of diphtheria toxoid varies from 20 Lf to 30 Lf and that of tetanus toxoid (TT) varies from 5 Lf to 25 Lf per dose. The vaccines need to be stored at 2–8°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 or tetanus of three doses of the vaccine exceeds 95%. Disease may occur in vaccinated individuals but is milder.

Efficacy

The efficacy of different wP products varies substantially not only in different studies in different parts of the world but also varies with the

case definition of the disease employed.[7] For higher efficacy trials, the efficacy estimates vary from 83% to 98% and 36% to 48% in lower-efficacy trials. The pooled-efficacy of wP vaccine against pertussis in children was 78% according to a systematic review in 2003.[8] The efficacy of wP alone ranged from 61% to 89%, and the efficacy of combination DTwP vaccines ranged from 46% to 92%.[8] There is no known immune correlate of protection for pertussis vaccines. Immunity against all three components wanes over the next 6–12 years and thus regular boosting is needed.

Adverse Effects

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 three primary doses. Serious adverse effects have been reported with DTwP vaccines but are rare. The frequency of these side effects/1,000 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 (HHEs), 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 wP vaccines in the past. It has now been proved beyond doubt that the wP vaccine is not causally associated with any of these adverse events. Absolute contraindications to any pertussis vaccination (including DTwP vaccine) are history of anaphylaxis or development of encephalopathy within 7 days following previous DTwP vaccination. In case of anaphylaxis, further immunization with any diphtheria or tetanus or 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 and tetanus (DT) vaccines may be used. Events such as persistent inconsolable crying of more than 3 hours duration or hyperpyrexia (fever > 40.5°C) or 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 or evolving neurological illnesses are 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 4–5 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 second 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 years and older due to increased risk of side-effects. It is essential to immunize even those recovering from DTP as natural disease does not offer complete protection.

Diphtheria, Tetanus, and Acellular Pertussis Vaccines

Background

The introduction of the whole-cell vaccines paid rich dividends in terms of decline in disease morbidity and mortality. Once disease rates declined, concerns about frequent local side-effects, as well as public anxiety about the safety of wP vaccines, led to the development of acellular pertussis (aP) 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

All aP vaccines are associated with significantly lesser side-effects, and thus the replacement of the wP vaccines was mainly driven by the safety profile of these vaccines. The other important advantage of the aP vaccines is the reproducible production process with its use

of purified antigens and the removal of lipopolysaccharides (LPS) and other parts of the bacterial cell wall during the purification of soluble antigenic material. These vaccines contain ≥1 of the separately purified antigens pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (PRN), and fimbrial hemagglutinins 1, 2, and 3 (FIM type 2 and type 3). Vaccines differ from one another not only in the number and quantity of antigen components, but also with regard to the bacterial clone used for primary antigen production, methods of purification and detoxification, incorporated adjuvants, and the use of preservatives, such as thiomersal.[9] Nearly two-dozen aP vaccines were designed, many were evaluated in immunogenicity and reactogenicity trials, and the efficacy and safety of a number were evaluated in field trials.

Efficacy and Preference of a Particular Acellular Pertussis Vaccine Product

The efficacy and duration of protection with diphtheria, tetanus, and acellular pertussis (DTaP) vaccines against diphtheria or tetanus and pertussis is similar to that afforded by the whole-cell vaccines. There is considerable controversy on the relative efficacy of different aP vaccines with varying number of components. Several randomized pertussis vaccine efficacy studies were conducted in Europe and Africa to compare the safety and efficacy of the aP and the wP vaccines for the prevention of laboratory-confirmed pertussis disease in infants.[7]

Efficacy is influenced by both the choice of antigen and its quantity. Thus, the monocomponent vaccine, with 50% more PT, provides better protection against severe disease; while the two component vaccines appear better in preventing mild to moderate disease. The efficacies in these trials varied from 54% to 89%.[7] However, a few countries like Japan, Denmark, Sweden, etc. have shown consistent control of pertussis disease with aP vaccines in their national immunization program.

There is as yet no consensus about the antigenic composition of an ideal aP vaccine. The exact contribution of the different aP antigens to protection is not clear. Current generation of aP available from

different manufacturers should be considered as different and unique products because of the presence of one or more different components in different concentrations, and with different degree of adsorption to different adjuvants. Further, these individual antigens may be derived from different strains of *B. pertussis* and have been purified by different methods.[10] This is the reason why direct comparison of protective efficacy of different aP vaccines in human is not possible.

Different researches have studied the impact of number of components in an aP vaccine on relative protective efficacy of different aP products. In a recent retrospective study in the US following a huge outbreak of pertussis in California, the researchers found that 5-component aP vaccine had an estimated efficacy of 88.7% [95% confidence interval (CI), 79.4–93.8%].[11] According to a systematic review involving 49 randomized controlled trials (RCTs), aP vaccines containing three or more components had much higher absolute efficacy (80–84%) than those containing only 1- and 2-components (67–70%).[8] A Cochrane review by Zhang et al. after studying six aP vaccine efficacy trials and 52 safety trials concluded that the efficacy of multicomponent (≥3) aP vaccines varied from 84% to 85% in preventing "typical whooping cough" and from 71% to 78% in preventing mild disease. In contrast, the efficacy of one- and two-component vaccines varied from 59% to 75% against typical whooping cough and from 13% to 54% against mild disease.[12] However, a few countries have demonstrated high levels of effectiveness of mono- and bicomponent aP products in preventing pertussis by employing them in their immunization programs,[9] the available evidence[7] is not sufficient to establish any significant difference in vaccine effectiveness of aP vaccines with differing numbers of components.[9]

The effectiveness of vaccination programs on a national level depends not only on the efficacy of the vaccine but also other factors such as the vaccination schedule and adherence, transportation, and storage of the vaccine, and herd immunity in the population.

Adverse Effects

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 or 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. After the primary series, the rate and severity of local reactions tend to increase with each successive DTaP dose.

Correlate of Protection of Whole Cell Pertussis and Acellular Pertussis Vaccines

Till date there is no single absolute or surrogate correlate of protection is known for pertussis disease and vaccines. Antibody levels against PT, PRN, and FIM can be used as markers of protection, but no established protective antibody levels are known. The mechanism of immunity against *B. pertussis* involves both humoral and cellular immune responses which are not directed against a single protective antigen. In addition to the PT, the vaccines usually contain one or more attachment factors, which also may be protective. Immune response to current wP vaccines mimics the response to infection in animal models and differs from the response to aP vaccines. The "murine intracerebral challenge test" has been considered as a "gold-standard" for wP vaccines and has been used to standardize and assess the potency of wP vaccines.[13] But until now there has been no animal model in which protection correlates with aP vaccines efficacy in children, and these vaccines do not pass the original "murine intracerebral challenge test". The respiratory challenge by aerosol or intranasal of immunized mice-model has been used to study pertussis pathogenesis and immunity and can correlate with efficacy of aP vaccines, but not yet accepted as a regulatory tool. In animal model, duration of protection is longer after wP vaccines compared to aP vaccines, suggesting a role for cell-mediated immunity for long-term protection **(Table 1)**.

TABLE 1: Composition of available aP vaccines (in combination) brands in India.

Product	*Infanrix Hexa**	*Hexaxim**	*Pentaxim*†	*Tetraxim*‡	*Adacel*§	*Boostrix*§
Tetanus toxoid	40 IU	40 IU	40 IU	40 IU	20 IU	20 IU
Diphtheria toxoid	30 IU	20 IU	30 IU	30 IU	2 IU	2 IU
Acellular pertussis						
Pertussis toxoid (PT)	25 µg	25 µg	25 µg	25 µg	2.5 µg	8 µg
Filamentous hemagglutinin (FHA)	25 µg	25 µg	25 µg	25 µg	5 µg	8 µg
Pertactin (PRN)	8 µg	–	–		3 µg + 5 µg FIM 2 and 3	2.5 µg

*Combination of DTaP, IPV, Hib, and hepatitis B
†Combination of DTaP, IPV and Hib
‡Combination of DTaP and IPV
§Tdap vaccine
(DTaP: diphtheria, tetanus, acellular pertussis; IPV: inactivated polio vaccine; Hib: *Haemophilus influenzae* type b; Tdap: tetanus toxoid and reduced quantity diphtheria and acellular pertussis)

Recommendations for Use

The vaccines should be stored at 2–8°C and the recommended dose is 0.5 mL intramuscularly. 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 wP vaccines unlike popular belief. 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.

Recent Outbreaks of Pertussis and Choice of Whole Cell Pertussis versus Acellular Pertussis Vaccines

Since 2009, large outbreaks of pertussis are regularly reported from many countries like USA, UK, Australia, Chile, Brazil, Colombia, Pakistan, etc. employing both aP and wP vaccines despite having very high-vaccination coverage.[9] Reasons for the resurgence of pertussis were found to be complex and varied by country. Waning of protective immunity is noted with both wP and aP vaccines, and

also after acquisition of immunity after natural infection. The shorter duration of protection and probable lower impact of aP vaccines on infection and transmission are likely to play critical roles.[9] Whereas little is known about the duration of protection following aP vaccination in developing countries, many studies in industrialized world documented faster waning with aP vaccines and showed that protection waned after 4–12 years.[11,14-17]

The factors that have probably contributed to the increasing numbers of recorded cases include higher disease awareness, improved surveillance sensitivity, and the enhanced diagnostic sensitivity of the now widely used polymerase chain reaction (PCR).[9] World Health Organization (WHO) analyzed the epidemiology data from 19 countries with high-vaccine coverage with history of good disease control. True resurgence was seen only in five countries, four using aP vaccines (Australia, Portugal, USA, and UK) and one using wP vaccine (Chile).[18] In Australia, the 18th month booster dose of DTaP was dropped in 2003 which was followed by resurgence in 2008-2012. In Portugal, 6 years after aP introduction, there was increased incidence in infants <1 year suggesting true resurgence, though changes potentially magnified by increased PCR testing. In England and Wales, increased incidence was noted in infants <3 months (too young to be vaccinated). Data from the US suggest waning of immunity following aP vaccine. In Chile, the resurgence of pertussis observed in 2011 and 2012 was preceded by a drop in vaccine coverage in under 4 year olds (from 91.3% in 2005 to 77.0% in 2011). There are many countries (Norway, Finland, Denmark, and Sweden) using aP vaccines for the last 10–20 years in their national program with good control of pertussis and no evidence of resurgence. There are some countries (e.g. Brazil and Columbia) using wP with consistently high-vaccination coverage and recent increase in pertussis incidence. This may be attributed to the changes in the surveillance system and the natural cyclic disease trends.[9]

Several randomized trials conducted in the 1990s to document efficacy of aP vaccines also compared their efficacy with wP vaccines. Studies to date indicate that aP vaccines are more effective than low-efficacy wP vaccines, but may be less effective than the highest-efficacy wP vaccines. At least five trials found that wP vaccines had

greater efficacy than aP vaccines.[7] Many later trials have also hinted that the efficacy of the aP vaccine may not be as robust as reported in the initial studies.[19-21] Studies after the outbreaks in US, UK, and Australia have now concluded that the change from wP to aP vaccines contributed to the increase in pertussis cases.[22-24] Recent data from US and Australia have suggested reduced durability of vaccine-induced immunity after the aP vaccination in comparison of wP vaccines.[11,17] These findings suggest that priming with wP is more effective at sustained prevention of pertussis disease than aP vaccines. Witt and colleagues, after reviewing data from the Kaiser Permanente, North California, concluded that "a wholly acellular pertussis vaccine series was significantly less effective and durable than one that contains at least one dose of the traditional whole cell vaccine."[25]

The current evidence is tilted in favor of wP vaccines as far as effectiveness of the pertussis vaccines is concerned.[7] However, the industrialized world would not take the risk of reverting to wP vaccines considering the low acceptance of these vaccines by the public in the past.[7] **Table 2** summarizes a few key differences in different attributes related to wP and aP vaccines.

Tetanus Toxoid and Reduced Quantity Diphtheria and Acellular Pertussis Vaccine

Vaccination of Adolescents and Adults

Pertussis in adolescents and adults is responsible for considerable morbidity in these age groups and also serves as a reservoir for disease transmission to unvaccinated or partially vaccinated young infants.[7] Pertussis is increasingly reported from older children, adolescents, and adults. According to one serological study from US, 21% (95% CI, 13–32%) of adults with prolonged cough had pertussis.[26] The pertussis burden is believed to be substantially more than the number of reported cases; approximately 600,000 cases are estimated to occur annually just among adults.[27] 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.[7]

TABLE 2: Comparative evaluation of whole-cell pertussis (wP) and acellular pertussis (aP) vaccines in terms of different attributes.

Characteristics	*wP vaccines*	*aP vaccines*
Mechanism of action	Th-1 bias	Th-2 bias
Correlate of protection	Not known	Not known
Animal model (for potency)	Known	Not known
Immunogenicity data (India)	Available	Available
Efficacy (global)	Variable data	Robust data
Efficacy (India)	No trial	No trial
Effectiveness (global)	Well established	Not established universally
Effectiveness (India)	Established	No data
Priming	Superior	Inferior
Duration of protection/ waning	Longer	Shorter
Herd effect	Documented	No herd effect
Minor adverse effects	1 episode in 2–10 injections	Equal to control
Serious adverse effects	Very rare	Very rare (at par with wP)
Acceptance (global)	Poor	Good
Acceptance (India)	Good (no documentation of resistance)	Good

Objectives and rationale of adolescents and adult pertussis vaccination: There are two main objectives—first, to protect vaccinated persons against pertussis, and second, to reduce the reservoir of pertussis in the population at large and thereby potentially decreases exposure of persons at increased risk for complicated infection (e.g. infants).[7] There is a definite need of protecting very young infants not covered by current vaccination recommendations by vaccinating adults and close contacts (cocooning).

Vaccines

Immunity against pertussis following primary or booster DTwP/ DTaP vaccination wanes over the next 6–12 years. 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 (Tdap) vaccine instead of tetanus and diphtheria (Td). The standard strength DTwP and DTaP vaccines cannot be used for vaccination of children 7 years and above due to increased reactogenicity.

Table 1 provides details of available Tdap vaccines in India. The vaccine should be stored between 2°C and 8°C, must not be frozen. The dose is 0.5 mL intramuscularly (IM). Immunogenicity studies have shown that antibody response to a single dose of Tdap booster in previously vaccinated children/adolescents is similar to that following three doses of full strength DTwP or DTaP vaccines. Vaccine efficacy against clinical disease exceeds 90%. The most common side effect with Tdap is pain at the local injection site in about 70% of vaccines, 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.

Global Experience with Tdap

Several developed countries have instituted routine booster immunization of adolescents and adults with Tdap instead of Td in their national immunization programs.[9] The Indian Academy of Pediatrics (IAP) has also recommended only a single one-time dose of Tdap to adolescents aged 10–12 years of age.[7] The Center for Disease Control and Prevention-Advisory Committee on Immunization Practices (CDC-ACIP) recommended routine administration of Tdap booster for adolescents in 2005, the vaccine coverage still remains low, with only 56% of adolescents and 8.2% of adults vaccinated in 2012.[28] There is no data on the coverage of Tdap in adolescents and adults in India since it is being used exclusively in private health sector.

Efficacy and Effectiveness of Tdap

Wei et al. evaluated effectiveness of Tdap booster among adolescents in the Virgin Islands in 2007, and found effectiveness of 61.3%

(95% CI: −52.5–90.2) and 68.3% (95% CI: −126.4–95.6) against probable and laboratory-confirmed pertussis, respectively.[21] A recent unpublished trial reported that Tdap was modestly effective [vaccine effectiveness: 55.2% (95% CI: 44.1–64.1%, p <0.001)] at preventing PCR-confirmed pertussis among Kaiser Permanente Northern California (KPNC) adolescents and adults. According to ACIP data presented in February 2013 meeting, the Tdap effectiveness was noticed ranging from 66% to 78% in field observational studies. The preliminary data suggest effectiveness wanes within 3–4 years among aP vaccine recipients and there was no evidence of herd immunity.[7]

MATERNAL IMMUNIZATION TO PREVENT INFANT PERTUSSIS

Immunization of adolescents and adults, and postpartum administration of Tdap failed to have appreciable impact on laboratory-confirmed pertussis in very young infants.[7] Several strategies like maternal immunization including pregnant women, cocooning and neonatal immunization have been proposed to reduce the burden of pertussis in those infants too young to have been immunized. Among all these strategies, immunization during pregnancy appears to be most effective strategy to have the most impact on infantile pertussis, especially during the first few weeks after birth. The effective transplacental transmission of maternal pertussis antibodies would protect the infant against pertussis during the first months of life. Though the transplacentally acquired antibodies may be detectable at least up to first few weeks of life (at 6–8 weeks), the age at which the first pertussis-containing vaccine is due, however, the concentration of antibodies required for protection against pertussis in newborns is not known.[7] In 2011, the ACIP recommended a dose of Tdap to all pregnant women after 20 weeks of gestation to provide protection for both the mother and her newborn during the infant's earliest weeks of life.[29]

Safety of Tdap during pregnancy: There are limited safety data on Tdap administration in pregnant women; however, existing Tdap safety data from the CDC, United States Food and Drug Administration (US FDA), and the pharmaceutical pregnancy registries do not indicate

any adverse safety effect.[30] Even 3–6 doses of wP vaccines were administered during single pregnancy in five different clinical trials conducted in US and no serious untoward local or systemic reactions were noted.[31]

There are a few concerns regarding maternal immunization, they include ultimate titters achieved with a dose of Tdap during pregnancy, the duration of maternal antibodies, and finally, the interference with proper take of pertussis vaccines during primary immunization due to high concentrations of maternal antibodies.[7] However, a recent study demonstrated that infants whose mothers had received Tdap vaccine during pregnancy had higher pertussis antibody concentrations between birth and the first vaccine dose than the cohort whose mothers did not receive the vaccine. There was some blunting of the response to the infant series; but the children did develop adequate antibodies by the end of the complete series.[32] The antibody titer to PT in acellular vaccine was, however, not affected by the prevaccination antibody levels. Further studies are needed to evaluate the impact of maternal antibody levels to primary immunization in young children, if maternal Tdap is to be routinely used where infants receive wP vaccines in the primary series.[14]

The results of this study are quite reassuring and add evidence to support the recommendation of vaccinating pregnant mothers to protect their children against pertussis.

CURRENT STATUS OF PERTUSSIS VACCINATION IN INDIA

Pertussis continues to be a serious public health problem in India. India is employing only wP vaccines in their national immunization program since the adoption of EPI in 1978. Though aP vaccines are also licensed and available, they are mainly prescribed by the private sector and coverage is still miniscule. Private health sector is responsible for offering vaccination to only 9% of the population in India.[1] Though the coverage of DTwP vaccine in India has increased,[1] there is poor documentation of large-scale outbreaks of pertussis in the country unlike the recent large-scale outbreaks reported in many developed countries. Either many large-scale outbreaks are totally ignored and go unreported or wP vaccines are providing adequate protection. There

are two scenarios of pertussis epidemiology in a given population based on coverage of pertussis vaccine. Since the overall coverage is not very high, pertussis in major parts of the country continues mainly to be a problem of young children. However, many states having very good immunization rates behave like developed countries with high coverage in pediatric age group with resultant more frequent disease in adolescents and adults.[7] Regarding the safety of wP vaccines, there is still no report of higher rates of serious adverse event following immunizations (AEFIs), and public acceptance of the vaccine is still not a serious concern.[7]

INDIAN ACADEMY OF PEDIATRICS RECOMMENDATIONS ON PERTUSSIS VACCINATION

Public Health Perspectives

Pertussis is a highly prevalent pediatric illness having significant morbidity and mortality in the country. There is an urgent need of an effective surveillance to evaluate both the burden of infection and the impact of immunization. The current status of pertussis immunization, in the form of DTwP vaccination is still suboptimal in many states.[1]

The Advisory Committee on Vaccines and Immunization Practices (ACVIP) unambiguously supports the current immunization policy of employing only wP vaccines (in the form of DTwP) in UIP because of its proven efficacy, safety, adequate public acceptance, and absence of documentation of significant waning. There is insufficient marginal benefit to consider changing from wP-containing vaccine to aP-containing vaccine.[7]

Individual Use

Since there is scarcity of data on vaccine efficacies of both wP and aP vaccines in India and other developing countries, most of the recommendations of the academy in regard to pertussis vaccination are based on the experience gained and data obtained from the use of these vaccines in industrialized countries. However, the continuous decline in reported pertussis cases in last few decades has demonstrated good effectiveness of wP vaccine (of whatever quality) in India. There is no data on the effectiveness of aP vaccines in India.

Protection against severe pertussis in infants and early childhood can be obtained with primary series of either wP or aP vaccine.[9]

Indian Academy of Pediatrics has now issued following recommendations on use of pertussis vaccines for office-practice in private health sector:

Primary immunization: The primary infant series should ideally be completed with three doses of vaccines. Goal is to achieve early and timely vaccination initiated at 6 weeks and no later than 8 weeks of age, and achieve high coverage (≥90%) with at least three doses of assured quality pertussis vaccine at all levels (national and subnational).

There is scarcity of data on comparative safety, immunogenicity, and efficacy of individual wP vaccines produced in various countries. Similarly, there is no data on either the efficacy of individual wP product or comparative evaluation of different available wP combinations in the Indian market. A few brands in India have achieved WHO prequalification, but not all the products have uniformly attained it. IAP urges the Government of India (GoI) to undertake studies on the quality of available wP and aP vaccines in Indian market. The National Regulatory Authority (NRA) must set indigenous national guidelines to manufacture and market different pertussis vaccines in the country.

The previous recommendation on the exclusive use of wP vaccine in primary immunization series is based on the following reasons:

- There is no data on the efficacy or effectiveness of aP vaccines in India and almost all the recommendations are based on the performance of these vaccines in industrialized countries. However, many of these countries have now reported upsurge and frequent outbreaks of the disease despite using highest quality aP vaccines with a very high coverage (close to 100%) since mid-1990s **(Fig. 1)**.
- The aP-containing combinations were licensed in India on the basis of immunogenicity studies only. However, in the absence of any known correlate of protection for aP vaccines, mere presence of antibodies cannot be relied as a surrogate for efficacy or protection.

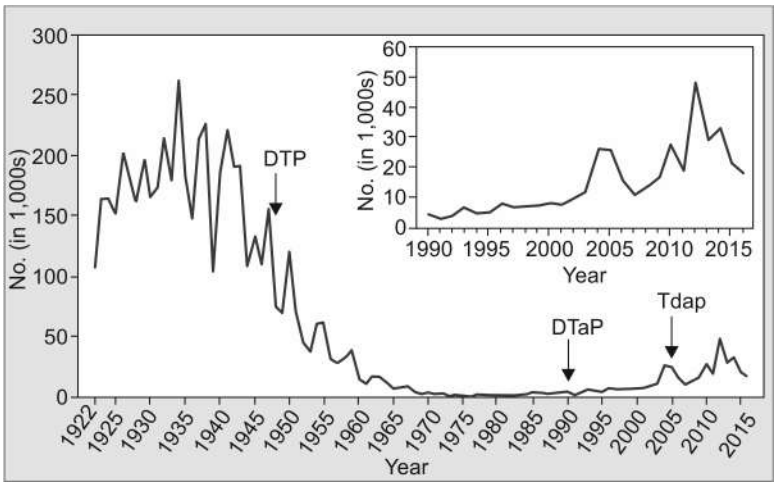


Fig. 1: Epidemiology of pertussis in relation to introduction of pertussis vaccines in the USA.
Source: Centers for Disease Control and Prevention (CDC)

- The studies from USA, Australia, and other industrialized countries post-2009 outbreaks have demonstrated superior priming with wP vaccines and more durability of immunity following wP vaccination than aP vaccines.
- There is strong evidence of effectiveness, real-life performance of wP vaccines from India where the widespread use of them have markedly reduced the incidence of pertussis after the launch of UIP. We have achieved a good control of pertussis (high effectiveness, not merely the efficacy) with whatever type of wP was available in the country despite with a modest coverage of around 60–70%.
- World over, the widespread use of wP vaccines had almost eliminated pertussis from almost all the countries that had employed them.

However, none of these countries are planning to revert back to whole-cell pertussis vaccines as that can result in an increase in the prevalence of the disease due to poor acceptance of a vaccine that is much more reactogenic WHO clearly mentions that countries currently using the wP vaccine in their national programs should continue the same for the primary series, while those using the aP

vaccine should continue the same and consider additional boosters and strategies such as immunization of mothers in case of pertussis resurgence.

ACVIP currently recommends that the primary series should be completed with three doses of either wP or aP vaccines, irrespective of the number of components. wP vaccine is definitely superior to aP vaccine in terms of immunogenicity and duration of protection but more reactogenic. In view of parental anxiety and concerns for its reactogenicity, aP vaccine can also be administered even in the primary series. The primary aim is to increase the vaccination coverage with either of the vaccines. DTaP containing combination vaccines are in use in developed countries with a great success. A hexavalent vaccine with whole cell pertussis component is also available in market which is having very limited data.

However, the aP vaccines may be preferred to wP vaccines in those children with history of severe adverse effects after previous dose/s of wP vaccines, children with progressive neurologic disorders, if resources permit. There is no evidence of superiority for any aP vaccines based on number of components. The schedule is same as with wP (DTwP) vaccines. Like DTwP vaccines, DTaP vaccines must not be used in children 7 years or older because of increased reactogenicity. The contraindications are the same for both the vaccines.

Boosters: The first and second booster doses of pertussis vaccines should also be of wP vaccine. However, considering a higher reactogenicity, aP vaccine/combination **(Table 1)** can be considered for the boosters, if resources permit.

Administration and schedule: The standard dose of pertussis vaccine is 0.5 mL; this is administered intramuscularly in the anterolateral thigh of children aged <12 months and in the deltoid muscle in older age groups. The standard primary vaccination schedule is three primary doses at 6, 10, and 14 weeks and two boosters at 15–18 months and 4–5 years. Early completion of primary immunization is desirable as there is no effective maternal antibody for protection against pertussis. The booster should be given ≥6 months after the last primary dose. The last dose of the recommended primary series should be completed

by the age of 6 months. All infants, including those who are human immunodeficiency virus (HIV)-positive, should be immunized against pertussis.

Schedule for catch up vaccination: Three doses at 0, 1, and 6 months interval should be offered. The second childhood booster is not required if the last dose has been given beyond the age of 4 years. It is essential to immunize even those recovering from pertussis as natural disease does not offer complete protection.

Recommendations for adolescents and adults: Immunity against pertussis following primary or booster wP or aP vaccination wanes over the next 4–12 years. The Academy therefore recommends offering Tdap vaccine instead of Td or TT vaccine to all children or adolescents or adults who can afford to use the vaccine in the schedule discussed below:

- 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.
- Persons aged 7 years through 10 years who are not fully immunized with the childhood DTwP/DTaP vaccine series, should receive Tdap vaccine as the first dose in the catch-up series; if additional doses are needed, Td vaccine should be used. For these children, an adolescent Tdap vaccine is not required.
- 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.
- Tetanus toxoid, and reduced quantity diphtheria and acellular pertussis can now be given regardless of time elapsed since the last vaccine containing TT or diphtheria toxoid.
- There is no data at present to support repeat doses of Tdap.
- Indian Academy of Pediatrics recommends decennial Td booster for those who have received one dose of Tdap (5 years for wound management).

Only aP-containing vaccines should be used for vaccination in those aged >7 years.

Tetanus toxoid, and reduced quantity diphtheria and acellular pertussis during pregnancy: Maternal immunization, particularly of pregnant

women may be an effective approach to protect very young infants and neonates. IAP therefore now suggests immunization of pregnant women with a single dose of Tdap during the third trimester (preferred during 27 weeks through 36 weeks of gestation) regardless of number of years from prior Td or Tdap vaccination. Tdap has to be repeated in every pregnancy irrespective of the status of previous immunization (with Tdap). Even if an adolescent girl who had received Tdap 1 year prior to becoming pregnant will have to take it since there is rapid waning of immunity following pertussis immunization.

Interchangeability of brands: In principle, the same type of wP-containing or aP-containing vaccines should be given throughout the primary course of vaccination. However, if the previous type of vaccine is unknown or unavailable, any wP vaccine or aP vaccine may be used for subsequent doses, as it is unlikely to interfere with the safety or immunogenicity of these vaccines.[9]

TETANUS AND DIPHTHERIA VACCINE

Background

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

Studies show that diphtheria antibody levels decline over time resulting in increasing susceptibility of adolescents and adults to diphtheria. For diphtheria, the average duration of protection is about 10 years following a primary series of three doses of diphtheria toxoid.[33] Considering the current epidemiology of diphtheria in India (i.e. low-endemic), a booster against diphtheria is desirable, but not mandatory. Boosting at the age of 12 months, at school entry, and just before leaving school are all possible options.[33] 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.

Vaccine

Tetanus and diphtheria contains 5 Lf of TT and only two units of diphtheria toxoid, is stored at 2–8°C and is administered intramuscularly in a dose of 0.5 mL.[34] 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 (swollen limbs and Arthus type 2 reactions).

Recommendations for Use

This vaccine is indicated as replacement for DTwP/DTaP/DT for catch-up vaccination in those aged above 7 years (along with Tdap), and as replacement for TT in all situations where TT was previously recommended. In individuals who have completed primary and booster vaccination with DTwP/DTaP, Td boosters every 10 years provide sufficient protection.[35]

Tdap/Td in Pregnancy

WHO has evolved exhaustive guidelines for administration of Tdap/Td in pregnant women.[34]

- *Unimmunized*: For pregnant women who have not been previously immunized, one dose of Tdap/Td and another dose of Td at least 1 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 Td should be administered 1 month later and at least 2 weeks before delivery. A single dose of Tdap/Td should be administered in each subsequent pregnancy.
- *Fully immunized*: Five childhood doses (three primary doses plus two boosters) and one adolescent booster Tdap: one dose of Tdap is necessary in every pregnancy.

Tdap/Td in Wound Management

All patients presenting with skin wounds or infections should be evaluated for tetanus prophylaxis. Cleaning of the wound, removal of devitalized tissue, irrigation, and drainage are important to

TABLE 3: Tetanus prophylaxis in wound management.

	Doses of IT	*Clean and minor wounds*	*All other wounds*	*Given in past*
	Td/Tdap	TIG*	Td/Tdap	TIG*
Unknown, <3 doses, and immunodeficient	Yes	Yes	Yes	Yes
≥3 doses	No†	No	No‡	No

Including, but not limited to, wounds contaminated with dirt, feces, soil, and 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

prevent anaerobic environment which is conducive to tetanus toxin production. The indications for Tdap/Td and tetanus immunoglobulin (TIG) are as below **(Table 3)**.

Evidence suggests that tetanus is highly unlikely in individuals who have received three 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 tetanus toxoid-containing vaccine (DTwP/DTaP/Tdap/Td) at 0, 1, and 6 months depending on the age of the child and nature of previous doses received for more comprehensive protection. For partially immunized children, catch-up vaccination entails administration of at least three doses of tetanus toxoid-containing vaccine including previous doses received. Children with unknown or undocumented history should be treated as unimmunized.

DT VACCINE

This vaccine comprises diphtheria and tetanus toxoid in similar amounts as in DTwP/DTaP, should be stored at 2–8°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 **(Boxes 1 and 2)**.

BOX 1: Diphtheria and tetanus toxoids and pertussis (DTP) vaccine.

Routine vaccination:

- Recommended schedule: Three primary doses at 6, 10, and 14 weeks and two boosters at 15–18 months and 4–5 years
- Minimum age: 6 weeks
- The first booster (4th dose) may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose
- DTaP or DTwP vaccine/combination may be used for the primary immunization series
- DTaP may be preferred to DTwP in children with history of severe adverse effects after previous dose/s of DTwP or children with neurologic disorders.
- First and second boosters may also be of DTwP. However, considering a higher reactogenicity, DTaP can be considered for the boosters

Catch-up vaccination:

- Catch-up schedule: The second childhood booster is not required if the last dose has been given beyond the age of 4 years
- Catch up below 7 years: DTwP/DTaP at 0, 1, and 6 months
- Catch up above 7 years: Tdap, Td, and Td at 0, 1, and 6 months

BOX 2: Tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine.

Routine vaccination:

- Recommended schedule: One dose of Tdap to all adolescents aged 11 years through 12 years
- Minimum age: 7 years (Adacel® is approved for 11–64 years by ACIP and 4–64 years old by FDA, while Boostrix® is approved for 10 years and older by ACIP and 4 years of age and older by FDA in US)
- Tdap during pregnancy: One dose of Tdap vaccine to pregnant mothers/adolescents during each pregnancy (preferred during 27 weeks through 36 weeks of gestation) regardless of number of years from prior Td or Tdap vaccination

Catch-up vaccination:

- Catch up above 7 years: Tdap, Td, Td at 0, 1, and 6 months
- Persons aged 7 years through 10 years who are not fully immunized with the childhood DTwP/DTaP vaccine series, should receive Tdap vaccine as the first dose in the catch-up series; if additional doses are needed, use Td vaccine. For these children, an adolescent Tdap vaccine should not be given
- Persons aged 11 years through 18 years who have not received Tdap vaccine should receive a dose followed by tetanus and diphtheria toxoids (Td) booster doses every 10 years thereafter
- Tdap vaccine can be administered regardless of the interval since the last tetanus and diphtheria toxoid-containing vaccine

REFERENCES

1. WHO and UNICEF (2018). WHO and UNICEF estimates of immunization coverage: 2017 revision [online]. Available from: http://www.who.int/immunization/monitoring_surveillance/data/ind.pdf. [Last Accessed October 2019]
2. Singhal T, Lodha R, Kapil A, et al. Diphtheria—down but not out. Indian Pediatr. 2000;37:728-37.
3. Patel UV, Patel BH, Bhavsar BS, et al. A retrospective study of diphtheria cases, Rajkot, Gujarat. Indian J Comm Med. 2004;24:161-3.
4. Khan N, Shastri J, Aigal U, et al. Resurgence of diphtheria in the vaccination era. Indian J Med Microbiol. 2007;25:434-37.
5. Central Bureau of Health Intelligence (2018) National Health Profile (NHP) of India 2018. [online] Available from: http://cbhidghs.nic.in/WriteReadData/1892s/Chapter%203.pdf. [Last Accessed October 2019]
6. WHO (2019). WHO Vaccine-Preventable Diseases: Monitoring System 2018 Global Summary [online]. Available from: http://apps.who.int/immunization_monitoring/globalsummary/countries?countrycriteria%5Bcountry%5D%5B%5D=IND&commit=OK. [Last Accessed October 2019]
7. Vashishtha VM, Bansal CP, Gupta SG. Pertussis vaccines: Position paper of Indian Academy of Pediatrics (IAP). Indian Pediatr. 2013;50:1001-9.
8. Jefferson T, Rudin M, DiPietrantonj C. Systematic review of the effects of pertussis vaccines in children. Vaccine. 2003;21:2003-14.
9. WHO. Pertussis vaccines: WHO position paper. August 2015. Wkly Epidemiol Rec. 2015;90:433-60.
10. WHO. Guidelines for the production and control of the acellular pertussis component of monovalent or combined vaccines. WHO Technical Report Series No. 878, 1998. Available from: http://www.who.int/biologicals/publications/trs/areas/vaccines/acellular_pertussis/WHO_TRS_878_ A2.pdf.
11. Misegades LK, Winter K, Harriman K, et al. Association of childhood pertussis with receipt of 5 doses of pertussis vaccine by time since last vaccine dose, California, 2010. JAMA. 2012;308: 2126-32.
12. Zhang L, Prietsch SO, Axelsson I, et al. Acellular vaccines for preventing whooping cough in children. Cochrane Database Syst Rev. 2012;3: CD001478.
13. Kendrick PL, Eldering G, Dixon MK, et al. Mouse protection tests in the study of pertussis vaccine; a comparative series using the intracerebral route for challenge. Am J Public Health Nations Health. 1947;37: 803-10.

14. Edwards KM, Decker MD. Pertussis Vaccines. In: Plotkin SA, Orenstein WA, Offit P, Edwards KM (Eds). Plotkin's Vaccines, 7th edition. Netherlands: Elsevier; 2018. pp. 711-61.
15. Klein NP, Bartlett J, Rowhani-Rahbar A, et al. Waning protection after fifth dose of acellular pertussis vaccine in children. N Engl J Med. 2012;367:1012-9.
16. Wendelboe AM, Van Rie A, Salmaso S, et al. Duration of immunity against pertussis after natural infection or vaccination. Pediatr Infect Dis J. 2005;24:S58-61.
17. Witt MA, Katz PH, Witt DJ. Unexpectedly limited durability of immunity following acellular pertussis vaccination in preadolescents in a North American outbreak. Clin Infect Dis. 2012;54:1730-35.
18. WHO (2014). SAGE pertussis working group. Background paper. SAGE April 2014. Available from: http://www.who.int/immunization/sage/meetings/2014/april/1_Pertussis_background_FINAL4_web.pda?ua=. [Last Accessed October 2019]
19. Rendi-Wagner P, Kundi M, Mikolasek A, et al. Hospital-based active surveillance of childhood pertussis in Austria from 1996 to 2003: estimates of incidence and vaccine effectiveness of whole-cell and acellular vaccine. Vaccine. 2006;24:5960-5.
20. Lacombe K, Yam A, Simondon K, et al. Risk factors for acellular and whole-cell pertussis vaccine failure in Senegalese children. Vaccine. 2004;23:623-8.
21. Wei SC, Tatti K, Cushing K, et al. Effectiveness of adolescent and adult tetanus, reduced-dose diphtheria, and acellular pertussis vaccine against pertussis. Clin Infect Dis. 2010;51:315-21.
22. Witt MA, Arias L, Katz PH, et al. Reduced risk of pertussis among persons ever vaccinated with whole cell pertussis vaccine compared to recipients of acellular pertussis vaccines in a large US cohort. Clin Infect Dis. 2013;56:1248-54.
23. Sheridan SL, Ware RS, Grimwood K, et al. Number and order of whole cell pertussis vaccines in infancy and disease protection. JAMA. 2012;308:454-6.
24. Liko J, Robinson SG, Cieslak PR. Priming with whole-cell versus acellular pertussis vaccine. N Engl J Med. 2013;368:581-2.
25. Witt MA, Arias L, Katz PH, et al. Reduced risk of pertussis among persons ever vaccinated with whole cell pertussis vaccine compared to recipients of acellular pertussis vaccine in a large US cohort. Clin Infect Dis. 2013;561:1248-54.
26. Wright SW, Edwards KM, Decker MD, et al. Pertussis infection in adults with persistent cough. JAMA.1995;273:1044-6.
27. CDC (2006). Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis

vaccine [online] Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5517a1.htm. [Last Accessed October 2019]
28. Stokley S, Cohn A, Dorell C, et al. Adolescent vaccination-coverage levels in the United States: 2006–2009. Pediatrics. 2011;128:1078-86.
29. CDC. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) in pregnant women and persons who have or anticipate having close contact with an infant aged <12 months—Advisory Committee on Immunization Practices (ACIP), 2011. Morb. Mortal. Weekly Rep. 2011;60:1424-6.
30. Gall SA, Myers J, Pichichero M. Maternal immunization with tetanus-diphtheria-pertussis vaccine: effect on maternal and neonatal serum antibody levels. Am J Obstet Gynecol. 2011;204:334.e1-5.
31. CDC. Prevention of pertussis, tetanus and diphtheria among pregnant and postpartum women and their infants. Morbidity and Mortality Weekly Report. Recomm.d Rep. 2008;57:1-51.
32. Hardy-Fairbanks AJ, Pan SJ, Decker MD, et al. Immune Responses in Infants Whose Mothers received Tdap vaccine during pregnancy. Pediatr Infect Dis J. 2013;32(11):1257-60.
33. WHO. Diphtheria vaccine: WHO position paper. Weekly Epidemiol Rec. 2017;92:417-36.
34. WHO. Tetanus vaccines: WHO position paper. Weekly Epidemiological Rec. 2006;81:196-207.
35. CDC (2011). Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis (Tdap) Vaccine from the Advisory Committee on Immunization Practices, 2010 [online]. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6001a4.htm. [Last Accessed October 2019]

3.5 *HAEMOPHILUS INFLUENZAE* TYPE B CONJUGATE VACCINES

Shivananda S

BACKGROUND

Capsulated *Haemophilus 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 before natural protective immunity is acquired by the age of 3–4 years. Noncapsulated Hib disease causing bronchitis, otitis media, sinusitis, and pneumonia is not amenable to prevention at present and can occur at all ages. Data from the Invasive Bacterial Infections Surveillance (IBIS) Group from six referral hospitals in India show that Hib is a common cause of pneumonia and meningitis in India.[1]

GLOBAL BURDEN OF Hib DISEASE

In spite of the availability of an effective vaccine against Hib for more than a decade, Hib continues to be a leading cause of mortality and morbidity worldwide, especially in developing countries. Globally, in 2010, there were estimated 120 million episodes of pneumonia in children younger than 5 years and of these 14 million progressed to severe episodes. 1.3 million episodes of pneumonia led to death and 81% of deaths occurred in the first 2 years of life.[2]

Global estimates of burden of disease caused by Hib in children younger than 5 years suggest that Hib caused about 8.13 million serious illnesses worldwide in 2000 (uncertainty range 7.33–13.2 million) and estimated that Hib caused 371,000 deaths (2,47,000–5,27,000) in children aged 1–59 months.[3] In prospective, microbiology-based studies in childhood pneumonia, the second most common organism isolated in most studies is Hib (10–30%).[4]

In unvaccinated populations, Hib is the dominant cause of nonepidemic bacterial meningitis during the first year of life. Even with prompt and adequate antibiotic treatment, 3–20% of patients

with Hib meningitis die. Where medical resources are limited, fatality rates for Hib meningitis may be much higher, and severe neurological sequelae are frequently observed in survivors (in up to 30–40%).[5]

Hib BURDEN IN INDIA

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 a large proportion of pneumonia may be nonbacteremic. During 1993–1997, a prospective surveillance was conducted in 5,798 patients aged 1 month to 50 years who had diseases likely to be caused by *H. influenzae*. Out of a total of 125 *H. influenzae* infections detected, 97% of which were caused by Hib, 108 (86%) isolates were from children aged <5 years. The clinical spectrum of these children included meningitis (70%), pneumonia (18%), and septicemia (5%). The case-fatality rate was 11% overall and 20% in infants with Hib meningitis.[1] In 1995, Bahl et al.[6] 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. Another hospital-based study conducted in Delhi by Patwari et al.,[7] in 1996, found 15% of 132 children <12 years suffered from pneumonia due to Hib.

In a later cohort study of 17,951 children aged 0–18 months enrolled from July 2005 to December 2006, the cohort population presented with 227, 231, and 131 events of suspected pneumonia and 164, 72 and 89 events of suspected meningitis at study hospitals at Chandigarh, Kolkata and Vellore, respectively. Amongst hospitalized patients 8–30% children had purulent meningitis and Hib was detected in 20–29 % of cases by culture or latex agglutination test (LAT). Case fatality of pneumonia ranged from 0.77% to 2.35% and that of meningitis ranged from 2.68% to 4.71 % at these study centers.[8]

The World Health Organization (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 is due to pneumonia. These statistics coupled with the evidence of large number of Hib pneumonia brought out in the above studies highlight the urgency to take effective measures against Hib disease in India.

VACCINES

All Hib vaccines are conjugated vaccines where the Hib capsular polysaccharide (polyribosylribitol 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. diphtheriae* toxin protein), PRP-OMP (carrier *Neisseria meningitidis* protein outer membrane protein 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 three doses of HbOC and PRP-T are recommended for primary vaccination, only two 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 2–8°C and the recommended dose is 0.5 mL intramuscularly.

Serologic Correlate of Protection and Efficacy

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 1 μg/mL. Indirect protection to the unimmunized susceptible children as a result of diminished Hib transmission (~50% of children exhibited anti-PRP titers ≥5 μg/mL; a level that impedes Hib upper respiratory carriage) has also been observed while conducting serological assessment of the Hib immunization program in Mali.[9]

Effectiveness

Developed countries where the vaccine was introduced for universal immunization have witnessed virtual elimination of 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 1990s. Most of the cases of invasive Hib disease occurred in the late second year of life. The major factor responsible for this phenomenon was omission of the second year booster.

Waning of Immunity and Need of Boosters

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 recognized now that immunological memory is insufficient for protection against Hib disease. Hence, a booster dose is mandatory for sustained protection. Primary immunization with either pentavalent vaccine is reported to induce an excellent immunity lasting till the second year of life. A booster dose with DTwP-Hib vaccine effectuated a good anamnestic response to all vaccine components, being especially strong for Hib in children previously vaccinated with pentavalent vaccine.[10]

Safety

Side effects are mild and usually local. The committee reviewed the postmarketing surveillance data on the safety of Hib and Hib containing combination vaccines in India and found a total of 98 (46 serious and 49 nonserious) adverse event following immunization (AEFI) episodes for 53.51 million doses (overall frequency 1.83/million doses, and for serious AEFI 0.85/million) from October 2004 through December 2011, suggesting that there was no safety concern of Hib vaccines as reported frequently in lay media. The committee strongly supports the Government of India's (GOI's) efforts to introduce this vaccine in all the states in the country.[11]

RECOMMENDATIONS FOR USE

Public Health Perspective

The Indian Academy of Pediatrics (IAP) Advisory Committee on Vaccines and Immunization Practices (ACVIP) recommends offering the Hib vaccine to all children. Hib conjugate vaccines

were recommended by IAP in early 2000s, introduced in private sector without much debate on safety issues, except for questions pertaining to its high cost.[12] 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-effectiveness. 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 Universal Immunization Program (UIP). In India pentavalent vaccine (Pentavac by M/s Serum Institute of India) was introduced in Kerala and Tamil Nadu in 2011 and later extended to the states of Goa, Pondicherry, Karnataka, Haryana, Jammu and Kashmir, Gujarat, and Delhi during the second half of 2012 to the first quarter of 2013. To date, 83 AEFI cases, some of which were associated with fatality, have been reported after vaccine introduction from Kerala, Tamil Nadu, and Jammu and Kashmir. However, a special causality subcommittee formed by the National AEFI Committee examined these instances and concluded that the infant deaths reported from these states were not causally related to pentavalent vaccine. The NTAGI in 2013 recommends scale-up of the pentavalent vaccine to the remaining states of India with simultaneous strengthening of the AEFI and expansion of sentinel surveillance systems. The Academy also endorses the continued use of pentavalent vaccine in the UIP. The IAP members are using these vaccines in their clinical practice for more than a decade. IAP had conducted a scientific study amongst around 1,000 pediatricians and found that more than 80% of them are using this Hib-containing pentavalent vaccine in their clinical practice for more than last 5–15 years. Majority of them had never encountered any serious AEFI, including death.[13]

INDIVIDUAL USE

Indian Academy of Pediatrics ACVIP recommends use of Hib vaccine for all children below the age of 5 years.

SCHEDULE AND DOSES

The vaccination schedule for Hib consists of three doses when initiated below 6 months, two doses between 6 months and 12 months and

1 dose between 12 months and 15 months, with a booster at 16–18 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 or anatomic hyposplenia irrespective of age. Hib vaccines are now used mostly as combination vaccines with DTwP/DTaP/Hep B/inactivated poliomyelitis vaccine (IPV).

CATCH-UP VACCINATION

When infants and children under 5 years of age have missed scheduled vaccine doses or start of Hib vaccination has been delayed, a catch-up schedule should be commenced. **Table 1** is designed to assist in planning a catch-up program.

TABLE 1: Recommended catch-up schedule when start of Hib vaccination has been delayed.

Vaccine	*Trade name*	*Age now*			
		3–6 months	*7–11 months*	*12–14 months*	*15–59 months*
PRP-OMP[1,2]	PedvaxHIB	2 doses, 1–2 months apart and booster at 12 months	2 doses, 1–2 months apart and booster at least 2 months later, at 12–15 months	1 dose, and booster at least 2 months after previous dose[4]	Single dose[3,4]
Hib (PRP-OMP) -hepB	Comvax				
HbOC[3]	HibTITER	3 doses, months apart, and booster at 12 months	2 doses, 2 months apart, and booster at 12 months and at least 2 months after previous dose	1 dose, and booster at 18 months	Single dose[3,4]
PRP-T[3]	Hiberix ActHIB				

[1]Extremely preterm babies (<28 weeks or <1,500 g) who commence catch-up Hib vaccination with PRP-OMP between 3 months and 11 months of age require a three-dose primary series (not two doses). The third dose should be given 1–2 months after the second dose of PRP-OMP. The booster dose should be given at 12 months as usual.
[2]Where possible, use the same brand of Hib vaccine throughout the primary course.
[3]When a booster is given after the age of 15 months, any of the three available conjugate Hib vaccines can be used.
[4]Depending on the combination used, further doses of hepatitis B or IPV are required.

Haemophilus influenzae type B (Hib) conjugate vaccine

Routine vaccination:

- *Minimum age*: 6 weeks.
- Primary series include Hib conjugate vaccine at ages 6, 10, and 14 weeks with a booster at age 12 through 18 months.

Catch-up vaccination:

- Catch-up is recommended till 5 years of age.
- *6–12 months*: Two primary doses 4 weeks apart and one booster.
- *12–15 months*: One primary dose and 1 booster
- *Above 15 months*: Single dose.
- If the first dose was administered at age 7 through 11 months, administer the second dose at least 4 weeks later and a final dose at age 12–18 months at least 8 weeks after the second dose.

REFERENCES

1. Invasive Bacterial Infections Surveillance (IBIS) Group of the International Clinical Epidemiology Network. Are *Haemophilus influenzae* infections a significant problem in India? A prospective study and review. Clin Infect Dis. 2002;34:949-57.
2. Walker CL, Rudan I, Liu L, et al. Global burden of childhood pneumonia and diarrhea. Lancet. 2013;381:1405-16.
3. Watt JP, Wolfson LJ, O'Brien KL, et al. Burden of disease caused by *Haemophilus influenzae* type b in children younger than 5 years: global estimates. Lancet. 2009;374:903-11.
4. Rudan I, Boschi-Pinto C, Biloglav Z, et al. Epidemiology and etiology of childhood pneumonia. Bull World Health Organ. 2008;86:408-16.
5. WHO Position Paper on *Haemophilus influenzae* type b conjugate vaccines. Wkly Epidemiol Rec. 2006;81:445-52.
6. Bahl R, Mishra S, Sharma D, et al. A bacteriological study in hospitalized children with pneumonia. Ann Trop Paediatr. 1995;15(2):173-7.
7. Patwari AK, Bisht S, Srinivasan A, et al. Aetiology of pneumonia in hospitalized children. J Trop Pediatr. 1996;42:15-20.
8. Gupta M, Kumar R, Deb AK, et al. Multi-center surveillance for pneumonia and meningitis among children (<2 year) for Hib vaccine probe trial preparation in India. Indian J Med Res. 2010;131:649-58.
9. Hutter J, Pasetti MF, Sanogo D, et al. Naturally acquired and conjugate vaccine-induced antibody to *Haemophilus influenzae* type b (Hib) polysaccharide in Malian children: Serological assessment of the Hib immunization program in Mali. Am J Trop Med Hyg. 2012;86:1026-31.
10. Sharma H, Yadav S, Lalwani S, et al. Antibody persistence of two pentavalent DTwP-HB-Hib vaccines to the age of 15–18 months, and response to the booster dose of quadrivalent DTwP-Hib vaccine. Vaccine. 2013;31:444-7.

11. Indian Academy of Pediatrics Committee on Immunization. Consensus recommendations on Immunization and IAP Immunization Timetable 2012. Indian Pediatr. 2012;49:549-64.
12. Vashishtha VM. Introduction of Hib containing pentavalent vaccine in national immunization program of India: The concerns and the reality! Indian Pediatr. 2009;46:781-2.
13. Vashishtha VM, Dogra V, Choudhury P, et al. *Haemophilus influenzae* type b disease and vaccination in India: Knowledge, attitude and practices of pediatricians. WHO South East Asia J Public Health. 2013;2:101-5.

3.6 PNEUMOCOCCAL VACCINES

Abhay K Shah

INTRODUCTION

Streptococcus pneumoniae (*Pneumococcus*) is a major cause of morbidity and mortality worldwide. As per the World Health Organization (WHO), pneumococcal disease (PD) is the world's number 1 vaccine-preventable cause of death among infants and children younger than 5 years of age. According to PAHO (Pan American Health Organization), PD causes two deaths every hour among children younger than 5 years of age in the Americas annually. As per WHO, vaccination is the only available tool to prevent PD and *"the recent development of widespread microbial resistance to essential antibiotics underlines the urgent need for more efficient pneumococcal vaccines."*

EPIDEMIOLOGY

Pathogen

Streptococcus pneumoniae is a gram-positive, catalase-negative, facultatively anaerobic organism that grows as a single coccus or as diplococci (identifiable because of their lanceolate shape) and also in chains of variable length. Polysaccharide capsule surrounding the cell wall is responsible for virulence, type specific identification, and stimulation of protective antibody in the host. More than ninety immunologically distinct capsular polysaccharides have been identified (but most clinical cases are caused by relatively few types. The distribution of serotypes that cause disease varies by age, disease syndrome, disease severity, geographic region, and over time.[1] All types are not equally invasive. The composition and quantity of capsular polysaccharide plays roles in virulence, the strain producing the largest amount of polysaccharide is likely to be the most virulent.

Host

The causative agent, *S. pneumoniae*, frequently colonizes the human nasopharynx, and is transmitted mainly through respiratory droplets.

Infants and young children are thought to be the main reservoir of this agent with cross-sectional point prevalences of nasopharyngeal carriage ranging from 27% in developed to 85% in developing countries.[1]

Disease Spectrum

Spectrum of disease ranges from asymptomatic nasopharyngeal carriages, to noninvasive and invasive pneumococcal disease (IPD).

The organism can infect the middle ear, sinuses, and lungs by contiguous spread, causing noninvasive diseases like otitis media, sinusitis, nonbacteremic pneumonia, or can invade the blood stream causing invasive diseases like meningitis, sepsis, and bacteremic pneumonia. Less common PDs include soft tissue infections (such as buccal and periorbital cellulites, erysipelas, glossitis, abscess), pyogenic arthritis, osteomyelitis, primary peritonitis and salpingitis, and endocarditis. Pneumococcal bacteremia in patients with sickle cell disease, congenital asplenia, or post splenectomy causes a rapidly progressive, fulminant course marked by abrupt onset, progressive purpura, disseminated intravascular coagulation, and death in 24–48 hours. The spectrum resembles Waterhouse-Frederickson syndrome.[2] Rare complications of pneumococcal infection include hemolytic uremic syndrome and rhabdomyolysis.

Mode of Transmission

Pneumococci are transmitted from person to person by respiratory droplets. Most disease is episodic, but epidemic disease has been reported in enclosed situations, such as military barracks and prisons and in children attending day care centers. Communicability decreases within 24 hours of effective antibiotic therapy.

Serotype Distribution

A review of more than 70 studies has shown that out of > 90 serogroups only 10 serogroups are responsible for most pediatric infections; serogroups 1, 6, 14, 19, and 23 are the major encountered serogroups in each continent around the world in pediatric age group.[3] While wide variety of serotypes causes noninvasive diseases such as otitis media

and sinusitis, serotypes 1, 5, 6A, 6B, 14, 19F, and 23F are common causes of IPD globally in children <5 years of age. Prior to introduction of pneumococcal conjugate vaccines (PCVs), 6–11 serotypes accounted for ≥70% of all IPD occurring in children worldwide. After introduction of PCV-7, surveillance studies from the United States showed a decrease in cases of IPD due to vaccine serotypes and an increase in cases due to nonvaccine serotypes, the "replacement phenomenon".[4] Among non-PCV-7 serotypes, 1 and 5 cause significant PD in India[5] as well as in other developing countries.[6] Serotypes 1, 5, and 14 together accounts for 28–43% of IPD across regions and for about 30% of IPD in 20 of the world's poorest countries.[7] Serotype 3 usually causes noninvasive disease but can also cause IPD which is associated with increased mortality.[8] Serotype 19A which is prevalent worldwide causes disease in all age groups and is highly multidrug resistant.[9]

Serotypes 23F and 19F are responsible for 9–18% of cases globally. Serotype 18C is common in regions with a large proportion of high-income countries (i.e. Europe, North America, and Oceania). Some serotypes such as 6B, 9V, 14, 19A, 19F, and 23F are more likely than others to be associated with drug resistance.[10]

Inadequate coverage of serotypes by PCV-7 has led to the formulation of PCV-10 that provides protection against 1, 5, and 7 and PCV-13 which protects against 3, 6A, and 19A, in addition to protection against PCV-7 and PCV-10 serotypes.

Burden of Pneumococcal Diseases

Pneumococcal diseases occur worldwide, though the incidence of disease and mortality varies by region. PD is a serious global problem with an estimated 14.5 million episodes of IPD and approximately 500,000 deaths each year in children under 5 years of age, almost all from low- and middle-income countries.[3] *S. pneumoniae* constitutes for 30% of bacterial pneumonias and is a leading cause of fatal bacterial pneumonia in developing countries. Approximately 20–25% of acute respiratory infection deaths occur in young infants (less than 2 months of age) and 50–60% of deaths occur in infants. Most illnesses are sporadic. Outbreaks of PD are uncommon, but may occur in closed populations, such as nursing homes, childcare centers, or

other institutions. However, large outbreaks of meningitis caused by serotype 1 have been reported from the African meningitis belt.

Disease occurs in all age groups, with the highest rates of disease in children under 2 years of age and among the elderly. IPD is the easiest to measure and its incidence is often used as a measure of the morbidity of severe PDs. The greater burden of severe PDs morbidity is from pneumonia. However, the magnitude of morbidity from pneumococcal pneumonia is difficult to ascertain because of the difficulty with its microbiological diagnosis. On average, about 75% of IPD cases and 83% of pneumococcal meningitis occur in children aged <2 years, but these incidences vary considerably, as does the distribution of cases in age strata below 2 years. For pneumonia, between 8.7% and 52.4% of cases occur in infants aged <6 months.[1] Case fatality rates (CFRs) can be high for IPD, ranging up to 20% for septicemia and 50% for meningitis in developing countries.[1]

Global

Disease rates and mortality are higher in developing than in industrialized settings, with the majority of deaths occurring in Africa and Asia. Children with human immunodeficiency virus (HIV) infection are at substantially increased risk of serious PD. Before widespread immunization with 7-valent PCV, the mean annual incidence of IPD in children aged <2 years was 44.4/100,000 per year in Europe and 167/100,000 in the United States. In comparison, the annual incidence of IPD in children <2 years in Africa ranged from 60/100,000 to 797/100,000.[1]

Indian Scenario

Pneumococcal disease is also the number one vaccine-preventable cause of death in children under 5 years, globally and in India.[11] There is no useful data on the burden of milder pneumococcal illnesses, such as sinusitis and otitis media.

Burden of pneumococcal diseases: The incidence of IPD in India has not been measured in any study. There is no nationally representative study of any PD incidence from the community. Most of the available data on PDs is from hospitals and on meningitis.[12] According to a

2-year prospective study at three Bengaluru hospitals in south India, incidence of IPD in the 1st year of study among less than 2-year old children was found to be 28. 28 cases per 100,000 population in which pneumonia contributed 15.91 and acute bacterial meningitis (ABM) 6.82 cases per 100,000 population. The same study has documented an overall estimated IPD incidence of 17.78 cases per 100,000 1–59-month-old with highest burden amongst 6–11-month-old population (49.85 cases per 100,000) during the 2nd year of the study.[13]

Pneumonia burden: Pneumococcal pneumonia in particular is a major public health concern for children globally. This infection accounts for 18% of all severe pneumonia cases and 33% of all pneumonia deaths worldwide.[14,15] As in the global scenario, pneumonia due to *S. pneumoniae* (pneumococcal pneumonia) is responsible for a large portion of pneumonia episodes and deaths. In 2010, 3.6 million episodes of severe pneumonia and 0.35 million all-cause pneumonia deaths occurred in children under the age of 5 years in India. Among those, 0.56 million episodes of severe pneumonia (16%) and 0.10 million deaths (30%), respectively, were caused by pneumococcal pneumonia.[14] Pneumonia causes an estimated 408,000 deaths among under-five contributing to 19% of child mortality in India.

The pneumonia working group of Child Health Epidemiology Reference Group (CHERG) had estimated an incidence of 0.37 episodes per child year for clinical pneumonia among children <5 years in India for the year 2004.[16] One Indian study reported the incidence of severe clinical pneumonia ranged from 0.03 to 0.08 per child-year at three study sites.[17] Another Indian study finds that Indian children <5 years of age suffer nearly three episodes of respiratory infection per year, with heavier burden on younger children. Approximately, one in five episodes is a lower or severe lower respiratory infection.[18] The hospital-based Bengaluru study in south India quoted an incidence of 5,032.98 cases per 100,000 population of clinical pneumonia amongst 1–59-month-old children, whereas the chest X-ray confirmed incidence was found 1,113.50 cases per 100,000 in the same age group.[13]

Meningitis burden: There is also lack of community-based incidence of ABM in India. Only limited data from prospective population-based

incidence studies are available not only from India but also from entire Asia. A study from Vellore found an annual incidence of "possible", "probable" and "proven" ABM as 86, 37.4, and 15.9 per 100,000 children per year, respectively. Assuming that the probable and proven cases were truly ABM, the burden of disease was 53/100,000/year in under-five children.[11,19] According to the recent review on epidemiology of pneumococcal infections in India, pneumococci were responsible for 27–39% of all cases of ABM in children.[9,20]

Mortality Data

Global

WHO estimates that out of estimated 8.8 million global annual deaths amongst children <5 years of age in the year 2008, 476,000 [95% confidence interval (CI) 333,000–529,000] deaths occurred in HIV-uninfected children due to PDs.[1] However, the latest estimates of CHERG found pneumonia was responsible for 1.396 million (UR 1.189–1.642 million, 18.3%) and meningitis 0.180 million (UR 0.136–0.237 million, 2%) deaths of total estimated 7.6 million under-five deaths globally in 2010.[12]

India

Our data suggest that in 2010, 3.6 million (3.3–3.9 million) episodes of severe pneumonia and 0.35 million (0.31–0.40 million) all-cause pneumonia deaths occurred in children younger than 5 years in India. The states that merit special mention include Uttar Pradesh where 18.1% children reside but contribute 24% of pneumonia cases and 26% pneumonia deaths, Bihar (11.3% children, 16% cases, 22% deaths) Madhya Pradesh (6.6% children, 9% cases, 12% deaths), and Rajasthan (6.6% children, 8% cases, 11% deaths). Further, it was estimated that 0.56 million (0.49–0.64 million) severe episodes of pneumococcal pneumonia and 105,000 (92,000–119,000) pneumococcal deaths occurred in India. The top contributors to India's pneumococcal pneumonia burden were Uttar Pradesh, Bihar, Madhya Pradesh, and Rajasthan in that order.[21] These results highlight the need to improve access to care and increase coverage and equity of pneumonia preventing vaccines in states with high pneumonia burden.

Pneumococci constitute around 5–35% of all pneumonia cases across different studies, the total number of estimated death caused by pneumococcal pneumonia would be ranging from 19,850 deaths per year to 138,950 deaths per year.

Drug Resistance

Antimicrobial resistant serotypes in *S. pneumoniae* have been evolving with widespread use of antibiotics. Particularly, among various types of antimicrobial resistance, macrolide resistance has most remarkably increased in many parts of the world, which has been reported to be >70% among clinical isolates from Asian countries. Penicillin resistance in pneumococci has complicated its treatment and has increased the urgency for its prevention by vaccination. About 85% resistant strains belong to six serotypes, i.e. 6B, 23F, 14, 9V, 18A and 18F. Multidrug resistance became a serious concern in the treatment of IPDs, especially in Asian countries.[22] After PCV-7 vaccination, serotype 19A has emerged as an important cause of IPDs which was also associated with increasing prevalence of multidrug resistance in pneumococci.[22] Penicillin-resistant isolates maybe cephalosporin-resistant and commonly exhibit resistance to non-β-lactam antibiotics such as trimethoprim-sulfamethoxazole and macrolides.

DISTRIBUTION AND PREVALENCE OF DIFFERENT PNEUMOCOCCAL SEROTYPES IN INDIA

The significance of knowing prevalence of distribution of different pneumococcal serotypes in the community is immense since each serotype had a distinct "personality" and represented a distinct disease. There are many studies highlighting distribution and prevalence of different pneumococcal serotypes in the country, including some recent studies done by vaccine manufacturers in India like Pneumonet by M/s Pfizer[13] and Alliance for Surveillance of Invasive Pneumococci (ASIP) by M/s GSK.[23]

There are only a few hospital-based studies mostly from South India. The Pneumonet study (2009–11) could do serotyping in only 36 isolates out of 9,950 subjects aging between 28 days and 5 years. Serotypes 6, 14, 18, 5, 19, and 1 were the most frequent

serotypes.[13] The surveillance of over 9,000 children from Bangalore has found 40 confirmed cases of IPD and shows the presence of nonvaccine pneumococcal serotypes included: 6A (n = 6, 16.7%); 14 (n = 5, 13.9%); 5 (n = 4, 11.1%); 6B (n = 4, 11.1%); 1, 18C, and 19A (n = 3 each, 8.3%); 9V (n = 2, 5.6%); and 3, 4, 10C, 18A, 18F, and 19F (n = 1 each, 2.8%). Serotypes 6A, 14, 6B, 1, 18C, 19A, 9V, 4, 10C, and 18A showed antibiotic resistance.[24] Another Indian study found that the most common pneumococcal serotypes causing invasive infections in children less than 5 years of age were 14, 19F, 5, 6A, and 6B.[25] Of the 114 *S. pneumoniae* isolates studied, 110 (96.4%) were nonsusceptible to cotrimoxazole and 30% were nonsusceptible to erythromycin, 5.2% of the isolates were nonsusceptible to penicillin, and only 0.8% was nonsusceptible to cefotaxime.[25]

Two large studies Invasive Bacterial Infection Surveillance (IBIS) and ASIP having 314 and 225 isolates respectively, are again hospital based. According to IBIS study,[5] the most common serotypes out of total 314 serotypes were 6, 1, 14, 4, 5, 45, 12, and 7 in children under 5 years of age. Serotypes 1 and 5 accounted for 29% of disease.[5] The multicentric ASIP study[23] is the most recent one and still undergoing, included children from 2 months to 5 years of age. A total of 225 serotypes were isolated from 3,572 subjects. Serotypes 14 (16%), 5 (14.6%), 1 (11.1%), 19F (9.7%), and 6B (6.7%) were most frequent serotype.[23] However, this study also does not have representation from all over the country and major part of central India is not represented. The large studies from Asian and other neighboring countries like Pneumo Adip,[26] Asian Network for Surveillance of Resistant Pathogens (ANSORP),[27,28] SAPNA,[29] etc. did not have adequate representation of isolates from India. Another hospital-based study from Delhi amongst individuals aged between 2 years and 77 years studied 126 clinical isolates of *S. pneumoniae*. Serotypes 19, 1, and 6 were more frequently isolated. Thirty percent of the strains were comprised of serotypes 1, 3, 5, 19A, and 7F, and 30 new sequence types were encountered in this study.[30] In recent report from Vellore, out of 244 isolates from IPD patients over a period of January 2007 to June 2011, the most common serotypes in this study were 1, 5, 19F, 6B, 14, 3, 19A, and 6A in that order.[31]

Though a limited number of serotypes cause most IPD worldwide and the serotypes included in existing PCVs responsible for 49–88% of deaths in developing countries of Africa and Asia where PD morbidity

and mortality are the highest,[10] still there is a need of establishing a real-time multisite comprehensive PD surveillance including both population- and hospital-based surveillance arms. The surveillance should not be a one-time project but should be an ongoing initiative to pick natural variations in the seroepidemiology. The surveillance project should have three important objectives—to collect data on serotype distribution, to guide appropriate PCV formulations, to identify trend of antimicrobial resistance amongst different serotypes, and lastly, to assess the impact of vaccine introduction [in national immunization program (NIP) on the serotype distribution and replacement, if any].[19]

PNEUMOCOCCAL VACCINES

Currently, two types of vaccines are licensed for use:

1. Pneumococcal polysaccharide vaccine (PPSV)
2. Pneumococcal conjugate vaccines.

Pneumococcal Polysaccharide Vaccine

The unconjugated PPSV is a 23 valent vaccine (PPSV 23) containing 25 μg per dose of the purified polysaccharide of the following 23 serotypes of pneumococcus—1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F. These serotypes account for over 80% of serotypes associated with serious diseases in adults. It is a T-cell independent vaccine that is poorly immunogenic below the age of 2 years, has low immune memory, does not reduce nasopharyngeal carriage, and does not provide herd immunity. The vaccine is administered as a 0.5 mL dose either intramuscularly in the deltoid muscle or subcutaneously. Each 0.5 mL dose contains 25 μg of each of the 23 polysaccharide antigens in normal saline solution with either phenol or thiomerosal as a preservative. It is stored at 2–8°C. 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 logic hyporesponsiveness.

Immunogenicity

A single dose of PPSV23 results in the induction of serotype-specific immunoglobulin G (IgG), IgA, and IgM antibodies; the IgG

antibodies predominantly belong to the Ig G2 subclass. Though the total antibodies, as measured using the ELISA (enzyme-linked immunosorbent assay), are similar between age groups, functional antibody responses are lower in the elderly compared to young adults.

Efficacy and Effectiveness

Data on the efficacy and effectiveness of PPV23 is conflicting.[26,27] A systematic review commissioned by WHO concluded that the evidence was consistent with a protective effect against IPD and pneumonia in healthy adults and against IPD in the elderly. There was no evidence of efficacy against invasive disease or pneumonia in other high-risk populations with underlying diseases or highly immunosuppressed individuals in both adults and children.[28] One study in Uganda in HIV-infected adults showed an increased risk of pneumonia among those vaccinated with PPSV23.[29]

Pneumococcal Conjugate Vaccines

In order to overcome the immunological limitations of PPSV, the individual polysaccharides of a set of pneumococcal serotypes were conjugated to carrier proteins in order to make them immunogenic in infants, confer more long-lasting protection, and induce immunological memory. Pharmaceutical companies developing conjugate vaccines are using same protein carriers—cross-reactive material (CRM^{197}); a nontoxic mutant diphtheria toxin, diphtheria toxoid, tetanus toxoid; or a meningococcal outer membrane protein complex, which were used successfully to make conjugate Hib vaccines.[9]

The serotype composition and the protein carrier(s) for conjugated vaccines are shown in **Figure 1**. Three of these vaccines containing 7, 10, or 13 serotypes of *Pneumococcus*, respectively (PCV-7, PCV-10, and PCV-13) were licensed and marketed globally; of these, PCV-10 and PCV-13 are currently marketed.

A 9-valent vaccine (PCV-9) was evaluated in clinical trials in South Africa and the Gambia,[32,33] but was reformulated with additional serotypes and marketed as a 13-valent vaccine (PCV-13). Two 11-valent vaccines (PCV-11) formulations with similar serotype

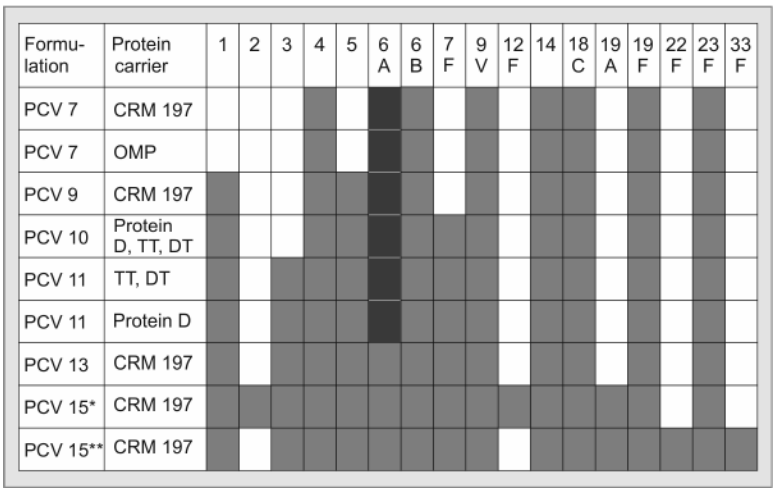


Fig 1: Serotype composition of the pneumococcal conjugate vaccine formulations that have been evaluated in phase III clinical efficacy trials or under clinical development.

Serotypes in the vaccine Serotypes with cross protection

*Under production in India by the support of DBT

**Under production in US by Merck

composition, but different protein carriers were also evaluated in phase 3 clinical trials. One with diphtheria and tetanus toxoid as the protein carrier was tested in the Philippines, but not further developed or licensed.[34] The other PCV-11 formulation with protein D as the protein carrier, was evaluated for efficacy against acute otitis media (AOM), but was further reformulated and licensed as a 10-valent vaccine (PCV-10).[35] An Indian company with active support of Department of Biotechnology (DBT), Government of India is developing 15-valent vaccine containing two additional serotypes, 2 and 12F to existing PCV-13. Merck is also developing 15-valent vaccine with two additional serotypes, 22F and 33F to existing PCV-13. Both these formulations are using CRM197 as a carrier protein.[36]

Vaccine Compositions

PCV-13

PCV-13 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 PCV-7, individually conjugated to a nontoxic diphtheria cross-reactive material (CRM) carrier protein (CRM197). A 0.5-mL PCV-13 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, 5 mL of succinate buffer, and no thimerosal preservative. Except for the addition of six serotypes, P80, and succinate buffer, the formulation of PCV-13 is same as that of PCV-7.

PCV-10

PCV-10 covers three additional serotypes besides PCV-7, i.e. 1, 5, and 7F. Three different carrier proteins are used in this formulation **(Table 1)**. It contains aluminum phosphate as an adjuvant.

The choice of nontypeable *Haemophilus influenzae* (NTHi) 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. PCV-10 is a preservative-free vaccine and adsorbed on aluminum phosphate.

Vaccine Immunogenicity and Efficacy

Serological correlates of protection: Any new PCV has to meet the following criteria laid down by the WHO:[1]

- Immunoglobulin G (IgG) (for all common serotypes collectively and not individually) of equal to or more than 0.35 μg/mL measured by the WHO reference assay (or an alternative)
- The serotype-specific IgG geometric concentration ratios.

TABLE 1: 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 *H. influenzae (NTHi) protein D*		Tetanus toxoid	Diphtheria toxoid

Immunogenicity

Comparisons of opsonophagocytic activity (OPA) antibody titers of serotypes that are common to the new vaccine and the licensed comparator should focus on serotype-specific geometric mean titer (GMT) ratios rather than the previously used threshold functional titer ≥ 1:8.

Both the vaccines have comparable immunogenicity in terms of the proportion of subjects achieving serotype specific IgG antibody levels ≥0.35 μg/mL in the dosage schedules indicated by the manufacturer. The immunogenicity of the vaccines has also been tested using different schedules.

Efficacy

The efficacy of PCV has been evaluated in different populations in both industrialized and developing countries in different parts of the world and against a number of different clinical outcomes.

i. *Invasive pneumococcal disease:* IPD was the primary outcome for the pivotal clinical trials of PCV. This outcome is very specific and represents the more serious forms of disease caused by the pneumococcus. While the trials used different formulations of the vaccine administered in infants in either a 6, 10, and 14 weeks schedule or a 2, 4, and 6 months schedule, the efficacy estimates were fairly consistent. In a systematic review and meta-analysis from seven studies, a pooled vaccine efficacy of 80% (95% CI 58–90%, P < 0.0001) was observed against vaccine type invasive disease and 58% (95% CI 29–75%, P = 0.001) against total invasive disease (irrespective of serotype).[37]

ii. *Pneumonia:* Since pneumococcal pneumonia is difficult to diagnose, most trials opted to measure efficacy against pneumonia from any cause that was associated with alveolar consolidation, using a standardized WHO definition and process for interpreting radiographs.[38] The results of five trials that used the standardized process are summarized in **Table 2**.[32-34,39,40] Given the diversity in vaccine formulations and vaccination schedules used and in the populations in which the vaccines were tested, the results were

TABLE 2: Efficacy of PCV against all-cause radiological pneumonia.

Study site	*Vaccine*	*Vaccine efficacy (%) (95% CL)*	*Reference*
Northern California, USA	PCV-7	25.5 (6.5, 40.7)	37
Soweto, South Africa (HIV negative)	PCV-9	25 (4, 41)	30
The Gambia	PCV-9	37 (27, 45)	31
Philippines	PCV-11	23 (–1, 41)	32
Latin America	PCV-10	23 (9, 36)	38

remarkably consistent. The pooled estimate of vaccine efficacy against radiologically defined pneumonia was found to be 27% (95% CI 15–36%, P < 0.0001).[36] Though most of the reduction is in cases of pneumonia that met the WHO definition for radiologically defined pneumonia, reduction in cases of pneumonia that did not meet this definition have also been observed in clinical efficacy trials.[41] Thus, the full impact of PCV on pneumonia extends beyond the impact on radiologically defined pneumonia. Studies in South Africa have also shown reductions in hospitalization with virus-associated lower respiratory infection, suggesting that coinfection with pneumococcus contributes to severity of disease, resulting in hospitalization; receipt of PCV reduces the risk of severe disease associated with respiratory viruses that requires hospitalization.[42]

Otitis media: The PCVs were efficacious in preventing AOM caused by the serotypes of pneumococcus present in the vaccine, with very similar point estimates of efficacy, ranging from 56% to 57.6%. In two of these trials of two different formulations of PCV-7, increases in AOM due to other serotypes of pneumococcus and other organisms increased, such that the overall impact on otitis media was not significant.[43,44] However, the PCV7-CRM197 was observed to protect against recurrent or more severe forms of AOM, including otitis requiring tympanostomy tube placement.[45-47] In the third trial with PCV-10, the protection against vaccine-type pneumococcal otitis was not completely offset by increases in otitis by other serotypes of pneumococcus or other bacteria; vaccine efficacy against all otitis media of 33.6% (95% CI 21–44.3) was observed.[35] In this trial,

significant protection was also observed against AOM caused by NTHi with observed efficacy 0.35% (95% CI 1.8–57.4); this protection was attributed to the immune response to protein D of NTHi, which was the protein carrier in this formulation of the vaccine.[35] The Clinical Otitis Media and Pneumonia Study (COMPAS) in Latin America showed that PCV-10 has a vaccine efficacy of 16.1% against otitis media.

Vaccine Effectiveness

Many countries in which PCVs were introduced as part of routine immunization have shown reduction in vaccine type invasive disease, not only in the targeted children, but also in older populations as a result of the indirect effects of the vaccine through reduction in nasopharyngeal carriage and transmission of the organism.[48-51] Most of the available data on the effectiveness of PCV are with PCV-7. But available data using the newer PCV-10 and 13 formulations also show similar effectiveness, including against the additional serotypes included in these formulations.[52-55] Impact of PCV was seen in developing countries also like Kenya where the vaccine was introduced in 2011 and impressive reductions have been observed in the rates of IPD. Several studies have also documented significant reductions in pneumonia hospitalization following the introduction of PCV.[52,56] After introduction of PCV-13 in US there was 90% decline in the 6 serotype driven predominantly by 19A and 7F. Following introduction of PCV-13 into the national immunization programs of Argentina, Uruguay, and United Kingdom, reductions in hospitalized chest X-ray confirmed pneumonia and empyema cases were noted. Similarly, following PCV-13 introduction in Nicaragua—a low-middle income country, reduction in hospitalization and outpatient visits for pneumonia was found in children 1 year of age. However, at least one study failed to document any reduction in radiologically defined pneumonia.[57] In one trial using PCV-9, conducted in a high mortality setting in Gambia, reduction in overall mortality of 16% (95% CI 3–28) was observed.[44] Finland introduced PCV-10 in its national immunization program in 2010. The vaccine efficacy was found to be 98% against vaccine serotypes.

Duration of Protection

In South Africa, results of surveillance showed that 6.3 years after vaccination with PCV-9, vaccine efficacy remained significant against IPD (78%; 95% CI, 34–92%). This was consistent with immunogenicity data showing that specific antibody concentrations among HIV-uninfected children remained above the assumed protective levels compared to unvaccinated HIV-uninfected controls during this period.

Effectiveness of Incomplete Series

In pivotal clinical trials, the effectiveness of one dose of PCV-13 was estimated as 48%, two doses 87%, and 2 + 1 doses 100%. One dose catch up for toddlers showed 83% effectiveness.

Safety

The safety of PCV has been well studied and all formulations are considered to have an excellent safety profile in various studies.[47,58,59] The main adverse events (AEs) observed are injection-site reactions, fever, irritability, decreased appetite, and increased and/or decreased sleep that were reported about 10% of the vaccines. Fever with temperature > 39°C was observed in 1/100 to <1/10 vaccines, vomiting and diarrhea in 1/1,000 to <1/100, and hypersensitivity reactions and nervous system disorders (including convulsions and hypotonic-hyporesponsive episodes) were reported in 1/10,000 to <1/1,000 of the vaccines.[1]

Serotype Replacement

Early observations, which showed that though PCV reduced nasopharyngeal carriage with vaccine serotypes, carriage with nonvaccine serotypes increased, led to concerns about replacement disease due to serotypes not contained in the vaccines. Surveillance in populations in which PCV was first introduced, documented increases in the incidence rates of IPD caused by nonvaccine serotypes, though the magnitude of this increase was variable.[48,60] Because of these observations, the WHO commissioned a systematic review of

the data on serotype changes following the introduction of PCV in childhood immunization programs.[50] It indicated that while serotype replacement did occur, in all countries there was a net reduction in IPD, including pneumococcal meningitis, in children less than 5 years of age. The net benefit in older populations was variable. The predominant serotypes causing replacement disease were those found in the higher valency formulations of PCV. WHO recommends that surveillance for replacement disease should continue, especially in developing countries where the potential for replacement may be different from that in industrialized countries.[1]

PCV-10 versus PCV-13: Coverage of Serotypes

According to a few recent Indian studies, there is significant difference in the coverage of serotypes contained in both these vaccines and the serotypes responsible for PDs in hospitalized children in India. ASIP study (2011–2012) based on 225 serotypes, estimated the coverage of PCV-13 and PCV-10 around 73.3% and 64%, respectively.[23] Pneumonet study (2009–2011) based on only 36 pneumococcal serotypes found the coverage of PCV-13 and PCV-10 to be 91.67% and 63.89%, respectively.[5] Shariff M et al. study (2007–2010) based on 126 serotypes estimated the coverage of PCV-13 and PCV-10 to be 73% and 54%, respectively.[30] ANSORP study (2008–2009) based on 23 isolates estimated the coverage of PCV-13 and PCV-10 to be 95.7% and 82.6%, respectively. In the Vellore study, the proportion of serotypes that are included in the vaccines PCV-7, 10, and 13 for all ages was 29%, 53%, and 64%, respectively, and 54%, 66%, and 71%, respectively, for children <2 years.[31] So, the serotype coverage difference between PCV-13 and PCV-10 ranges from 9.3% to 27.8% based on the recent studies in India. However, the systematic review commissioned by WHO concluded that the coverage of serotypes included in PCV-10 and PCV-13 reached ≥ 70% of IPD in every region of the world (range: 70–84% and 74–88%, respectively).[1] As per one Indian study carried out at the Christian Medical College and Hospital (CMCH), a multispecialty tertiary care, 2082 bedded hospital, situated at Vellore district in Tamil Nadu, India, *the results indicated that PCV-10 can protect against 64% of serotypes causing invasive pneumococcal infections. Use of PCV-13*

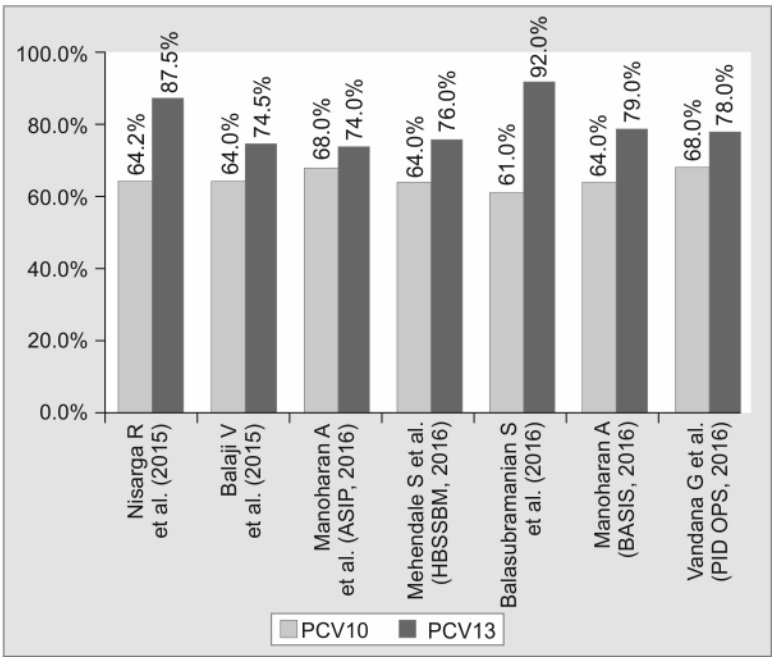


Fig. 2: Serotype coverage difference between PCV-10 and PCV-13 in different studies.
Source: Vaccine. 2017;35(35):4501-9.

in this region can provide increase in protection up to 74.6% against serotypes causing invasive pneumococcal infections.[3]

The recently published systematic review on serotype distribution and antimicrobial susceptibility from India clearly shows the serotype coverage difference between PCV-10 and PCV-13. The vetted average difference is more than 11% **(Fig. 2)**.

RECOMMENDATIONS FOR USE

Pneumococcal Polysaccharide Vaccine

Public Health Perspective

In developing countries, WHO does not recommend the use of PPV in high-risk populations with underlying diseases, as a part of National Immunization Program. However, it can be used in certain high-risk

individuals as per the discretion of the treating clinicians. IAP ACVIP endorses WHO recommendation and does not recommend broader use of this vaccine alone in high risk populations with underlying disease.

Individual Use

See further in the section on recommendations for use of PCV in high-risk children.

Pneumococcal Conjugate Vaccines

Public Health Perspective

In developing countries, WHO does not recommend the use of PPV in high risk populations with underlying diseass, as a part of national immunization program. However it can be used in certain high risk individuals as per the discretion of the treating clinicians IAP ACVIP endorses WHO recommendation and does not recommend broader use of this vaccine alone in high risk populations with underlying disease.

Individual Use

A. Healthy children:

Indication: Both PCV-10 and PCV-13 are licensed for active immunization for the prevention of PDs caused by the respective vaccine serotypes in children from 6 weeks to 5 years of age. In addition, PCV-13 is also licensed for the prevention of PD in adults > 50 years of age in India. US (FDA) licensed PCV-13 for use in the age group of 6–17 years also.

In a recently carried out, an open-label study in India, 200 healthy participants 6–17 years of age received PCV-13. PCV-13 elicited robust functional antibody immune responses. No AEs were reported by caregivers at the 1-month follow-up visit. The immunogenicity results together with the known favorable risk-benefit profile of PCV-13 support extension of the indication to this age group in India.[61]

PCV-13 has been licensed by Drugs Controller General of India (DCGI) for age group of 6–17 years. However, disease burden in this age group is questionable for its routine use in this age group.

Administration schedule: The vaccines are given by injection into the anterolateral aspect of the thigh in infants and into the deltoid muscle in older age groups. The Indian Academy of Pediatrics Advisory Committee on Vaccines and Immunization Practices (IAP ACVIP) recommends following schedule of PCV-10 and PCV-13 **(Table 3)**.

Primary schedule (for both PCV-10 and PCV-13):

- Three primary doses with an interval of at least 4 weeks between doses, plus a booster at least 6 months after the third dose (3p + 1 schedule). The first dose can be given as early as 6 weeks of age; the booster dose is given preferably between 12 and 15 months of age.
- Previously unvaccinated infants aged 7–11 months should receive two doses, the second dose at least 4 weeks after the first, followed by a third dose in the 2nd year of life.
- For PCV-10, unvaccinated children 12 months to 5 years of age should receive two doses, with an interval between the first and second dose of at least 2 months.
- For PCV-13, unvaccinated children aged 12–24 months should receive two doses at least 2 months interval. Children aged 2–5 years should receive a single dose; adults >50 years of age should receive a single dose.
- Routine use of PCV-10/13 is not recommended for healthy children aged more than 5 years. Minimum age for administering

TABLE 3: Recommended schedule for use of PCV-13/PCV-10 among previously unvaccinated infants and children by age at time of first vaccination.

Age at first dose	*Primary series*		*Booster dose*	
	PCV-13	*PCV-10*	*PCV-13*	*PCV-10*
6 weeks–6 months	Three doses	Three doses	One dose 12–15 months*	One dose at 12–15 months**
7–11 months	Two doses*	Two doses*	One dose during 2nd year	One dose during 2nd year
12–23 months	Two doses†	Two doses†	NA	NA
24–59 months	One dose	Two doses†	NA	NA

* At least 6 months after the third dose
† At least 8 weeks apart
(NA: not applicable)

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 2 months (8 weeks).

Interchangeability: When primary immunization is initiated with one of these vaccines, the remaining doses should be administered with the same product. Interchangeability between PCV-10 and PCV-13 has not yet been documented. However, if it is not possible to complete the series with the same type of vaccine, the other PCV product should be used.

PCV-13 is administered intramuscularly as a 0.5 mL dose and is available in latex-free, single-dose, prefilled syringes. PCV-13 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 PCV-13 and PPV-23 has not been studied, and concurrent administration is not recommended.

B. High-risk group of children: Administration of PPSV23 after PCV-13/PCV-10 among children aged 2–18 years who are at increased risk for PD should be undertaken as per following instructions:

- Children aged ≥2 years with underlying medical conditions **(Table 4)** should receive PPSV23 after completing all recommended doses of PCV-13/PCV-10. These children should be administered one dose of PPSV23 at age ≥2 years and at least 8 weeks after the most recent dose of PCV.
- Children who have received PPSV23 previously also should receive recommended PCV-13/PCV-10 doses.
- For children aged 24 through 71 months with certain underlying medical conditions, administer one dose of PCV-13/10 if three doses of PCV were received previously or administer two doses of PCV-13/10 at least 8 weeks apart if fewer than three doses of PCV were received previously.
- A single dose of PCV-13/10 may be administered to previously unvaccinated children aged 6 through 18 years who have anatomic or functional asplenia (including sickle cell disease), HIV infection, or an immune compromising condition, cochlear implant, or cerebrospinal fluid leak.

TABLE 4: Children at high risk for pneumococcal disease, suitability of PCV-13 versus PCV-10 for Indian children.

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
	Sickle cell disease and other hemoglobinopathies
	Congenital or acquired asplenia, splenic dysfunction
Children with immune compromising conditions	HIV infection
	Chronic renal failure and nephrotic syndrome
	Diseases associated with treatment with immune suppressive 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)

(HIV: human immunodeficiency virus)

- Administer PPSV23 at least 8 weeks after the last dose of PCV to children aged 2 years or older with certain underlying medical conditions like anatomic or functional asplenia (including sickle cell disease), HIV infection, cochlear implant, or cerebrospinal fluid leak.
- An additional dose of PPSV (i.e. second dose) should be administered after 5 years to children with anatomic/functional asplenia or an immunocompromising condition. No more than two PPSV23 doses are recommended.
- PPSV should never be used alone for prevention of PDs amongst high-risk individuals.

- When elective splenectomy, immune compromising therapy, or cochlear implant placement is being planned, PCV-13/PCV-10 and/or PPSV23 vaccination should be completed at least 2 weeks before surgery or initiation of therapy.
- The ACVIP now stresses the need of treating prematurity (PT) and very-low birth weight (VLBW) infants as another high-risk category for pneumococcal vaccination. These infants have up to ninefold higher incidence of IPD in VLBW babies as compared to full-size babies.[12] PCV-13/10 must be offered to these babies on a priority basis.[6]

Among non-PCV-7 serotypes, 1 and 5 cause significant PD in India as well as in other developing countries.[62] Serotype 3 usually causes noninvasive disease but can also cause IPD which is associated with increased mortality.[63] Serotypes 6A and 19A were not included in PCV-7 as it was thought that cross-protection would be provided by the immune response to serotypes 6B and 19F.[64] Though some cross-protection was observed for serotype 6A, but no significant clinical cross-protection was observed against serotypes 6C and 19A.[65,8] Serotype 19A which is prevalent worldwide causes disease in all age groups and is highly multidrug resistant.[9,66,67] Inadequate coverage of serotypes by PCV-7 has led to the formulation of PCV-13 and PCV-10 that provides additional protection against 1, 5 and 7F, 3, 6A and 19A, in addition to protection against PCV-7 serotypes.

The direct protection rendered by the serotype included in a vaccine formulation is definitely superior to any cross-protection offered by the unrelated serotypes even of the same group in any PCV formulation.

There is still limited data on the prevalence of pneumococcal serotypes from all the regions of the country, particularly on the prevalence of different serotypes in the community including serotypes 3, 6A, and 19A, and non-NTHi. Further, in the absence of head-to-head trials, it is difficult to determine if either vaccine has a clear advantage over other. Though based on recent pneumococcal serotype surveillance studies from different parts of the country, PCV-13 definitely has some edge over PCV-10.

PUBLIC HEALTH PERSPECTIVES

Despite absence of a nationally representative data, there is significant burden of PDs, particularly pneumonia in the country. The currently available PCV formulations are safe and efficacious and the additional serotypes in PCV-10 and 13 represent significant progress in efforts to control PD. WHO continues to recommend that these vaccines be prioritized for inclusion in the national programs in countries with high child mortality.[1]

The choice of formulation will depend on the prevalence of the vaccine serotypes in the country, vaccine supply, and pricing. As of March 2018, a total of 142 countries have introduced PCV into their NIP, while 17 countries have announced plans to introduce PCV into their NIP. Majority (103) of the countries were using PCV-13, whereas 31 countries use PCV-10 and 8 countries were using both (PCV-10 and 13).[68.]

On May 13th, 2017, PCV-13 was launched by the Union Health Ministry of India under the Universal Immunization Programme (UIP) of selected Indian states of Himachal Pradesh and parts of Bihar (17 out of 38 districts) and Uttar Pradesh (6 out of 75 districts). This was followed with the introduction of PCV-13 in Madhya Pradesh and Rajasthan (9 out of 33 districts) in 2018. Eventually PCV-13 will be introduced in all states of India in phased manner in the coming years; however, timeline for PCV-13 introduction in other states is yet to be announced. The Global Alliance for Vaccine and Immunization (GAVI) will support PCV provision in India until 2021, and then after, PCV-13 cost in India will be borne by the government of India. India is introducing PCV-13 in (2 + 1) schedule with two primary doses at weeks 6 and 14, followed with a booster dose at 9th month.[69]

Cost-effectiveness

Cost-effectiveness evaluations of PCV have been conducted in several countries with varying results. The variability in results is related to the assumptions used in the analysis. The inclusion of indirect effects of vaccination had a big impact on the outcome of the analysis. One analysis of the cost-effectiveness of PCV in low-income countries

that considered only the direct effects of the vaccine concluded that the vaccines would be highly cost-effective in these high-mortality settings.[70]

Choice of Schedule

The WHO recommends a minimum of three doses of vaccine, given in either a 3p + 0 or a 2p + 1 schedule. If a three dose primary series is used, the first dose may be given as early as 6 weeks of age with a minimum of 4 weeks between doses. If 2p + 1 schedule is chosen, the first dose may be given as early as 6 weeks of age, preferably with an 8-week interval between the two primary doses and the booster dose administered between 9 months and 15 months. In countries where disease incidence peaks before 32 weeks of age, the 2p + 1 schedule may leave some infants unprotected during the peak period of risk, especially in the absence of herd effect.[1] Catch-up immunization of children older than 12 months of age at the time of vaccine introduction may accelerate the impact of vaccination through rapid induction of herd immunity. Older children with high risk of disease, e.g. those with asplenia, should also be targeted for vaccination.

Shortened Vaccination Schedule for Public Use Consideration

Schedules of PCV are an area of intense debate. One exciting prospect will be to study a shortened vaccination schedule as this will moderately cut down the cost incurred on pneumococcal mass vaccination program. Based on data from immunogenicity studies and on effectiveness data in children who received incomplete courses of PCV, several countries adopted schedules other than those used in the initial clinical efficacy trials.

The most common immunization schedules used are three primary doses with one booster dose (3p + 1), three primary doses with no booster (3p + 0), and two primary doses with one booster dose (2p + 1). Two systematic reviews have been conducted to evaluate the value of the respective schedules.[71,72] Most of the studies are based on PCV-7. The primary doses have been given in a 2, 4, and 6 months schedule or in a 6, 10, and 14 weeks schedule, with the booster doses

between 9 months and 18 months of age. In general, there is evidence to support to use of all three schedules.

3 + 1 schedule: The gold standard regimen of 3 + 1 has been defined by the US licensure trials.[73] This schedule is three doses in infancy, generally 2 months apart with a booster in the 2nd year of life.

3 + 0 schedule: It consists of three primary doses with no booster. However, a limitation of this shortened schedule for countries with a significant burden of disease caused by serotype 1 is that the extended period of susceptibility to serotype 1 and the invasive nature of that serotype may require prolonged levels of antibody in the 2nd year of life, especially after 18 months of age.[32]

2 + 1 schedule: In the 2p + 1 schedule, the GMT of antibody is higher when the two doses are given with an interval of 2 months between doses, as compared to a 1 month interval. For certain serotypes (6B and 23F), the antibody levels in the interval between the two primary doses and the booster dose may be lower than when three primary doses are given, but following the booster dose the antibody levels may exceed those following a 3p schedule. Thus, while the 2p + 1 schedule may leave some infants incompletely protected during the interval between the primary series and the booster dose (i.e. between 6 months and 12 months of age), it may confer some advantage in terms of protection against serotypes that cause disease slightly later in life (e.g. serotype 1) and in the duration of protection, in comparison to schedules without a booster dose. However, one should refrain from using 2 + 1 schedule for individual in office practice and can be used only in NIP.

Variant 2 + 1 schedule: In this schedule, the booster is brought in line with the WHO scheduled visit of 9 months (hence, a 6-week, 14-week, plus 9-month schedule) because there is no further visit around 12 months in the infant EPI schedules. This could also be described as a prolonged variant of the 3 + 0 schedule, which is the final schedule that has been tested in large efficacy trials in South Africa and the Gambia.[32]

This schedule may address the limitation of 3+0 schedule, but the effectiveness of this schedule or other prolonged schedules in protection against serotype 1 remains under investigation.[35]

RECENT UPDATES IN PNEUMOCOCCAL VACCINES

PCV-15

PCV-7 has been highly effective in reducing global PD burden. However, development of increased rates of pneumococcal nonvaccine serotypes reported after the implementation of PCV-7 led to introduction of PCV-10 and PCV-13 which in turn provided extended serotype coverage and significant proportion of pneumococcal IPD that globally exists today can be prevented by them. After PCV-7 introduction, but prior to PCV-13 introduction, in countries with established PCV-7 immunization programs there was relative increases in IPD, due to serotypes not covered by currently available multivalent PCVs (PCV-10, PCV-13), such as 22F, 33F, 15B/C, and 11A.[74-77]

In Europe, serotype 22F was one of the most frequently reported non-PCV-13 serotypes in 2010 among children <5 years of age.[74] In the United States, four non-PCV-13 serotypes comprised a cumulative total of 32% of the penicillin nonsusceptible (PNS) isolates in 2007: 15A (11%), 23A (8%), 35B (8%), and 6C (5%).[75] In Norway, PCV-13 replaced PCV-7 as a routine childhood vaccine starting in 2010. Prior to PCV-13 introduction (2007–2009), serotypes 22F, 15B/C, and 38 were among the increasing causes of non-PCV-13 serotype IPD.[78] In the United Kingdom, in 2008–2010, the average numbers of non-PCV-13 serotype IPD cases reported among children <5 years of age were highest for serotypes 22F, 15B/C, and 33F (n = 34, 22, and 15 cases, respectively). During the time period from 2000–2006 to 2008–2010, the incidence rate (adjusted for potential biases) of IPD for non-PCV-13 serotypes 22F and 15C increased by approximately threefold among children <5 years of age.[79] After PCV-13 introduction, in a case-based study conducted at eight pediatric hospital centers in the United States, invasive disease isolates were prospectively identified during a surveillance period beginning from January 1, 2007, through December 31, 2011. In 2010–2011 (post-PCV-13 introduction), non-PCV-13 serotypes 33F (n = 16) and 22F (n = 12) followed by serotypes 12, 15B, 15C, and 23A (n = 7 for each of the serotypes) were the most common causes of invasive pneumococcal infection.[50] Hence, invasive

disease serotypes not covered by currently available PCVs are already evident[76,80,81] and might become prominent causes of reported disease as circulating vaccine invasive serotypes decrease in countries using PCV-10 or PCV-13. In turn, a 15-valent PCV, which includes serotypes 22F and 33F, is being developed to offset some of the projected replacement serotypes that are anticipated to accompany routine PCV-10 or PCV-13 use.[82] A 15-valent pneumococcal conjugate vaccine (PCV-15) containing serotypes in PCV-7 and eight additional serotypes (1, 3, 5, 6A, 7F, 19A, 22F, 33F) was developed and evaluated in toddlers 12–15 months of age. Thus, PCV-15 contains 22F and 23F that are two additional serotypes plus all serotypes present in PCV-13.

Based on phase I and II studies of PCV-15 findings, Merck are initiating a comprehensive phase III program to further evaluate this investigational vaccine. The first trial NCT03480763 aims to evaluate the safety, tolerability, and immunogenicity of PCV-15 (V114) and Prevnar 13 in healthy adults aged 50 or older. It also seeks to examine the safety of sequential administration of PCV-15 (V114) or Prevnar 13 followed by Pneumovax 23 one year later.

Safety Summary

The overall safety profile of PCV-15 relative to PCV-13 was generally acceptable, although a higher proportion of PCV-15 recipients reported local and systemic adverse experiences during the safety follow-up period.

The most common injection site and systemic AEs observed among recipients of PCV-15 and PCV-13 were those solicited in the trial. The majority of these events were reported as mild (grade I) to moderate (grade II) in intensity.[36]

Safety and immunogenicity of PCV-15 containing serotypes included in PCV-13 plus serotypes 22F and 33F were evaluated in infants (Study identification: V114-003. CLINICALTRIALS.GOV identifier:NCT01215188).[83] Infants received adjuvanted PCV-15, nonadjuvanted PCV-15, or PCV-13 at 2, 4, 6, and 12–15 months of age. Safety was monitored for 14 days after each dose. Serotype-specific IgG geometric mean concentrations (GMCs) and OPA GMTs were measured at postdose-3, predose-4, and postdose-4. Safety

profiles were comparable across vaccination groups. At postdose-3, both PCV-15 formulations were noninferior to PCV-13 for 10 of 13 shared serotypes but failed noninferiority for three serotypes (6A, 6B, and 19A) based on proportion of subjects achieving IgG GMC ≥0.35 μg/mL. Adjuvanted PCV-15 and nonadjuvanted PCV-15 were noninferior to PCV-13 for 11 and 8 shared serotypes, respectively, based on postdose three comparisons of GMC ratios. PCV-15 induced higher antibodies to serotypes 3, 22F, and 33F than PCV-13.[84]

20 Valent Pneumococcal Vaccine (20vPnC-Prevenar 20)[85]

Pfizer's 20vPnC candidate includes the 13 serotypes contained in Prevnar 13 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) plus seven additional serotypes (8, 10A, 11A, 12F, 15BC, 22F, and 33F). Together, the 20 serotypes included in 20vPnC are responsible for the majority of currently circulating PD in adults in the United States and globally. All seven of the new serotypes included in 20vPnC are global causes of IPD, and six of the seven serotypes (8, 10A, 11A, 15BC, 22F, and 33F) are associated with high case-fatality rates. In addition, four of these serotypes (11A, 15B/C, 22F, and 33F) are associated with antibiotic resistance and/or meningitis (10A, 15B/C, 22F, and 33F).

The safety and immunogenicity findings from phase 2 study (444 adult subjects, 60–64 years age) showed robust OPA responses for all 20 vaccine serotypes in the 20vPnC group. The OPA geometric mean fold rises from baseline ranged from 6.1 to 68.6 for the serotypes in common with Prevnar 13, and 9 to 112.2 for the seven additional serotypes not included in Prevnar 13. Injection site reactions (redness, swelling, or pain) and systemic event rates were similar after vaccination with 20vPnC or Prevnar 13, with severe injection site reactions or systemic events reported in less than 1% of 20vPnC recipients. No deaths or serious AEs considered related to vaccine were reported in the study. These findings supported progression to phase 3 clinical development for the adult indication, which started in December 2018.

Phase 3 pivotal development program for 20vPnC includes three clinical trials (NCT03828617, NCT03835975, and NCT03760146). Combined, all the three trials more than 6,000 adult subjects are being

enrolled, including populations of vaccine-naïve adults and adults with prior pneumococcal vaccination. The first and the largest pivotal phase 3 trial is enrolling an estimated 3,880 adults and is designed to compare immune responses after 20vPnC administration to responses in control subjects ≥ 60 years old receiving 13-valent PCV and 23-valent PPSV; evaluate the immunogenicity of 20vPnC in adults 18–59 years of age; and describe the 20vPnC safety profile in adults ≥18 years old. Another phase 3 trial was initiated on February 12, 2019 and is planned to enroll an estimated 875 adults. It is designed to describe the safety and immunogenicity of 20vPnC in adults 65 years of age or older with prior pneumococcal vaccination. A third phase 3 trial was initiated on February 14, 2019, and is planned to enroll an estimated 1,610 adults. The study is designed to provide additional safety data and evaluate three different lots of 20vPnC in adults 18 through 49 years of age.

PNEUMOSIL™[86]

Serum Institute of India is collaborating with PATH for the speedy development of a 10-valent PCV, focusing on the serotypes prevalent in 70.4% of the affected population [Asia, Africa, LAC (Latin America and the Caribbean), India].

A phase 3, randomized, double-blind study of the safety, tolerability, lot-to-lot consistency, immunogenicity, and noninterference with concomitant vaccinations of Serum Institute of PNEUMOSIL in Healthy Infants in The Gambia is being carried out on 2,250 healthy infants (6–8 weeks of age), receiving 3 doses of either PNEUMOSIL (three groups receiving vaccine from different lots) or Synflorix (one group) at 6, 10, and 14 weeks of age. The first 675 randomized subjects will receive a booster dose of either PNEUMOSIL or Synflorix at 9 months of age that matches the treatment assignment for the priming phase. Standard EPI vaccinations in The Gambia will be given concomitantly with all four doses of the study vaccines. Out of the 675 booster subjects, subjects who consented for further evaluation will participate for the assessment of immune persistence 12 (+1) months after the booster vaccination. Study is estimated to be complete by December 2019.

A WAY FORWARD

In the long run, as the geographic distribution of predominant serotypes changes, effective vaccine coverage provided by PCVs may not be optimal worldwide. Furthermore, manufacturing complexity and the high cost of PCVs limit the ability to sustain production in developing countries. Alternative strategies for the development of serotype-independent pneumococcal vaccines that include common proteins are underway. There are a growing number of investigational pneumococcal protein-based vaccines that have recently been or are currently being evaluated in clinical trials.

They are:

- Protein-based, serotype-independent subunit vaccines
- Combination (protein vaccine antigens plus PS-conjugates) vaccine
- Pneumococcal whole-cell vaccine (WCV) comprised of killed *S. pneumoniae* organisms enable the simultaneous presentation of multiple surface protein antigens.

Pneumococcal conjugate vaccines.

Routine vaccination:

- Minimum age: 6 weeks
- Both PCV-10 and PCV-13 are licensed for children from 6 weeks to 5 years of age (although the exact labeling details may differ by country). Additionally, PCV-13 is licensed for the prevention of PDs in adults >50 years of age.
- Primary schedule (for both PCV-10 and PCV-13): three primary doses at 6, 10, and 14 weeks with a booster at age 12 through 15 months.

Catch-up vaccination:

- Administer one dose of PCV-13 or PCV-10 to all healthy children aged 24 through 59 months who are not completely vaccinated for their age.
- For PCV 13: Catch-up in 6–12 months: two doses 4 weeks apart and one booster; 12–23 months: two doses 8 weeks apart; and 24 months and above: single dose
- For PCV-10: Catch up in 6–12 months: two doses 4 weeks apart and one booster; 12 months to 5 years: two doses 8 weeks apart
- Vaccination of persons with high-risk conditions:
  - PCV and pneumococcal polysaccharide vaccine (PPSV) both are used in certain high-risk group of children.
  - For children aged 24 through 71 months with certain underlying medical conditions, administer one dose of PCV-13 if three doses of PCV were received previously, or administer two doses of PCV-13 at least 8 weeks apart if fewer than three doses of PCV were received previously.

Contd...

Contd...

- A single dose of PCV-13 may be administered to previously unvaccinated children aged 6 through 18 years who have anatomic or functional asplenia (including sickle cell disease), HIV infection, or an immunocompromising condition, cochlear implant, or cerebrospinal fluid leak.
- Administer PPSV23 at least 8 weeks after the last dose of PCV to children aged 2 years or older with certain underlying medical conditions.

Pneumococcal polysaccharide vaccine

- Minimum age: 2 years
- Not recommended for routine use in healthy individuals
- Recommended only for the vaccination of persons with certain high-risk conditions.
- Administer PPSV at least 8 weeks after the last dose of PCV to children aged 2 years or older with certain underlying medical conditions like anatomic or functional asplenia (including sickle cell disease), HIV infection, cochlear implant, or cerebrospinal fluid leak.
- An additional dose of PPSV should be administered after 5 years to children with anatomic/functional asplenia or an immune compromising condition.
- *PPSV should never be used alone for prevention of PDs amongst high-risk individuals.*
- Children with following medical conditions for which PPSV23 and PCV are indicated in the age group 24 through 71 months:
  - Immunocompetent children with chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure); chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy); diabetes mellitus; cerebrospinal fluid leaks; or cochlear implant
  - Children with anatomic or functional asplenia (including sickle cell disease and other hemoglobinopathies, congenital or acquired asplenia, or splenic dysfunction)
  - Children with immune compromising conditions: HIV infection, chronic renal failure and nephrotic syndrome, diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas and Hodgkin disease; or solid organ transplantation, congenital immune deficiency.

REFERENCES

1. WHO Publication. Pneumococcal vaccines WHO position paper. 2012;14(87):129-44. Available from http://www.who.int/wer [Accessed October, 2019].
2. Mufson MA. Pneumococcal Infections. JAMA. 1981;246:1942.
3. Balaji V, Jayaraman R, Verghese VP, et al. Pneumococcal serotypes associated with invasive disease in under five children in India & implications for vaccine policy. Indian J Med Res. 2015;142:286-92.
4. Byington CL, Samore MH, Stoddard GJ, et al. Temporal trends of invasive disease due to *Streptococcus pneumoniae* among children in

the intermountain west: emergence of nonvaccine serogroups. Clin Infect Dis. 2005;41:21-9.
5. Invasive Bacterial Infection Surveillance (IBIS) Group, International Clinical Epidemiology Network (INCLEN). Prospective multi centre hospital surveillance of *Streptococcus pneumoniae* disease in India. Lancet. 1999;353:1216-21.
6. Le CF, Yusof MY, Shamala D, et al. Current trends in pneumococcal serotype distribution in Asia. J Vaccines Vaccin. 2011;S2:001.
7. Pneumococcal vaccines. IAP Guidebook on Immunization. New Delhi: Jaypee Brothers; 2013. p. 173.
8. Kaplan SL, Barson WJ, Lin PL, et al. Serotype 19A is the most common serotype causing invasive pneumococcal infections in children. Pediatrics. 2010;125:429-36.
9. Reinert R, Jacobs MR, Kaplan SL. Pneumococcal disease caused by serotype 19A: review of the literature and implications for future vaccine development. Vaccine. 2010;28:4249-59.
10. Johnson HL, Deloria-Knoll M, Levine OS, et al. Systematic evaluation of serotypes causing invasive pneumococcal disease among children under five: The pneumococcal global serotype project. PLoS Med 2010;7:pii:e1000348.
11. Immunization Technical Support Unit (ITSU). The Power of Vaccines: Protecting India's Future. Available from http://www.jhsph.edu/research/centers-and-institutes/ivac/resources/factsheets/The%20Power%20of% 20Vaccines%20Brochure.pdf. [Accessed May, 2017].
12. Indian Academy of Pediatrics Committee on Immunization (IAPCOI). Consensus recommendations on immunization and IAP immunization timetable 2012. Indian Pediatr. 2012;49:549-64.
13. Nisarga RG, Balter I, Premalatha R, et al. Prospective, active hospital-based epidemiologic surveillance for IPD and pneumonia burden among infants and children in Bangalore south zone, India. Comprehensive review characterizing the epidemiology of *Streptococcus pneumoniae* in India. The 8th International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD). Iguaçu Falls, Brazil, 11–15 March 2012, Abstract#A-428-0023-00743.
14. Rudan I, O'Brien KL, Nair H, et al. Child Health Epidemiology Reference Group (CHERG). Epidemiology and etiology of childhood pneumonia in 2010: estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries. J Glob Health. 2013;3:010401.
15. International Vaccine Access Centre. 2016 Pneumonia & Diarrhea Progress Report. Available from http://www.jhsph.edu/research/centers-and-institutes/ivac/resources/IVAC-2016-Pneumonia-Diarrhea-Progress-Report.pdf. [Accessed May, 2017].

16. Rudan I, Boschi-Pinto C, Biloglav Z, et al. Epidemiology and etiology of childhood pneumonia. Bull World Health Organ. 2008;86:408-16.
17. Gupta M, Kumar R, Deb AK, et al. Multicenter surveillance for pneumonia & meningitis among children (<2 yr) for Hib vaccine probe trial preparation in India. Indian J Med Res. 2010;131:649-65.
18. Broor S, Parveen S, Bharaj P, et al. A prospective three-year cohort study of the epidemiology and virology of acute respiratory infections of children in rural India. PLoS One. 2007;2:e491.
19. Minz S, Balraj V, Lalitha MK, et al. Incidence of *Haemophilus influenzae* type b meningitis in India. Indian J Med Res 2008;128:57-64.
20. Johnson HL, Kahn GD, Anne M. et al. Comprehensive review characterizing the epidemiology of *Streptococcus pneumoniae* in India. The 8th International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD). Iguaçu Falls, Brazil. 2012. Abstract#A-428-0023-00743.
21. Farooqui H, Jit M, Heymann DL, et al. Burden of Severe Pneumonia, Pneumococcal Pneumonia and Pneumonia Deaths in Indian States: Modelling Based Estimates. 2015 https://doi.org/10.1371/journal.pone.0129191
22. Song JH. Advances in pneumococcal antibiotic resistance. Expert Rev Resp Med. 2013;7(5):491-8.
23. Manoharan A. Surveillance of invasive disease caused by *Streptococcus pneumoniae* or *Hemophilus influenzae* or *Neisseria meningitides* in children (<5 Years) in India. Alliance for Surveillance of Pneumococci (ASIP). Poster Discussion 2: Bacterial Infections 1,13:30 to 15:30 Hours, May 30, 2013 at the 31st Annual Meeting of the European Society for Paediatric Infectious Diseases; May 28–June 1, 2013. Milan, Italy.
24. Nisarga R, Premlatha R, Shivanada, et al. Hospital-based surveillance of invasive pneumococcal disease and pneumonia in South Bangalore, India. Indian Pediatr. 2015;52:205-11.
25. Jaiswal N, Singh M, Das RR, et al. Distribution of serotypes, vaccine coverage, and antimicrobial susceptibility pattern of *Streptococcus pneumoniae* in children living in SAARC countries: A systematic review. PLoS One. 2014;9:e108617.
26. Moberley SA, Holden J, Tatham DP, et al. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2008;(1):CD000422.
27. Huss A, Scott P, Stuck AE, et al. Efficacy of pneumococcal vaccination in adults: A meta-analysis. CMAJ. 2009;180:48-58.
28. World Health Organization. 23-valent pneumococcal polysaccharide vaccine: WHO position paper. Weekly Epidemiological Record 2008;83:373-84.
29. French N, Nakiyingi J, Carpenter LM, et al. 23-valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double-blind, randomized and placebo controlled trial. Lancet. 2000;355:2106-11.

30. Shariff M, Choudhary J, Zahoor S, et al. Characterization of *Streptococcus pneumoniae* isolates from India with special reference to their sequence types. J Infect Dev Ctries. 2013;7:101-9.
31. Molander V, Ellison C, Balaji V, et al. Invasive pneumococcal infections in Vellore, India: clinical characteristics and distribution of serotypes. BMC Infectious Dis. 2013;13:532.
32. Klugman KP, Madhi SA, Huebner RE, et al. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. N Eng J Med. 2003;349:1341-8.
33. Cutts FT, Zaman SM, Enwere G, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in the Gambia: Randomised, double-blind, placebo-controlled trial. Lancet. 2005;365:1139-46.
34. Lucero MG, Nohynek H, Williams G, et al. Efficacy of an 11-valent pneumococcal conjugate vaccine against radiologically confirmed pneumonia among children less than 2 years of age in the Philippines: A randomized, double-blind, placebo-controlled trial. Pediatr Infect Dis J. 2009;28:455-62.
35. Prymula R, Peeters P, Chrobok V, et al. Pneumococcal capsular polysaccharides conjugated to protein D for prevention of acute otitis media caused by both *Streptococcus pneumoniae* and non-typeable *Haemophilus influenzae*: a randomised double-blind efficacy study. Lancet. 2006;367:740-8.
36. Skinner JM, Indrawati L, Cannon J, et al. Pre-clinical evaluation of a 15-valent pneumococcal conjugate vaccine (PCV15-CRM197) in an infant-rhesus monkey immune genicity model. Vaccine. 2011;29: 8870-6.
37. Lucero MG, Dulalia VE, Nillos LT, et al. Pneumococcal conjugate vaccines for preventing vaccine-type invasive pneumococcal disease and X-ray defined pneumonia in children less than two years of age. Cochrane Database Syst Rev. 2009;(4):CD004977.
38. Cherian T, Mulholland EK, Carlin JB, et al. Standardized interpretation of paediatric chest radiographs for the diagnosis of pneumonia in epidemiological studies. Bulletin of the World Health Organization. 2005;83(5):353-9.
39. Hansen J, Black S, Shinefield H, et al. Effectiveness of hepta valent pneumococcal conjugate vaccine in children younger than 5 years of age for prevention of pneumonia: Updated analysis using World Health Organization standardized interpretation of chest radiographs. Pediatr Infect Dis J. 2006;25(9):779-81.
40. Tregnaghi MW, Saez-Llorens X, Lopez P, et al. Evaluating the efficacy of 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein-D conjugated vaccine (PHID-CV) against community acquired

pneumonia in Latin America. Proceedings of the European Society of Pediatric Infectious Diseases 2011, The Hague, Netherlands; 2011.
41. Madhi SA, Klugman KP. World Health Organisation definition of "radiologically-confirmed pneumonia" may under-estimate the true public health value of conjugate pneumococcal vaccines. Vaccine. 2007;25(13):2413-9.
42. Madhi SA, Klugman KP, The Vaccine Trialist Group. A role for *Streptococcus pneumoniae* in virus-associated pneumonia. Nat Med. 2004;10:811-3.
43. Kilpi T, Ahman H, Jokinen J, et al. Protective efficacy of a second pneumococcal conjugate vaccine against pneumococcal acute otitis media in infants and children: randomized, controlled trial of a 7-valent pneumococcal polysaccharide-meningococcal outer membrane protein complex conjugate vaccine in 1666 children. Clin Infect Dis. 2003;37:1155-64.
44. Eskola J, Kilpi T, Palmu A, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. N Eng J Med. 2001;344(6):403-9.
45. Fletcher MA, Fritzell B. Pneumococcal conjugate vaccines and otitis media: An appraisal of the clinical trials. IntJ Otolaryngol. 2012;2012:312935.
46. Sarasoja I, Jokinen J, Lahdenkari M, et al. Long-term effect of pneumococcal conjugate vaccines on tympanostomy tube placements. Pediatr Infect Dis J. 2013;32:517-20.
47. Poehling KA, Szilagyi PG, Grijalva CG, et al. Reduction of frequent otitis media and pressure-equalizing tube insertions in children after introduction of pneumococcal conjugate vaccine. Pediatrics. 2007;119(4):707-15.
48. Singleton RJ, Hennessy TW, Bulkow LR, et al. Invasive pneumococcal disease caused by nonvaccine serotypes among alaska native children with high levels of 7-valent pneumococcal conjugate vaccinecoverage. JAMA. 2007;29:1784-92.
49. Pilishvili T, Lexau C, Farley MM, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. J Infect Dis. 2010;201:32-41.
50. Miller E, Andrews NJ, Waight PA, et al. Herd immunity and serotype replacement 4 years after seven-valent pneumococcal conjugate vaccination in England and Wales: An observational cohort study. Lancet Infect Dis. 2011;11:760-8.
51. Poehling KA, Talbot TR, Griffin MR, et al. Invasive pneumococcal disease among infants before and after introduction of pneumococcal conjugate vaccine. JAMA. 2006;295:1668-74.
52. Grijalva CG, Pelton SI. A second-generation pneumococcal conjugate vaccine for prevention of pneumococcal diseases in children. Curr Opin Pediatr. 2011;23(1):98-104.

53. Miller E, Andrews NJ, Waight PA, et al. Effectiveness of the new serotypes in the 13-valent pneumococcal conjugate vaccine. Vaccine. 2011;29:9127-31.
54. Palmu AA, Jokinen J, Borys D, et al. Effectiveness of the ten-valent pneumococcal *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV10) against invasive pneumococcal disease: A cluster randomized trial. Lancet. 2013;381(9862):214-22.
55. Jardine A, Menzies RI, McIntyre PB. Reduction in hospitalizations for pneumonia associated with the introduction of a pneumococcal conjugate vaccination schedule without a booster dose in Australia. Pediatr Infect Dis J. 2010;29:607-12.
56. O'Grady KF, Carlin JB, Chang AB, et al. Effectiveness of 7-valent pneumococcal conjugate vaccine against radiologically diagnosed pneumonia in indigenous infants in Australia. Bull World Health Organ. 2010;88:139-46.
57. Dicko A, Odusanya OO, Diallo AI, et al. Primary vaccination with the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV) in infants in Mali and Nigeria: A randomized controlled trial. BMC Public Health. 2011; 11:882.
58. Lalwani S, Chatterjee S, Chhatwal J, et al. Immunogenicity, safety, and reactogenicity of the 10-valent pneumococcal non-typeable *Hemophilus influenzae* protein D conjugate vaccine (PHiD-CV) when co-administered with the DTPw-HBV/Hib vaccine in Indian infants: A single-blind, randomized, controlled study. Hum Vaccines Immunother. 2012,8:612-22.
59. Vanderkooi OG, Scheifele DW, Girgenti D, et al. Safety and immunogenicity of a 13-valent pneumococcal conjugate vaccine in healthy infants and toddlers given with routine pediatric vaccinations in Canada. Pediatr Infect Dis J. 2012,31:72-7.
60. Shinefield H, Black S, Ray P, et al. Efficacy, immunogenicity and safety of heptavalent pneumococcal conjugate vaccine in low birthweight and preterm infants. Pediatr Infect Dis J. 2002;21:182-6.
61. Agarkhedkar S, Juergens C, Balasundaram K, et al. Safety and immunogenicity of 13-valent pneumococcal conjugate vaccine in children 6–17 years of age in India: An open-label trial. Pediatr Infectious Dis. 2017;36(11):e283-e285.
62. Martens P, Worm SW, Lundgren B, et al. Serotype-specific mortality from invasive *Streptococcus pneumoniae* disease revisited. BMC Infect Dis. 2004;4:21.
63. Paradiso PR. Advances in pneumococcal disease prevention: 13-valent pneumococcal conjugate vaccine for infants and children. Clin Infect Dis. 2011;52:1241-7.

64. Park IH, Moore MR, Treanor JJ, et al. Differential effects of pneumococcal vaccines against serotypes 6A and 6C. J Infect Dis. 2008;198:1818-22.
65. Hausdorff WP, Hoet B, Schuerman L. Do pneumococcal conjugate vaccines provide any cross-protection against serotype 19A? BMC Pediatr. 2010;10:4.
66. Hulten KG, Kaplan SL, Lamberth LB, et al. Changes in *Streptococcus pneumoniae* serotype 19A invasive infections in children from 1993 to 2011. J Clin Microbiol. 2013;51:1294-7.
67. Sinha A, Levine O, Knoll MD, et al. Cost-effectiveness of pneumococcal conjugate vaccination in the prevention of child mortality: An international economic analysis. Lancet. 2007;369:389-96.
68. International Vaccine Access Center. A report on current global access to new childhood vaccines. Johns Hopkins Bloomberg School of Public Health 2018. Available from https://view-hub.org/resourcesfile/VIEW-hubReports_Resources/2018_03/IVAC_VIEW-hub_Report%202018Mar.pdf. [Accessed February 2019].
69. Sachdeva A. Pneumococcal Conjugate Vaccine Introduction in India's Universal Immunization Program. Indian Pediatr. 2017;54:445-6.
70. Conklin L, Knoll MD, Loo J, et al. Landscape analysis of pneumococcal conjugate vaccine dosing schedules: A systematic review Sub-report on the 3-dose schedules A Project of the AVI Technical Assistance Consortium (AVI-TAC) Final Report 1.0. Geneva: World Health Organization; 2011.
71. Scott P, Rutjes AW, Bermetz L, et al. Comparing pneumococcal conjugate vaccine schedules based on 3 and 2 primary doses: Systematic review and meta-analysis. Vaccine. 2011;29:9711-21.
72. Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group. Pediatr Infect Dis J. 2000;19:187-95.
73. Klugman KP, Madhi SA, Adegbola RA, et al. Timing of serotype 1 pneumococcal disease suggests the need for evaluation of a booster dose. Vaccine. 2011;29:3372-73.
74. Klugman KP, Black S, Dagan R, et al. Pneumococcal conjugate vaccine and pneumococcal common protein vaccines. In: Plotkin S, Orenstein WA, Offit P (Eds). Vaccines, 6th edition. Philadelphia: WB Saunders; 2008.
75. European Centre for Disease Prevention and Control. Surveillance of Invasive Pneumococcal Disease in Europe. Stockholm, Sweden: 2010.
76. Gertz RE, Li Z, Pimenta FC, et al. Active Bacterial Core Surveillance Team increased penicillin nonsusceptibility of nonvaccine-serotype invasive pneumococci other than serotypes 19A and 6A in post-7-valent conjugate vaccine era. J Infect Dis. 2010;201:770-5.

77. Le CF, Palanisamy NK, Yusof MY, et al. Capsular serotype and antibiotic resistance of *Streptococcus pneumoniae* isolates in Malaysia. PLoS One. 2011;6:e19547.
78. Adam HJ, Karlowsky JA, Nichol KA, et al. Baseline epidemiology of *Streptococcus pneumoniae* serotypes in Canada prior to the introduction of the 13-valent pneumococcal vaccine. Microb Drug Resist. 2012;18: 176-82.
79. Hanage WP, Bishop CJ, Huang SS, et al. Carried pneumococci in Massachusetts children: The contribution of clonal expansion and serotype switching. Pediatr Infect Dis J. 2011;30:302-8.
80. Kaplan SL, Barson WJ, Lin PL, et al. Early trends for invasive pneumococcal infections in children after the introduction of the 13-valent pneumococcal conjugate vaccine. Pediatr Infect Dis J. 2013;32:203-7.
81. Andrews N, Kaye P, Slack M, et al. Effectiveness of the 13 valent pneumococcal conjugate vaccine against IPD in England and Wales; Proceedings of the 8th International Symposium on Pneumococci and Pneumococcal Diseases; Iguacu Falls, Brazil. 11–15 March 2012.
82. Lehmann D, Willis J, Moore HC, et al. The changing epidemiology of invasive pneumococcal disease in aboriginal and non-aboriginal western Australians from 1997 through 2007 and emergence of nonvaccine serotypes. Clin Infect Dis. 2010;50:1477-86.
83. Buchwald U, Peterson J, Stacey H, et al. Safety and immunogenicity of 15-valent pneumococcal conjugate vaccine (PCV-15) compared to PCV-13 in healthy older adults previously vaccinated with 23-valent pneumococcal polysaccharide vaccine (PPV23). POSTER ID Week 2018; San Francisco, CA, USA; October 3-7, 2018.
84. Greenberg D, Hoover PA, Vesikari T, et al. Safety and immunogenicity of 15-valent pneumococcal conjugate vaccine (PCV15) in healthy infants. Vaccine. 2018;36(45):6883-91.
85. Pfizer announces serotypes included in 20-valent pneumococcal conjugate vaccine candidate being investigated for the prevention of invasive disease and pneumonia in adults aged 18 years and older. Available from https://www.pfizer.com/news/press-release/press-release-detail/pfizer_announces_serotypes_included_in_20_valent_pneumococcal_conjugate_vaccine_candidate_being_investigated_for_the_prevention_of_invasive_disease_and_pneumonia_in_adults_aged_18_years_and_older [Accessed October, 2019].
86. Phase 3 Study of 10-valent Pneumococcal Conjugate Vaccine (PNEUMOSIL) in Healthy Infants. Available from https://clinicaltrials.gov/ct2/show/NCT03197376. [Accessed October, 2019].

3.7 ROTAVIRUS VACCINES

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EPIDEMIOLOGY

Rotaviruses are globally the leading cause of severe, dehydrating diarrhea in children aged <5 years. In low-income countries, 80% of primary rotavirus infections occur among infants <1-year-old, whereas in high-income countries, the first episode may occasionally be delayed until the age of 2–5 years. According to Global Enteric Multicenter Study (GEMS), the four most common pathogens responsible for moderate-to-severe diarrhea among children in sub-Saharan Africa and south Asia were *Rotavirus*, *Cryptosporidium*, enterotoxigenic *Escherichia coli*, and *Shigella*.[1]

In most developing countries, rotavirus epidemiology is characterized by one or more periods of relatively intense rotavirus circulation against a background of year-round transmission, whereas in high-income countries with temperate climates, distinct winter seasonality is typically observed. World Health Organization (WHO) estimates that in 2008, approximately 453,000 (420,000–494,000) rotavirus gastroenteritis (RVGE)-associated child deaths occurred worldwide. These fatalities accounted for about 5% of all child deaths and cause-specific mortality rate of 86 deaths per 100,000 populations aged <5 years.[2] More than 80% due to rotavirus diarrhea occur in low-income countries.[3] Globally, the number of rotavirus deaths in children <5 years of age declined from 528,000 (range, 465,000–591,000) in 2000 to 215,000 (range, 197,000–233,000) in 2013. The predicted annual rotavirus detection rate declined slightly over time from 42.5% (95% confidence interval [CI], 37.4%–47.5%) in 2000 to 37.3% (95% CI, 34.2%–40.5%) in 2013 globally.

ROTAVIRUS MORBIDITY, MORTALITY, AND BURDEN IN INDIA

National estimates of rotavirus attributable deaths among children under five years of age ranged from 47,100 (India) to fewer than 5 deaths (79 countries). Twenty-two percent of all rotavirus deaths

under five years of age occurred in India. Four countries (India, Nigeria, Pakistan and the Democratic Republic of the Congo) accounted approximately half (49%) of all rota deaths under age five in 2013. Indian Academy of Pediatrics (IAP) carried out a systematic review (unpublished) of burden of rotavirus diarrhea in under-five Indian children. An analysis of 51 studies from all over India over last four decades dealing with hospitalization with rotavirus diarrhea showed a stool positivity rate of 22.1%. Stool positivity rate for rotavirus is about 39% when studies year 2000 onward are only included. In community settings, analysis of 16 studies with diarrhea showed stool positivity for rotavirus at 18.6%. Rotavirus was identified as an etiological agent in 16.1% cases of nosocomial diarrhea. Most cases of rotavirus diarrhea were found to occur in the first 2 years of life. The most commonly affected age group was 7–12 months both in hospital and community settings. Highest numbers of cases were recorded in winter months.

It is difficult to estimate the impact of rotavirus diarrhea on under five mortality in India. In the Million Death Study, 3053 (13.2%) of 23,152 deaths among children younger than 5 years were due to diarrhea. This corresponds to approximately 334,000 diarrheal deaths nationally during 2005, or 1 in 82 Indian children dying from diarrhea before the age of 5 years.[4] The prevalence of rotaviral diarrhea among Indian children aged less than 5 years included in ENRSN (September 2012 to December 2014) was 39.6%. This is in conformity with the findings of the earlier round of NRSN (2005-2009).[5] Taking together data from the Million Death Study and the Indian Rotavirus Strain Surveillance Network (IRSSN), it is estimated that in 2013, an estimated 47,100 deaths, 872,000 hospitalizations, over 3.2 million outpatient visits, and 11.37 million diarrhea episodes occurred due to rotavirus in children <5 years of age. In the Vellore birth cohort study, the incidence of rotavirus diarrhea was 0.25 [95% confidence interval (CI) 0.22, 0.29] per child-year in children under 3 years and 0.49 (0.42, 0.58) per child-year in children under 1 year. 48% of children experienced at least one episode of rotavirus diarrhea by the age 3 years. It is estimated that India spends ₹ 2.0–3.4 billion (US$ 41–72 million) annually in medical costs to treat rotavirus diarrhea.[6]

HEALTHCARE-ASSOCIATED ROTAVIRUS INFECTIONS

Rotavirus accounts for 31–87% of healthcare-associated gastroenteritis out of which one-third is severe. The incidence is 0.3–4.8 per 1,000 hospital days.[7]

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. According to data generated by the extended IRSSN, most of the rotavirus cases occur in the cooler months of September to February. The highest prevalence is seen during December to February (56.4%).[8]

PATHOGEN

Rotavirus is an icosahedral ribonucleic acid (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 of 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]. The disease spreads 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 two decades. The universal occurrence of rotavirus infections even in settings with high standards of hygiene testifies to the high transmissibility of this virus.

In the systematic review (unpublished) carried out by Indian Academy of Pediatrics, a total of 47 studies could be identified which dealt with serotyping of rotavirus. Overall, G1 was the most common serotype isolated in Indian studies (32%), followed by G2 (24%), and G-untypable (15%). Emergence of G9 and G12 has been noticed in recent years. In P-serotyping, P[4] was most prevalent (23%) all over India, followed by P[6] (20%) and P-untypable or others (13%). Several studies have reported different G-P combinations, novel serotypes, group B and group C rotavirus. Data from the extended IRSSN (2012–14) showed a changing trend with G1P[8] accounting for 62.7% of isolates, G2P[4] 7.6%, G1P[4] 4.2%, G12P[6] 3.7%, G9P[8] 3.5%, G1P[6] 2.4%, G12P[8] 2.2%, and the rest being other G-P combinations and untypable strains.[8]

Protective Immunity

Protection against rotavirus infection is mediated by both humoral and cellular components of the immune system. Following the first infection, the serological response is directed mainly against the specific viral serotype (i.e. a homotypic response), whereas a broader, heterotypic antibody response is elicited following ≥1 subsequent rotavirus infections.[9] A study from Mexico showed that children with 1, 2, or 3 previous infections had progressively lower risk of subsequent rotavirus infection (adjusted relative risk, 0.62, 0.40, and 0.34, respectively) or of diarrhea (adjusted relative risk, 0.23, 0.17, and 0.08) than children who had no previous infections. Subsequent infections were significantly less severe than first infections ($p = 0.02$) and second infections were more likely to be caused by another G type ($p = 0.05$).[10] However, study from India reported that the risk of severe disease continued after several reinfections. Levels of reinfection were high, with only approximately 30% of all infections identified being primary. Protection against moderate or severe disease increased with the order of infection but was only 79% after three infections.[11] With G1P[8], the most common viral strain, there was no evidence of homotypic protection.[11]

Vaccines

Currently two live oral vaccines are licensed and marketed worldwide, human monovalent live vaccine and human bovine pentavalent live vaccine. Additionally, two live oral rotavirus vaccines are marketed in India, one in China and one in Vietnam.

Human Monovalent Live Vaccine (RV1)

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 power that is reconstituted before administration. Each 1-mL dose of reconstituted vaccine contains at least 106 median culture infective units of virus. The vaccine contains amino acids, dextran, Dulbecco's modified Eagle medium, sorbitol, and sucrose. The diluents contain calcium carbonate, sterile water, and xanthan. The vaccine contains no preservatives of thiomersal. The vaccine and the diluents should be stored at 2–8°C and must not be frozen. The vaccine should be administered promptly after reconstitution as 1 mL orally.

Human Bovine Pentavalent Live Vaccine (RV5)

Human bovine pentavalent live vaccine is a human bovine reassortant vaccine and consists of five reassortants between the bovine WC23 strain and human G1, G2, G3, G4, and P1A[8] rotavirus strains grown in Vero cells and administered orally. 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 phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, and tissue culture media. 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 2–8°C.

Indian Neonatal Rotavirus Live Vaccine, 116E

This vaccine developed by Bharat Biotech of India is a live, naturally attenuated vaccine containing monovalent, bovine-human reassortant strain characterized as G9P[11], with the VP4 of bovine rotavirus origin, and all other segments of human rotavirus origin.

The vaccine strain was isolated from asymptomatic infants, with mild diarrhea by Indian researchers in 1985 at All India Institute of Medical Sciences (AIIMS), New Delhi. Follow-up of these infants indicated that they were protected against severe rotavirus diarrhea for up to 2 years.[12] This strain was sent for vaccine development to the National Institute of Health (NIH) by Department of Biotechnology (DBT)-India and later transferred to Bharat Biotech International Limited in 2001 for further development.

It is a liquid vaccine. A single human dose of this vaccine is 0.5 mL containing not less than (NLT) 10^5 FFU (focus forming unit) of live rotavirus 116E.

In addition, it contains potassium phosphate, sucrose, potassium L-glutamate monohydrate, neomycin sulfate, kanamycin sulfate, and Dulbecco's Modified Eagle Medium. The commercial preparation does not contain any buffer. A recent study has shown that administration of ROTAVAC™ at a 0.5-mL dose volume without buffering agent was shown to be well-tolerated and immunogenic.[13]

It can be stored at –20°C till the expiry date. It can be stored up to 6 months at 5°C ± 3°C at any time during shelf-life.

Similar vaccine is also marketed by Abbott as Rotasure.

Bovine rotavirus pentavalent vaccine (BRV-PV)[14] (Rotasiil™) is a pentavalent rotavirus vaccine (BRV-PV) developed from five Bovine (UK) X Human Rotavirus Reassortant strains (serotypes G1, G2, G3, G4, and G9) received from the US National Institutes of Health (NIH) and further developed by the Serum Institute of India. The viruses are propagated in Vero cells.

The vaccine is supplied in a freeze dried form with each dose of 2.5 mL containing NLT $10^{5.6}$ FFU per serotype. The diluent is a citrate bicarbonate buffer solution also containing Eagle medium, glutamate, sucrose, and glycine.

Rotasiil™ is a thermostable vaccine and can be stored below 24°C till the duration of the shelf life of 30 months. The vaccine is stable for 3 years at 2–8°C, and 25°C, for 2 years at 37°C and for 6 months at 40°C.[14]

Rotavirus Vaccines' Efficacy and Effectiveness

Although the composition of the two vaccines (RV1 and RV5) is different, their efficacy and, largely, mechanism of action are similar.

Both prevent effectively severe rotavirus gastroenteritis (SRVGE) but are less efficacious against mild RVGE or rotavirus infection. Efficacy of these vaccines in Europe and the USA against SRVGE has been above 90% and in Latin America around 80%. Trials in Africa have yielded efficacy rates between 50% and 80%. In Malawi, the effectiveness of RV1 was 49%, compared to about 77% in South Africa. This study showed that a rotavirus vaccine significantly reduces the episodes of SRVGE 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. The possible reasons include poor nutritional status, coinfections with other enteral pathogens, interference by breastfeeding due to presence of high levels antirotavirus neutralizing antibodies in breast milk, and interference by maternal antibody or by coadministration of the oral poliovirus vaccine, which may reduce rotavirus antibody levels.[15]

However, since the incidence of severe rotavirus disease is significantly higher in high child mortality settings, the numbers of severe disease cases and deaths averted by vaccines in these settings are likely to be higher than in low mortality settings, despite the lower vaccine efficacy.

ROTAVAC™: In a Phase 3 randomized double-blind, placebo-controlled, multicenter trial at three sites in Delhi (urban), Pune (rural), and Vellore (urban and rural), infants aged 6–7 weeks were randomly assigned (2:1), to receive either three doses of the 116E vaccine or placebo at ages 6–7 weeks, 10 weeks, and 14 weeks (4 weeks interval). The primary outcome was incidence of SRVGE (≥11 on the Vesikari scale). Efficacy outcomes and adverse events were ascertained through active surveillance.[16]

Vaccine efficacy against SRVGE was overall, 53.6% (95% CI 35.0–66.9; p = 0.0013), 56.4% (36.6–70.1; p <0.0001) in the first year of life and 48.9% (95% CI 17.4–68.4; p = 0.0056) in the second year of life. Vaccine efficacy against severe gastroenteritis of any cause was overall 18.6% (1.9–32.3, p = 0.0305), 24.1% (5.8–38.7, p = 0.0123) at the end of the first year of life and 36.2% (20.5–48.7, p <0.0001) in the second year.[17]

Rotasiil™: Two phase 3 studies done in Niger and India have established the immunogenicity, safety, and efficacy of this vaccine.

In the Indian study, a total of 3,749 infants 6–8 weeks of age were randomized (1:1) to receive three oral doses of BRV-PV or placebo (N = 3751) at 6, 10, and 14 weeks of age along with routine vaccines. The study was conducted across 6 centers in India.

Vaccine efficacy against SRVGE, at the time of the primary endpoint (when the minimum number of cases needed for analysis were accrued) was 36% (95% CI 11.7, 53.6, p = 0.0067) in the per protocol (PP) analysis and 39.5% (95% CI 26.7, 50, p <0.0001) in the PP analysis over the entire follow-up period (until children reached 2 years of age). Vaccine efficacy against the very severe rotavirus cases (VSRVGE, Vesikari score >16) was 60.5% (95% CI 17.7, 81, p = 0.0131) at the time of the primary analysis and 54.7% (95% CI 29.7, 70.8, p = 0.0004) for the complete follow-period in the PP population. Vaccine efficacy against severe gastroenteritis of any etiology was negligible at 7.5% (–4.9–18.5, p = 0.2221).[18]

In the study done in Niger, the efficacy of three doses of vaccine as compared with placebo against a first episode of laboratory-confirmed SRVGE (Vesikari score, ≥11) beginning 28 days after dose 3 was 66.7% (49.9–7.9).[19]

Effectiveness of Rotavirus Vaccines

A systematic review of 48 peer-reviewed articles with postlicensure data from 24 countries over the first decade of global postlicensure (2006–2016), showed a greater vaccine effectiveness (VE) in low mortality countries (LMC) and a lower VE in high mortality countries (HMC) for both RV1 and RV5 **(Table 1)**.[20] VE tended to decline in the second year of life, particularly in medium- and high-mortality settings, and tended to be greater against more severe rotavirus disease. This is in conformity with the findings in the recent Cochrane review.[21] However, since the incidence of SRVGE is significantly higher in high mortality settings, the numbers of severe disease cases and deaths averted by vaccines in these settings are likely to be higher than in low mortality settings, despite the lower vaccine efficacy.

Observational studies in Mexico and Brazil after the introduction of RV1 reported a reduction in diarrhea-related deaths in infants and young children. After RV1 introduction, Mexico saw a 35% (95% CI: 29–39) reduction in the rate of diarrheal deaths predominantly

TABLE 1: Vaccine effectiveness for RV1 and RV5.

	RV1		*RV5*	
VE	*LMC*	*HMC*	*LMC*	*HMC*
Overall VE	84% (19–97)	57% (18–64)	90% (63–100)	45 (43–92)
RV hospitalization	88 (70–95)		94% (83–100)	
ED visits	80% (78–86)		81% (74–91)	
VSRVGE		64% (−114–83)		72% (58–80)

(HMC: high mortality countries; LMC: low mortality countries; RV: rotavirus vaccine; VE: vaccine effectiveness)

during the usual rotavirus season among children age appropriate for the vaccine.[22] After RV1 introduction in Brazil in 2006, 30% (95% CI: 19–41) and 39% (95% CI: 29–49) decreases in gastroenteritis mortality were noted in 2007 and 2008, respectively, when compared to the mortality rates in 2004–2005.[23] Thus, introduction of the vaccine into countries is likely to have a greater effect than that predicted on the basis of the efficacy trials. RV5 was also reported to reduce the number of cases of SRVGE by nearly half (48%) in infants evaluated in developing countries in Asia (Bangladesh and Vietnam) and by 39% in infants evaluated in developing countries in Africa (Ghana, Kenya, and Mali) through nearly 2 years of follow-up. These were the first studies demonstrating efficacy for any rotavirus vaccine in developing countries in Asia. For the two vaccines that are currently licensed for use in many countries, 22.1% of the strains identified in this study would be covered by RV1 and 47.9% by RV5, if only homotypic immunity is induced by vaccination, although reports from Europe indicate cross-protection across genotypes with use of RV1.

STUDIES IN INDIA

There is no efficacy study of the two rotavirus vaccines, RV1 and RV5, conducted in India. Both of these vaccines were licensed on the basis of immunogenicity studies. Based on 58% immunogenicity for RV1 and 83% for RV5—but by different ways of assessing immunogenicity—RV1 and RV5, were licensed[24,25] and used in the

private market. The only efficacy study conducted in the country so far was with Indian neonatal rotavirus vaccine, 116E. In 2014, the results of the efficacy trial with 116E became available, and at 55% efficacy, the performance of this vaccine was comparable to that of RV1 and RV5 in Africa and other countries in Asia.

In the immunogenicity studies of RV1 and RV5 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, and Bangladesh). Studies show no interference between rotavirus vaccines and other childhood vaccines including inactivated polio vaccine (IPV), pneumococcal, *Haemophilus influenzae* type b (Hib), diphtheria, tetanus, and acellular pertussis (DTaP), and hepatitis B. Data is insufficient for pertussis immunity. Immunogenicity studies about simultaneous administration of rotavirus vaccines with oral poliovirus vaccines (OPV) are available for RV1 and RV5, which show no reduction in immunogenicity against polio and no significant reduction in immunogenicity against rotavirus.[24,25]

Efficacy data of the Indian vaccines has been discussed above.

SAFETY AND RISK OF ACUTE INTUSSUSCEPTIONS OF ROTAVIRUS VACCINES

The available new generations of rotavirus vaccines are considered quite safe and the risk of acute intussusception is very small in comparison to previous vaccine.

Based on postmarketing surveillance data, the current rotavirus vaccines have been associated with an increased risk of intussusceptions (about 1–2/100,000 infants vaccinated) for a short period after administration of the first dose in some populations.[2] This risk is 5–10 times lower than that is observed with the previously licensed vaccine (1 case per 10,000 doses). A meta-analysis of intussusception risk following real-world rotavirus vaccination in Australia, Brazil, England, Mexico, Singapore, and the US, published in 2015, found an elevated risk of intussusception in the first 21 days following the first dose of Rotarix (OR 2.4; 95% CI 1.5–3.8) and the second dose (OR 1.8; 95% CI 1.3–2.4), or roughly 1.9 and 1.5 excess cases of intussusception per 100,000 children vaccinated,

respectively.[26] An analysis of the risk of intussusception following RotaTeq vaccination in Australia and the US also found a similar level of risk for the first and second dose.[27] No association between intussusception and rotavirus vaccination was found in a retrospective evaluation in South Korea, although the number of children included in the analysis was smaller than other postlicensure studies.[28]

In 2014, the African Intussusception Surveillance Network was established, which included seven countries using RV1 (Ethiopia, Ghana, Kenya, Malawi, United Republic of Tanzania, Zambia, and Zimbabwe), surveillance for intussusception (defined using Brighton case definition criteria) was conducted at 28 sentinel pediatric hospitals. No increased risk of intussusception was identified after either dose 1 or 2.[29]

A sentinel surveillance for intussusception in children aged under 2 years is being established at 19 hospitals. The surveillance combines retrospective surveillance for 69 months and prospective surveillance for 18 months with diagnosis being made by the Brighton Collaboration criteria. The combination of prospective and retrospective surveillance shall be informative about the trend of intussusception over the last 7 years in India. At four sites where rotavirus vaccines have been introduced, the change in intussusception trends shall be documented.[30]

Rotavac™: In the pivotal study, adverse effects profile was similar in both groups. Six cases of intussusception were recorded in the vaccine group and two in the placebo group, all of which happened after the third dose. The minimum interval between dosing and intussusception was 112 days in the vaccine group and 36 days in the placebo group. 25 (<1%) infants in the vaccine group and 17 (<1%) in the placebo group died; no death was regarded as related to the study product.[16]

Rotasiil™: In the Indian study, adverse effects profile was similar in both groups. 13 cases of intussusception were diagnosed; 6 occurred in the BRV-PV arm and 7 in the placebo arm. None occurred within 28 days of receiving a dose of BRV-PV or placebo.[18]

The Global Advisory Committee on Vaccine Safety (GACVS) of the WHO in its report in 2017, concludes that there is definite albeit a small risk of acute intussusceptions following use of current generation of

rotavirus vaccines. However, the benefits of rotavirus vaccination against severe diarrhea and death from rotavirus infection far exceed the miniscule risk of intussusceptions.[31]

RECOMMENDATIONS FOR USE

Public Health Perspectives

The Advisory Committee on Vaccines and Immunization Practices (ACVIP) acknowledges the morbidity and mortality burden of rotavirus and need for effective rotavirus vaccines. Such vaccines 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.

It is heartening to note that the Government of India, in March 2016, introduced the rotavirus vaccine (116E) in the Universal Immunization Programme (UIP) in four states namely Haryana, Himachal Pradesh, Andhra Pradesh, and Odisha. In phase 2, in February 2017, the available Indian vaccines have been expanded to five more states of Assam, Tripura, Madhya Pradesh, Rajasthan, and Tamil Nadu.

Initially, WHO recommended upper age limits for vaccination to minimize excess cases of intussusception. However, these recommendations were changed as it excluded substantial number of children from vaccination. A model was used to predict the number of deaths prevented by rotavirus vaccination and the number of intussusception deaths caused by rotavirus vaccination when administered without any age restriction. The model predicted that the restricted schedule would prevent 155,800 rotavirus deaths (5th–95th centiles, 83,300–217,700) while causing 253 intussusception deaths (76–689). As against it vaccination without age restrictions would prevent 203,000 rotavirus deaths (102,000–281,500) while causing 547 intussusception deaths (237–1160) (i.e. 154 deaths averted for 1 death caused by the vaccine).[2] WHO recommends administering

rotavirus vaccine to children up to 24 months of age concomitantly with diphtheria, tetanus and pertussis (DTP) vaccine.[2]

Schedule in UIP:[32] The rotavirus vaccine is to be administered in three doses at 6, 10, and 14 weeks along with the other UIP vaccines. The maximum upper age limit for giving first dose of rotavirus vaccine is 1 year. If the child has received first dose of rotavirus vaccine by 12 months of age, two more doses of the vaccine should be given with an interval of 4 weeks between two doses to complete the course.

Individual Use

Administration schedule: Vaccination should be strictly as per schedule discussed below, as there is a potentially higher risk of intussusceptions, 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 SRVGE.

In 2013, the IAP ACVIP opined that if RV1 vaccine is to be administered in a 2-dose schedule, the first dose should start at 10 weeks of age instead of 6 weeks in order to achieve better immune response. The second dose can be administered at 14 weeks to fit with existing national immunization schedule. However, 3-dose schedule of any rotavirus vaccine can start at 6 weeks of age with minimum interval of 4 weeks between the doses. This recommendation was based on two studies, the study conducted in South Africa in which the seroconversion of first dose of RV1 when administered at 6 weeks along with OPV was found to be only 13%[33] and the African trial of a 2-dose and 3-dose schedule of RV1 starting at 6 weeks of age, which showed that vaccine efficacy against severe rotavirus diarrhea for the first year with 2-dose schedule was 58.7 (95% CI 35.7–74) while for 3-dose schedule for the same was 63.7 (95% CI 42.4–77.8). However during second year there was significant difference in efficacy of both the schedules in both the countries.[34-36]

However, results from other studies have given variable conclusions. In the study in rural Ghana, three doses of human rotavirus vaccine (HRV) resulted in significantly improved antirotavirus immunoglobulin A (IgA) seroconversion frequencies and geometric mean concentrations (GMCs) as compared two doses given at the WHO-recommended ages of 6 and 10 weeks. In contrast, two doses of HRV given on a delayed schedule at 10 and 14 weeks of age increased the seroconversion frequency when compared to the 6- and 10-week arm, but this difference was not significant.

In the study in Pakistan administering RV1 in a 3-dose schedule at 6/10/14 weeks did not lead to significantly higher rotavirus IgA seroconversion at 18 weeks when compared to the cumulative seroconversion (highest IgA result at 14 or 18 weeks) following a 2-dose schedule at 6/10 weeks. Additionally, a delayed 2-dose schedule at 10/14 weeks did not lead to higher seroconversion compared to the cumulative result in the 6/10 group.

In a study done in Bangladesh comparing the immune response with normal breastfeeding and withholding breastfeeding at the time of vaccination in two cohorts administered RV1 at 6–10 weeks and 10–14 weeks, the immune response was not influenced by breast milk intake around vaccination. Delaying the time of immunization resulted in a substantial improvement in the immune response to the rotavirus vaccine.

Clinical trials from Pakistan and India, did not document enhanced immune responses with a 3-dose or 5-dose RV1 schedule.

In general, the available data suggests that the 6/10-week schedule is not as immunogenic as the 10/14-week schedule in low-to-middle-income countries (LMICs). However, this conclusion is based on a relatively small body of evidence, and the estimates for each schedule within each trial had a large amount of variability. Consequently, moderate differences that appear between different vaccine schedules may be due to random variability. Currently, there is no known correlate of protection for antirotavirus IgA levels. Therefore, even an association between vaccine schedule and immunogenicity does not provide evidence of a difference in disease protection.

It is probable that setting-dependent variability in rotavirus immunity and epidemiology may help explain discrepant result from vaccine studies in these different regions.

Following the rollout of rotavirus vaccines in LMIC of Africa and Asia, impact data against various endpoints are now available. In general, the impact data have been comparable to the efficacy data generated in phase 3 studies. These include Ghana: any-dose VE against rotavirus hospitalization was estimated at 60% (95% CI, –2% to 84%; P = 0.056), Malawi: VE for two doses of RV1 in rotavirus-negative individuals was 64% (95% CI 24–83), Zambia: VE against hospitalized children ≥6 months of age was 56% (95% CI, –34% to 86%), South Africa: adjusted VE using rotavirus-negative controls was 57% (95% CI 40–68) for two doses. A review of studies from 38 populations found that all rotavirus gastroenteritis events (RVGE) occurred in 1%, 3%, 6%, 8%, 10%, 22% and 32% children by age 6, 9, 13, 15, 17, 26 and 32 weeks, respectively. Mortality was mostly related to RVGE events occurring before 32 weeks of age.[37] The highest risk of mortality was noted in the children having earliest exposure to rotavirus, living in poor rural households, and having lowest level of vaccine coverage.[38] It is ideal if immunization schedule is completed early in developing countries where natural infection might occur early.[2]

Infants in developing countries may be at risk of developing RVGE at an earlier age than those in developed countries. They also tend to have a higher risk of mortality coupled with the risk of lower vaccine coverage. No observational study has compared different ages at first dose. A schedule of two doses at 10 and 14 weeks may result in incomplete course of vaccination, especially in developing countries because of restriction of upper age limit for rotavirus vaccine administration. Such children would remain immunologically susceptible to get rotavirus infection. Early administration of the first dose of rotavirus vaccine as soon as possible after 6 weeks of age has been recommended by WHO recently. Administration of RV1 or RV5 vaccine at 6 weeks has also been recommended and approved even in developed countries.

It is to be noted that 28 of the 40 Gavi-eligible countries using RV1 in their national immunization programs (NIPs) follow the 6–10 weeks, WHO approved schedule.

The WHO position paper recommends that first dose of rotavirus vaccination should be given with first dose of DPT vaccination both for RV1 and RV5, which effectively means starting the schedule at 6 weeks in India. The ACVIP endorses this recommendation and recommends a 6–10 weeks schedule for the RV1 vaccine.

Upper limits of immunization: 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 8 months (32 weeks) of age. Both vaccines should not be frozen. ACVIP recommends to follow manufactures' recommendations. 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 RV1 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 RV5, 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 AND PRECAUTIONS

Rotavirus vaccine should not be administered to infants who have a history of a severe allergic reaction (e.g. anaphylaxis) after a previous dose of rotavirus vaccine or to a vaccine component. History of

Rotavirus vaccination.

Routine vaccination:

- Minimum age: 6 weeks for all available vaccines
- An interval of 4 weeks should be maintained between doses.
- Only two doses of RV-1 are recommended at present with the first dose administered at 6 weeks of age and the second dose administered 4 weeks later.
- RV5 should be employed in a three-dose 6, 10, and 14 weeks-schedule. If any dose in series was RV5 or vaccine product is unknown for any dose in the series, a total of 3 doses of RV vaccine should be administered.

Catch-up vaccination:

- The maximum age for the first dose in the series is 14 weeks, 6 days.
- Vaccination should not be initiated for infants aged 15 weeks, 0 days or older.
- The maximum age for the final dose in the series is 8 months, 0 days.

intussusception in the past is also an absolute contraindication for rotavirus vaccines administration. Latex rubber is contained in the RV1 oral applicator, so infants with a severe (anaphylactic) allergy to latex should not receive RV1 vaccine. The RV5 dosing tube is latex-free.

Severe combined immunodeficiency (SCID) and history of intussusception are contraindications for use of both rotavirus vaccines.

Precautions for administration of rotavirus vaccine include manifestations of altered immunocompetence (other than SCID, which is a contraindication); moderate to severe illness, including gastroenteritis (vaccination to be postponed); preexisting chronic intestinal tract disease.

Rotavirus vaccine may be administered at any time before, concurrent with, or after administration of any blood product, including antibody-containing blood products.

REFERENCES

1. Kotloff KL, Nataro JP, Blackwelder WC, et al. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. Lancet 2013; 382: 209–22.
2. Rotavirus vaccine. WHO Position Paper 2013. Weekly epidemiological record. 2013; 88: 49–64.
3. Parashar UD, Gibson CJ, Bresse JS, et al. Rotavirus and severe childhood diarrhoea. Emerg Infect Dis 2006;12:304–16.

4. Morris SK, Awasthi S, Khera A, et al. and for the Million Death Study Collaborators. Rotavirus mortality in India: estimates based on a nationally representative survey of diarrhoeal deaths. http://www.who.int/bulletin/volumes/90/10/12-101873/en/
5. Kang G, Arora R, Chitambar SD, et al. Multicenter, hospital-based surveillance of rotavirus disease and strains among Indian children aged <5 years. J Infect Dis. 2009;200 (Suppl 1):S147-53. doi: 10.1086/605031.
6. Tate JE, Chitambar S, Esposito DH, et al. Disease and economic burden of rotavirus diarrhoea in India. Vaccine. 2009;27:F18–24.
7. Ramani S, Kang G. Burden of disease and molecular epidemiology of group A rotavirus infections in India. Indian J Med Res. 2007;125(5):619-32.
8. CP Girish Kumar et al. Rotavirus genotypes in India. Data from Indian Rotavirus Strain Surveillance Network (2012-2014). Poster presented at ds RNA conference in Oct 2015. (P1-40).
9. Angel J, Franco MA, Greenberg HB. Rotavirus immune responses and correlates of protection. Curr Opin Virol. 2012;2(4):419–25.
10. Velazquez FR, Matson DO, Calva JJ, et al. Rotavirus infection in infants as protection against subsequent infections. N Engl J Med. 1996;335: 1022–8.
11. Gladstone BP, Ramani S, Mukhopadhya I, et al. Protective effect of natural rotavirus infection in an Indian birth cohort. N Engl J Med. 2011;365:337–46.
12. Bhandari N, Sharma P, Taneja S, et al. A dose-escalation safety and immunogenicity study of live attenuated oral rotavirus vaccine 116E in infants: a randomized, double blind, placebo-controlled trial. J Infect Dis. 2009;200:421–9.
13. Ella R, Bobba R, Muralidhar S, et al. A Phase 4, multicentre, randomized, single-blind clinical trial to evaluate the immunogenicity of the live, attenuated, oral rotavirus vaccine (116E), ROTAVAC®, administered simultaneously with or without the buffering agent in healthy infants in India, Hum Vaccin Immunother. 2018;14(7): 1791-9. DOI: 10.1080/21645515.2018.1450709.
14. Zade JK, Kulkarni PS, Desai SA, et al. Bovine rotavirus pentavalent vaccine development in India Vaccine 32S (2014) A124–A128.
15. Vesikari T. Rotavirus vaccination: a concise review. Clin Microbiol Infect. 2012;18 (Suppl. 5): 57–63.
16. Bhandari N, Rongsen-Chandola T, Bavdekar A, et al. Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian infants: a randomised, double-blind, placebo-controlled trial. Lancet. 2014;383:2136–43.
17. Bhandari N, Rongsen-Chandola T, Bavdekar A, et al. Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian children in the second year of life. Vaccine. 32S (2014) A110–A116

18. Kulkarni PS, Desai S, Tewari T, et al. A randomized Phase III clinical trial to assess the efficacy of a bovine-human reassortant pentavalent rotavirus vaccine in Indian infants. Vaccine. 2017;35(45): 6228–37.
19. Isanaka S, Guindo O, Langendorf C. Efficacy of a low-cost, heat-stable oral rotavirus vaccine in Niger. N Engl J Med. 2017;376:1121-30.
20. Jonesteller CL, Burnett E, Yen C. Effectiveness of Rotavirus Vaccination: A Systematic. Review of the First Decade of Global Postlicensure Data, 2006–2016.Clin Infect Dis. 2017;65(5):840–50.
21. Soares-Weiser K, Maclehose H, Bergman H, et al. Vaccines for preventing rotavirus diarrhoea: vaccines in use. Cochrane Database Systematic Review, 2012, 11: CD008521. doi: 10.1002/14651858.CD008521.pub3. Review
22. Richardson V, Hernandez-Pichardo J, Quintanar-Solares M, et al. Effect of rotavirus vaccination on death from childhood diarrhea in Mexico. N Engl J Med. 2010;362:299–305.
23. Lanzieri TM, Linhares AC, Costa I, et al. Impact of rotavirus vaccination on childhood deaths from diarrhea in Brazil. Int J Infect Dis. 2011;15:e206–10.
24. Narang A, Bose A, Pandit AN, et al. Immunogenicity, reactogenicity and safety of human rotavirus vaccine (RIX4414) in Indian infants. Hum Vaccin. 2009;5:414–9; PMID: 19276664.
25. Lokeshwar MR, Bhave S, Gupta A, et al. Immunogenicity and safety of the pentavalent human-bovine (WC3) reassortant rotavirus vaccine (PRV) in Indian infants. Hum Vaccin Immunother. 2013;9:172–6. doi: 10.4161/ hv.22341.
26. Rosillon D, Buyse H, Friedland LR, et al. Risk of intussusception after rotavirus vaccination: meta-analysis of postlicensure studies. Pediatr Infect Dis J. 2015;34(7):763–8.
27. Yih WK, Lieu TA, Kulldorff M, et al. Intussusception risk after rotavirus vaccination in US infants. N Engl J Med. 2014;370(6):503–12.
28. Kim KY, Kim DS. Relationship between pentavalent rotavirus vaccine and intussusception: a retrospective study at a single center in Korea. Yonsei Med J. 2017;58(3):631–6.
29. http://www.who.int/vaccine_safety/committee/reports/Dec_2017/en/
30. Das MK, Arora NK , Bonhoeffer J. intussusception in young children: protocol for multisite hospital sentinel surveillance in India. Methods and Protoc. 2018;1(2):11. doi:10.3390/mps1020011
31. Patel MM, Clark AD, Glass RI, et al. Broadening the age restriction for initiating rotavirus vaccination in regions with high rotavirus mortality: benefits of mortality reduction versus risk of fatal intussusception. Vaccine. 2009;27(22):2916–22.
32. Operational guidelines. Introduction of Rotavirus vaccine in Universal Immunization Program in India. Immunization division, Ministry of Health and Family welfare, Government of India. December 2016.

33. Steele AD, De Vos B, Tumbo J, et al. Co-administration study in South African infants of a live-attenuated oral human rotavirus vaccine (RIX4414) and poliovirus vaccines. Vaccine 2010;n28:6542–8.
34. Madhi SA, Cunliffe NA, Steele D, et al. Effect of human rotavirus vaccine on severe diarrhea in African infants. N Engl J Med. 2010;362:289–8.
35. Cunliffe NA, Witte D, Ngwira BM, et al. Efficacy of human rotavirus vaccine against severe gastroenteritis in Malawian children in the first two years of life: a randomized, double-blind, placebo controlled trial. Vaccine. 2012;30(Suppl 1): A36–43.
36. Madhi SA, Kirsten M, Louw C, et al. Efficacy and immunogenicity of two or three dose rotavirus-vaccine regimen in South African children over two consecutive rotavirus-seasons: A randomized, double-blind, placebo-controlled trial. Vaccine 2012;30 (Suppl 1): A44–51.
37. World Health Organization. Detailed Review Paper on Rotavirus Vaccines (presented to the WHO Strategic Advisory Group of Experts (SAGE) on Immunization in April 2009). Geneva, World Health Organization, 2009. Available from: http://www.who.int/immunization/sage/3_Detailed_Review_Paper_on_Rota_Vaccines_17_3_2009.pdf. Accessed November 08, 2018.
38. Phua KB, Lim FS, Lau YL, et al. Rotavirus vaccine RIX4414 efficacy sustained during the third year of life: a randomized clinical trial in an Asian population. Vaccine. 2012;30:4552-7.

3.8 MEASLES, MUMPS, AND RUBELLA VACCINES

Abhay K Shah

MEASLES-RUBELLA: BURDEN OF DISEASE AND GENERAL PERSPECTIVE

Measles elimination contributes significantly in achieving Millennium Development Goal 4 (MDG-4). "One of the three indicators for monitoring progress toward achieving MDG-4 is the proportion of 1-year-old children immunized against measles".[1]

While measles is now rare in many industrialized countries, it remains a common illness in many developing countries. In countries where measles has been largely eliminated, cases imported from other countries remain an important source of infection. While India has made significant progress in child survival, measles remains a leading cause of death and disability among young children. An estimated 50,000–100,000 children die from measles annually, making it one of the leading causes of child death. When vaccine efficacy of 85% at 9 months of age is taken into account, approximately 41% (31% unimmunized + 15% of immunized who failed to seroconvert) of children in each birth cohort remain susceptible to measles due to dropout, left out, and failure to develop immunity.

The Universal Immunization Programme (UIP) of the Government of India (GoI) had included one dose of measles vaccine between 9 months and 12 months of age since 1985. From 2010, based on recommendations from national expert committees, GoI has decided to introduce a second dose of measles vaccine in the UIP. In the revised routine immunization (RI) schedule, every child will get two doses of measles-containing vaccine: the first dose between 9 months and 12 months of age and the second between 16 months and 24 months of age along with DTP (diphtheria, tetanus toxoids, and pertussis) booster dose. If a child has missed the first or the second dose, both doses can be given up to 5 years of age maintaining a gap of at least 30 days between the doses. However, it is very important that high coverage >80% is maintained for both doses of measles containing vaccine (MCV) in every district.

Since 2001, the Measles Initiative has supported 80 countries to deliver more than 1 billion doses of measles vaccine, helped to raise measles vaccination coverage to 85% globally, and reduced global measles deaths by 74%. These efforts have contributed significantly to reducing child mortality as per MDG-4.[2]

The Measles and Rubella Initiative is a global partnership aimed at ensuring no child dies of measles or is born with congenital rubella syndrome (CRS). Founded originally as the Measles Initiative in 2001, it is led by the American Red Cross, the United Nations Foundation, the US Centers for Disease Control and Prevention, United Nations International Children's Emergency Fund (UNICEF), and the World Health Organization (WHO).

The measles deaths have been reduced from 106,000 in 2005 to 65,000 in 2010 and 29,336 in 2012.[3,4] Still India contributes to almost 47% of the global measles deaths, reflecting poor performance.[5] With the highest birth cohort in the world, the highest number of measles deaths, and relatively poor vaccine coverage, India poses a challenge for the Global Measles Eradication goal.

In 2016, the number of measles deaths dropped to below 100,000 for the first time, an achievement that can largely be attributed to immunization. However, coverage with the first dose of measles-containing vaccine in The Global Alliance for Vaccines and Immunizations (GAVI)-supported countries has plateaued at 78%—a long way from the 95% herd-immunity target.

Coverage with a full course of rubella-containing vaccines (RCVs) in GAVI-supported countries amounted to 24% in 2017—a 7-percentage point increase from the year before. Since 2017, over 52 million children reached with a second dose of measles-rubella (MR) vaccine.[6]

To control measles, a country needs sustained >95% vaccination coverage. Among different states in India, there is a considerable difference in vaccination coverage. States like Kerala, Goa, Sikkim, and Punjab demonstrate almost 90% coverage, whereas states like UP, Bihar, MP, and Rajasthan report to have less than 70% coverage. Least coverage is reported from UP and Bihar with large number of measles cases.[7]

MEASLES-RUBELLA VACCINE

Standalone measles vaccine is no longer available. The measles vaccine is currently provided under UIP; the rubella vaccine will be a new addition. The number of WHO member states using RCV in their national childhood immunization schedule increased from 83 in 1996 to 149 in 2016; 14 countries have planned introduction of MR vaccine in 2017. It has proven to be a highly safe and effective vaccine.

India has committed to the elimination of measles and control of rubella by the year 2020. Rubella vaccine will be introduced as MR vaccine replacing both doses of the measles-containing vaccine at 9 months and 16–24 months. As per WHO, all countries that are providing two doses of measles vaccine using RI or supplemental immunization activities (SIAs), or both, should consider including RCVs in their immunization program.[8] Indian Academy of Pediatrics (IAP) also now recommends MR/measles, mumps, and rubella (MMR) in place of standalone measles vaccine at 9 months (IP 2018).[9] When the MR or MMR vaccines are used, the protective immune response to each of the components remains unchanged.[10] One dose of rubella vaccine probably induces lifelong protection.[8]

The exact rubella disease load in the community cannot be made out clinically as more than half of all cases are subclinical. This makes the estimation of those who are susceptible to the infection and hence at risk of having acute infection during pregnancy resulting in fetal CRS difficult.[11]

Switching from M to MR or MMR vaccine needs following considerations:

- Achieving and maintaining measles vaccination coverage of 80% or greater through routine and/or regular campaigns before including immunization against rubella, as recommended by WHO.
- Ensure availability of appropriate infrastructure and resources for immunization programs.
- Achieving ability to conduct high-quality campaigns to close the rubella immunity gap at the time of introduction.
- Improved record keeping is a strategic prerequisite to improve monitoring of progress toward coverage targets.

- Ensuring vaccine security (reliable supply of quality vaccine at an affordable price) through strong engagement with industry and partners, as well as accurate forecasting of vaccine supplies as changing from M vaccine to a combined MR vaccine increases the cost per dose by about INR 16.24 for MR vaccine and by INR 37.89–51.42 for MMR vaccine based on using 10-dose vials.[12]

The Vaccine

- The measles-rubella (MR) vaccine is prepared from the live, attenuated strains of Edmonston-Zagreb measles virus and Wistar RA 27/3 rubella virus. Both measles and rubella viruses are propagated on human diploid cells (HDCs). The vaccine is lyophilized and is provided with diluent. The product has the appearance of a yellowish-white dry cake. The vaccine meets the requirements of WHO when tested by the methods outlined in WHO, TRS 840 (1994). The diluent (sterile water for injections) supplied is specially designed for use with the vaccine. Only this diluent must be used to reconstitute the vaccine. Do not use diluents from other types of vaccine or for MR vaccine from other manufacturers. Water for injections must not be used for this purpose.
- It is a freeze-dried vaccine, available as single-dose and multidose vials and is to be administered subcutaneously. Each single-human dose when reconstituted in a volume of 0.5 mL contains not less than 1000 median cell culture infective doses ($CCID_{50}$) of live measles virus particles and 1,000 $CCID_{50}$ of rubella virus.
- The dose is 0.5 mL subcutaneously or intramuscularly, preferably over the upper arm/anterolateral thigh.
- Its shelf life is 24 months at 2–8°C. WHO recommends that opened vials of this vaccine should be discarded 6 hours after opening or at the end of the immunization session, whichever comes first. Measles-containing vaccines 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. Toxic shock syndrome (TSS) can be prevented by adhering to injection safety and if reconstituted multidose measles vaccine

is used within 4–6 hours. Leftover doses after this period must be discarded.

- Immunogenicity depends on the age of administration due to interference by pre-existing 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 human immunodeficiency virus (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% to 80% when given at the age of 9 months.
- If pregnancy is planned then an interval of 1 month should be observed after MR vaccination.
- The vaccine is contraindicated in the severely immunocompromised, in those with history of severe allergic reactions to the constituents and in pregnancy. The vaccine may contain traces of neomycin. Anaphylactic or anaphylactoid reactions to neomycin, history of anaphylactic, or anaphylactoid reactions are absolute contraindications. There are extremely rare reports of hypersensitivity reactions with MR vaccines in individuals who are allergic to cow's milk. Such individuals should not receive the vaccine. Low-grade fever, mild respiratory infections or diarrhea, and other minor illness should not be considered as contraindications. It is particularly important to immunize children with malnutrition. MR vaccine should not be administered in pregnant women. 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.

Side Effects

- The MR vaccine is a WHO prequalified vaccine, safe and effective. There is vaccine vial monitor on top of each vial, which indicates

the quality of the vaccine given. Side effects are very rare and usually mild. The measles vaccine may cause within 24 hours of vaccination mild pain and tenderness at the injection site. In most cases, they spontaneously resolve within 2–3 days without further medical attention. A mild fever can occur in 5–15% of vaccinees 7–12 days after vaccination and last for 1–2 days. Rash occurs in approximately 2% of recipients, usually starting 7–10 days after vaccination and lasting 2 days. The mild side effects occur less frequently after the second dose of a measles-containing vaccine and tend to occur only in person not protected by the first dose. Encephalitis has been reported following measles vaccination at a frequency of approximately one case per million doses administered although a causal link is not proven. Apart from local pain and tenderness, a mild measles-like illness appears 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 are no data to support causal relationship between measles vaccine and encephalitis, Guillain–Barré syndrome (GBS), subacute sclerosing encephalitis, and autism. There is no transmission of the vaccine virus from the vaccinees to the contacts.[12,13]

- The rubella component may commonly result in joint symptoms manifested as arthralgias (25%) and arthritis (10%) among adolescent and adult females that usually last from a few days to 2 weeks. However, such adverse reactions are very rare in children and in men receiving MR vaccine (0–3%). Symptoms typically begin 1–3 weeks after vaccination and last 1 day to 2 weeks. These transient reactions seem to occur in nonimmunes only, for whom the vaccine is important. Low-grade fever and rash, lymphadenopathy, myalgia, and paraesthesia are commonly reported. Thrombocytopenia is rare and has been reported in less than 1 case per 30,000 doses administered. Anaphylactic reactions are also rare. In susceptible individuals, the vaccine may very rarely cause allergic reactions like urticaria, pruritus, and allergic rash within 24 hours of vaccination.

Recommendations for Use

Overwhelming evidence has demonstrated that measles vaccination preferably combined with RCVs is among the most cost-effective public health tools available currently, provided universal coverage of not less than 95% is achieved. 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-containing vaccination in India.

Individual Use

Measles-rubella vaccine given at 9 months is an epidemiological compulsion and has almost 20% primary vaccine failure due to maternal antibodies. Therefore, at least two or three measles-containing vaccines are required for protection and in spite of this, 5–8% may remain susceptible. Thus, additional doses of measles-containing vaccine preferably as MMR vaccine at the age of 15 months and again between 4.5 years and 5 years give durable and possibly lifelong protection against measles.

Dosage and Regimen

- *First dose (MCV1)*: Typically delivered as MR/MMR at 9 months, or in accordance with WHO-recommended schedules.
- *Second dose (MCV2 as MMR)*: Ideally delivered at ages 15–18 months, or in accordance with WHO-recommended schedules.
- *Third dose* (MCV3) as MMR at 5 years of age.

The WHO recommends measles vaccine be administered at 9 months of age in countries with ongoing transmission of measles in which the risk of measles mortality among infants is high. In countries with low rates of transmission the WHO recommends the first dose of measles vaccine be given at 12 months to take advantage of higher seroconversion rates achieved at this age. In case of an outbreak, 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.

Public Health Perspectives

MR Campaign

The National Technical Advisory Group on Immunization (NTAGI) in June, 2014 had recommended the introduction of MR vaccine in RI program, following a nationwide MR campaign. Both doses of measles vaccine provided at 9–12 months and 16–24 months, will be replaced by MR vaccine under RI, immediately after the campaign.[13]

According to the Global Measles and Rubella Strategic Plan: 2012–2020, all six WHO regions (Africa, the Americas, South-East Asia, Europe, the Eastern Mediterranean, and the Western Pacific) have committed to measles elimination. Government of India, Ministry of Health and Family Welfare, has launched one of the world's largest MR vaccination campaigns as part of its national strategy to eliminate measles and rubella disease from the country by 2020. The phased MR campaign was just completed to vaccinate approximately 41 crore children in the age group of 9 months to 15 years.

MR Vaccination Campaign: Key Facts

- Age group between 9 months and less than 15 years
- One-dose campaign, irrespective of previous measles/rubella vaccination or disease status
- *Dose*: 0.5 mL, subcutaneous route using autodisable syringes
- *Vaccine*: 10-dose MR vial (WHO prequalified, manufactured by Serum Institute of India)
- Immediately after the completion of campaign, MR vaccine will be introduced in RI, replacing the currently given two doses of measles vaccine—at 9–12 months and 16–24 months
- The MR dose received during the campaign will be counted as the campaign dose and no MCV to be provided in the RI sessions during campaign period.

Government has already implemented the program and in many states school children are getting vaccinated where the program is

in campaign mode. There is a concern that in program areas, a few children especially in older age group may get additional doses as it may not be possible to screen vaccination status of every child. However, extra doses do no harm and in fact benefit miniscule of children who do not seroconvert even after two or three doses. It is also important to remember that programmatic issues always override individual interests. Many African countries nearly eliminated measles with vaccination in campaign mode and it is high time that India also eliminates measles.

Being a core member of Indian Expert Advisory Group for Measles and Rubella, and the National Task Force on MR Vaccination, IAP strongly supported and endorsed measles elimination and rubella control by 2020.[12] These platforms also include other development partners such as WHO, UNICEF, United Nations Development Programme (UNDP), Center for Disease Control, and other civil society organizations such as Indian Medical Association, and Lions Club international.

Measles-Rubella Follow-up Campaign

A follow-up campaign refers to a mass vaccination campaign organized as a periodic event (every 3–5 years, depending on the accumulation of susceptible cohorts) guided by country-specific surveillance data. The periodicity depends on the RI coverage, existence of pockets of unprotected children, and considering vaccine efficacy. These follow-up campaigns target children born after the last campaign to achieve and sustain a high level of population immunity. The target age group for immunization in these campaigns includes all children aged above 9 months who were born after the previous MR vaccination campaign.

Immunity to Measles and Rubella

In controlled studies, measles vaccine efficacy is 89% when given at 9 months and 99% when given at >12 months of age. Actual vaccine effectiveness under field conditions is usually lower. It is 85% when given at 9 months and 95% when given at >12 months of age.[13] Rubella vaccine is even more efficacious than measles, where the seroconversion rate is very high (99% when given after 1 year). Both

the development and the persistence of serum antibodies following MR vaccination are lower than, but parallel to, the response following natural measles/rubella infection. The peak antibody response occurs 6–8 weeks after infection or vaccination. Immunity conferred by vaccination against MR has been shown to persist for at least 20 years and is generally thought to be lifelong for most individuals.

RUBELLA VACCINE

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/newborn such as abortion, stillbirth, mental retardation, congenital heart disease, blindness, and cataract. Hence, the objective of vaccination against rubella is protection against 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 MR/MMR) in young children through public health measure with suboptimal coverage of the target population may be counterproductive 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. WHO estimates that 100,000 cases of CRS occur in developing countries alone. Comprehensive evidence about the true burden of CRS in India is not available.[14] However, Ministry of Health estimates that around 30,000 abnormal children are being born annually because of rubella. Many experts, however, say the accurate figure would be around 200,000.[15] The 2008 estimates suggest that the highest CRS burden is in South East Asia (approximately 48%), India being a major contributor, and Africa (approximately 38%).[16,17] Other developing countries have incidence rates of 0.6–4.1 per 1,000 live births.[18] In 2012 and 2013 (till 31st May), India reported 28 and 48 rubella outbreaks. Cost-benefit

studies in countries with RI coverage of >80% show that benefits of rubella vaccine outweigh the cost particularly when combined with measles vaccination.[19]

Susceptibility to rubella has been found to be high among adolescent girls in India. Studies conducted in Amritsar, Maharashtra, and Jammu report rubella susceptibility to be 36%, 23.6%, and 32.7% in prepubertal girls, adolescent females, and girls of 11–18 years, respectively.[20–22] It has been observed that around 40–45% of women in the childbearing age are susceptible to rubella.[23]

Rubella infection in women during early pregnancy is associated with CRS. Different studies, involving laboratory (serological) confirmation of CRS among symptomatic children, have reported the CRS occurrence of 4.2%, 10.27%, and 40%.[24–26] Furthermore, estimates suggest a wide range of the lifetime cost of treating a single CRS case, with some exceeding US $75,000 (INR 4,059,000).[27]

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 hours 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 postpubertal 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

Individual Use

ACVIP, for office practice, recommends the use of MR/MMR vaccine instead of monovalent rubella vaccine so as to provide additional protection against mumps and measles.

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The NTAGI observed that since the "disability component" of mumps is not a serious public health problem and since the addition of mumps component to UIP would result in a substantial increase (more than twice than that of rubella vaccine) in cost without commensurate public health benefits, MR vaccine should be introduced instead of MMR. Immediately after the completion of campaign, MR vaccine will be introduced in RI, replacing the currently given two doses of measles vaccine—at 9–12 months and 16–24 months.

Recently, many African countries have been using MR vaccine through SIAs successfully.[28] However, ACVIP thinks mumps is also having a significant burden though not adequately reported, and not targeting mumps in the ongoing MR elimination initiative is a missed opportunity.

MEASLES, MUMPS AND RUBELLA VACCINE

Globally, most countries use MMR vaccine instead of monovalent vaccines. ACVIP feels that the combined MMR vaccine is a better option than an MR vaccine because of the following reasons: mumps carries as much significance in terms of morbidity as rubella; complications of mumps are also many and can be profound—aseptic meningitis, encephalitis, orchitis, oophoritis, pancreatitis, deafness, transverse myelitis, facial palsy, ascending polyradiculitis, and cerebellar ataxia; like rubella, mumps in a pregnant woman can also give rise to fetal damage in the form of aqueductal stenosis leading to congenital hydrocephalus.[29] The epidemiology of mumps has not been investigated in India, but it is suggested that outbreaks occur every 5–10 years.[30] 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/HDC 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 2–8°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 0.5 mL subcutaneously. 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. About 5% 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 vaccine 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 were thrombocytopenia followed not be given to those with history of thrombocytopenic purpura following previous vaccination with measles/MMR. The vaccine may be safely given in those with history of egg allergy.

Recommendations for Use

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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%. States introducing MR should also establish surveillance as recommended by the subcommittee (for monitoring the burden and trend of CRS).[31]

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.

Individual Use

Advisory Committee on Vaccines and Immunization Practices 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. Three doses are recommended; one as MR/MMR at the age of 9 months, second as MMR at 15 months and third as MMR at school entry (4–6 years) or at any time 8 weeks after the previous 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-containing vaccine, two doses of MMR at 8 weeks interval suffices. 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 healthcare 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. Recently, mumps, measles, rubella, and varicella/chickenpox vaccine combining MMR and varicella vaccine (MMRV)

in a single shot has been introduced in the USA and a few other countries including India.

The academy believes that the burden of CRS and mumps is significant. Though exact community burden of CRS is lacking, the fact that a systematic review could be conducted on the eight multicentric studies on the prevalence of hospital-based CRS is in itself a proof of universality and existence of the problem. The documented 17% susceptibility rates among pregnant women should definitely be a cause of concern.

The burden of mumps is less specified and only sporadic outbreaks are reported.[30] Based on the data available at ID Surveillance program, the incidence of mumps is higher than measles and almost equal to varicella. It ranks 5th among top 10 infectious diseases captured through this surveillance utility.[32]

Though 120 countries (62%) have included mumps vaccine in their national immunization schedule, India is still not a member of this group. In India, outbreaks and sporadic cases have been reported throughout the year. Mumps is a prevalent viral disease with more than 90% cases going unreported.[33]

Hence, ACVIP stresses that both mumps and CRS are eligible to target for elimination and control. MMR vaccine is safe and effective. Mumps component of the MMR vaccine is about 88% (range: 31–95%) effective when a person gets two doses, and one dose is about 78% (range: 49–92%) effective. At the same time, the academy urges the government/Indian Council of Medical Research to take initiatives to strengthen ongoing rubella surveillance, preferably case-based, initiate efforts to measure community burden of CRS and investments in starting mumps surveillance.

Why Mumps is Important?

Mumps carries as much significance in terms of morbidity as rubella; complications of mumps are also many and can be profound—aseptic meningitis, encephalitis, orchitis, oophoritis, pancreatitis, deafness, transverse myelitis, facial palsy, ascending polyradiculitis, and cerebellar ataxia; like rubella, mumps in a pregnant woman can also give rise to fetal damage in the form of aqueductal stenosis leading to congenital hydrocephalus. Logistics also supports the use of MMR

vaccine instead of MR because with the same effort, money, and manpower, three common infectious diseases would be eliminated simultaneously instead of two.

Fortunately, we have effective and affordable vaccines to take on all the three diseases. While single dose of rubella/rubella-containing vaccines is sufficient to provide almost 100% protection against the disease, two or more doses of measles and mumps vaccines are needed to accord adequate protection.

We support the suggestion that at least 80% coverage must be achieved to offset any presumed epidemiological shift of rubella (and mumps) and consequently higher incidence of congenital complications.

According to available evidence, both these vaccines (MR/MMR) can be given safely at different ages including at 9 months of age. Most important thing is to achieve minimum 80% coverage of childhood vaccination, which will not allow virus to circulate freely and infect women of child-bearing age, thus avoiding any inadvertent epidemiological shift.

So, in conclusion, the ACVIP thinks reaching all children with measles vaccine gives us an opportunity to also reach them with rubella and mumps, in a combined vaccine. Congenital rubella syndrome can be completely prevented, and the academy fully supports efforts to prevent infant and childhood disability and the associated health, social, and economic costs. By preventing measles, rubella, and mumps together we produce significant savings for our country and communities.

Measles-rubella vaccine.

Routine vaccination:

- Minimum age: Measles vaccine is now replaced with MR/MMR vaccine and it is administered at minimum age of 9 months or 270 completed days.

Catch-up vaccination:

- Catch-up vaccination beyond 12 months should be MMR.
- Measles-containing vaccine can be administered to infants aged 6 through 11 months during outbreaks. These children should be revaccinated with two doses of measles-containing vaccines; the first at ages 12 through 15 months and at least 4 weeks after the previous dose, and the second dose at ages 4 through 6 years.

Measles, mumps, and rubella vaccine.

Routine vaccination:

- Minimum age: 9 months.
- Administer the first dose of MMR vaccine at 9 months of age, second dose at 15 months, and third dose at age 4 through 6 years.
- The third dose may be administered before age 4 years, provided at least 4 weeks have elapsed since the last dose.

Catch-up vaccination:

- Ensure that all school-aged children and adolescents have had two doses of MMR vaccine; the minimum interval between the two doses is 4 weeks.
- One dose if previously vaccinated with one dose.

REFERENCES

1. WHO SEARO. Measles Elimination and Rubella Control 2013. Available from http://www.searo.who.int /mediacentre /events/governance / rc/66/9.pdf. (Accessed on Nov 28, 2013)
2. (The Measles & Rubella Initiative Welcomes World Health Assembly Commitment to Measles and Rubella Elimination Goals. https://www.who.int/immunization/newsroom/measles_rubella_wha_elimination_goals_statement_may12/en/
3. Gupta A. India's Universal immunization programme. GAVI Alliance Board Meeting 2012. Available from www.gavialliance.org / about/.../12.../16--- country-presentation—India.
4. Measles and Rubella Initiative. Measles deaths decline, but elimination progress stalls in some regions. Available from http://www.unicef.org/ immunization/files/Note_to_media_FINAL_17-01-13(1).pdf.
5. Sinha K. Times of India report: 47% of global measles deaths in India. 2012.Apr 24 Available from http://articles. timesofindia.indiatimes.com /2012-04-24/science/31392204_1_measles-vaccine-second-dose-measles-mortality. (Accessed on 28th Nov 2013)
6. Measles and measles-rubella vaccine support https://www.gavi.org/support/nvs/measles-rubella/
7. UNICEF Coverage Evaluation survey, 2009 National Fact Sheet. Available from: http://www.unicef.org/india/ National_Fact_Sheet_CES_2009.pdf. (Accessed on November 28, 2013)
8. Rubella vaccines, Summary of WHO position paper published in WER July 2011. [Last accessed on 2013 May 14]. Available from http://www.who.int/immunization/position_papers/PP_rubella_July_2011_summary.pdf .
9. IAP ACVIP Recommendations Indian Pediatris December 2018.

10. New Delhi: Government of India; 2010. Ministry of Health and Family Welfare. Measles Catch-up Immunization Campaign, Guidelines for Planning and Implementation; p. 6
11. Rustgi R, Deka D, Singh S. Rubella serology in Indian adolescent girls and its relation to socio-economic status. J Obstet Gynaecol India. 2005;55:167–9.
12. Geneva: World Health Organization Press; 2012. World Health Organization. Global Measles and Rubella Strategic Plan: 2012-2020; pp. 10–21.
13. National operational guideline for introduction of Measles-Rubella vaccine 2017, Ministry of Health and Welfare, Govt. of India.
14. Dewan P, Gupta P. Burden of congenital rubella syndrome (CRS) in India: A systematic review. Indian Pediatr. 2012; 49: 377–99.
15. Sinha K. Times of India report: Now, India to roll out vaccine against Rubella. May 16, 2012. Available from http://articles.timesofindia.indiatimes.com/2012-05-16/india/31725540_1_rubella-vaccine-congenital-rubella-syndrome-combination-vaccine. (Accessed on Nov 28, 2013).
16. van den Ent MM, Brown DW, Hoekstra EJ, et al. Measles mortality reduction contributes substantially to reduction of all cause mortality among children less than five years of age, 1990–2008. J Infect Dis. 2011; 204 (Suppl 1): S18–23.
17. WHO. Global Measles and Rubella. Strategic Plan 2012–2020. Available from http://www.who.int /immunization /newsroom/Measles_Rubella_StrategicPlan_2012_2020.pdf. (Accessed on Nov 27, 2013)
18. Cutts FT, Robertson SE, Diaz-Ortega JL, et al. Control of rubella and congenital rubella syndrome (CRS) in developing countries, Part 1: Burden of disease from CRS. Bull World Health Organ. 1997; 75(1): 55–68.
19. Investing in immunization through the GAVI Alliance. The evidence base 2011. Website: www.gavialliance.com.
20. Singla N, Jindal N, Aggarwal A. The seroepidemiology of rubella in Amritsar (Punjab) Indian J Med Microbiol. 2004;22:61–3.
21. Sharma HJ, Padbidri VS, Kapre SV, et al. Seroprevalence of rubella and immunogenicity following rubella vaccination in adolescent girls in India. J Infect Dev Ctries. 2011;5:74–81.
22. Sharma H, Chowdhari S, Raina TR, et al. Serosurveillance to assess immunity to rubella and assessment of immunogenicity and safety of a single dose of rubella vaccine in school girls. Indian J Community Med. 2010;35:134–7.
23. Serum Institute of India Ltd. Health FAQ. Rubella. [Last accessed on 2013 May 14]. Available from: http://www.seruminstitute.com/content/faq_rubella.htm .

24. Vijayalakshmi P, Rajasundari TA, Prasad NM, et al. Prevalence of eye signs in congenital rubella syndrome in South India: A role for population screening. Br J Ophthalmol. 2007;91:1467–70.
25. Chakravarti A, Jain M. Rubella prevalence and its transmission in children. Indian J Pathol Microbiol. 2006;49:54–6.
26. Rajasundari TA, Sundaresan P, Vijayalakshmi P, et al. Laboratory confirmation of congenital rubella syndrome in infants: An eye hospital based investigation. J Med Virol. 2008;80:536–46.
27. Geneva: World Health Organization Press; 2012. World Health Organization. Global Measles and Rubella Strategic Plan: 2012-2020; pp. 10–21.
28. Status Report on Progress Towards Measles and Rubella Elimination. SAGE Working Group on Measles and Rubella (17 October 2013) Available from http://www.who.int/immunization/sage/meetings/2013/november/ Status_Report_Measles_Rubella21Oct2013_FINAL.pdf. (Accessed on Nov 28, 2013)
29. CDC. Available from http://www.who.int /biologicals /areas/vaccines/mmr/mumps/en. (Accessed on Nov 29, 2013).
30. John TJ. An outbreak of mumps in Thiruvananthapuram district. Indian Pediatrics 2004; 41: 298–300.
31. Ministry of Health & Family Welfare. National Technical Advisory Group on Immunization, 16 June 2008. Available from http://mohfw.nic.in/WriteReadData / l892s / 6664716297file23.pdf. (Accessed on Nov 29, 2013).
32. IDSurv, Infectious Disease Surveillance by IAP. Available at: www.idsurv.org.
33. India still behind in preventing contagious Mumps disease By Dr Rajasree Sundararajan INDIAN EXPRESS 4TH OCTIBER 2018

3.9 VARICELLA VACCINES

Abhay K Shah

BACKGROUND

Varicella-zoster virus (VZV) is a highly contagious herpes virus, which causes both varicella (chickenpox), usually during childhood, and herpes zoster (HZ) (shingles), usually much later in adult life. VZV is present worldwide and, in the absence of a varicella vaccination program, most people become infected by mid-adulthood.[1]

Varicella (chickenpox) is a febrile rash illness resulting from primary infection with the VZV. Humans are the only source of infection for this virus. Varicella severity and complications are increased among immunocompromised persons, infants, and adults. In otherwise healthy children, varicella is usually self-limiting. However, healthy children and adults may also develop serious complications and even die from Varicella.[2]

The most common complications in children are secondary bacterial infections. Pneumonia, usually viral, is the most common complication in adults. Groups at higher risk for severe complications are neonates, infants, pregnant women, adults, and immunocompromised persons. In neonates, varicella can be life-threatening, especially if the mother develops varicella within 5 days before or 2 days after delivery. Central nervous system complication includes cerebellar ataxia and even encephalitis.

MODE OF TRANSMISSION

Varicella-zoster virus is a double-stranded deoxyribonucleic acid (DNA) virus belonging to the *Herpesviridae* family. The virus is transmitted from person to person by direct contact with the varicella or HZ rash, inhalation of aerosolized droplets from respiratory tract secretions of patients with varicella, or rarely from the inhalation of aerosolized droplets from vesicular fluid of skin lesions of patients with varicella or disseminated HZ. The virus enters the host through the upper respiratory tract or the conjunctiva. After primary infection

with VZV, the virus remains dormant in the sensory nerve ganglia and can reactivate later in life, causing HZ.[3,4]

DISEASE BURDEN

The epidemiology of varicella differs between temperate and tropical climates. In tropical climates, VZV seroprevalence reflects a higher mean age of infection and higher susceptibility among adults as compared to temperate climates. There is a 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.[5] Seropositivity is lower in adults from tropical and subtropical areas.[6] A seroprevalence study from West Bengal reported only 42% rural adults were immune.[7]

Seroprevalence studies in healthcare workers or students have demonstrated seronegative prevalences ranging from <5% in USA, 14–19% in Saudi Arabia, 25% in India, and 50% in Sri Lanka.[1] Varicella shows a strong seasonality in temperate settings and in most tropical settings, with peak incidence during winter and spring, or in the coolest, driest months in the tropics. Periodic large outbreaks occur with an interepidemic cycle of 2–5 years.

A study from South India found that healthcare workers in the tropics may be vulnerable to hospital-acquired varicella infection and may further transmit infection to susceptible hospitalized patients, as well as to other susceptible children and adults.[8] Based on conservative estimates, the global annual varicella disease burden would include 4.2 million severe complications leading to hospitalization and 4,200 deaths.[9]

Infectious Disease Surveillance (IDsurv) Data

According to the academy's passive reporting system of 10 infectious diseases by the pediatricians (www.idsurv.org), a total of 816 (7.7%) cases of varicella were reported out of total 10,580 cases from December 2010 to December 11, 2013. Out of these 816 cases, 58.2% were between 5 years and 18 years, 18.6% between 3 years and 5 years,

and 15.4% between 1 year and 3 years of age. 63 (7.7%) cases were below 1 year of age. Only 12% were fully immunized while 74% were not immunized at all. 3% had severe disease, needed hospitalization, and there was no mortality.

PREVENTION OF VARICELLA

Natural Immunity

Varicella-zoster virus infection stimulates both humoral and cell-mediated immune response. Although commercially available enzyme-linked immunosorbent assay (ELISA) tests are designed to detect immunoglobulin G (IgG) antibodies formed in response to natural infection they are less sensitive than glycoprotein ELISA (gp-ELISA). The antibody titers peak at around 4–8 weeks and usually remain high for 6–8 months. Thereafter, the titers decline steadily.[10,11] Primary VZV infection induces cell-mediated immunity (CMI) by the proliferation of VZV-specific CD4+ and CD8+ T cells. The IgG antibodies against VZV persist lifelong. Although CMI responses also last for a long time, they usually start waning at around 50 years of age. This is the time that these individuals become prone to develop zoster.[12]

VACCINE

A vaccine based on live attenuated VZV (Oka strain)[13] was developed and clinically tested in the 1970s and 1980s. It was first licensed in Germany and Sweden in 1984. The vaccines are available either as monovalent (varicella only), or in combination with measles, mumps, and rubella (MMR) vaccine.[13]

Takahashi et al. developed a live attenuated vaccine from the Oka strain in Japan in the early 70s.[14] Varicella vaccines, in use today, are all derived from the original Oka strain but the virus contents may vary from one manufacturer to another. They differ in passage number in human diploid cells, the virus dose, antibiotics used, stabilizers, and other minor components incorporated. Vaccination induces both humoral and cellular immunity.

Monovalent varicella vaccines available in India currently are as under:

- Variped (MSD)
- Varilrix (GSK)
- Biovac-V (Mf. China, Mkt-Wockhardt)
- Varivax (Mf. China, Mkt-VHB Life Sciences)
- Nexipox (Mf. China, Mkt-NovoMedi Sciences)
- Zuvicella (Mkt Zuventus healthcare).

All vaccines are approved by Central Drugs Standard Control Organization (CDSCO) after phase II and III immunogenicity and safety studies. All varicella vaccines are freeze-dried and lyophilized. They are licensed for use in persons aged >12 months. All of them employ live attenuated varicella zoster virus (Oka strain). They do differ in the number of plaque-forming units (PFUs) from 1,300–2,500 PFUs—though a dose of 200 PFU is immunogenic. WHO does not specify a minimum number of PFUs per vaccine dose, but is important for national regulatory authority, which licenses the vaccine.[13]

Stabilizers are added to vaccine to ensure that the vaccine remains unchanged when it is exposed to heat, light, acidity, or humidity. It is necessary to have a look at these ingredients because the vaccines differ in their use and often claims are made based on these ingredients **(Table 1)**. WHO has not offered any guideline regarding choice of stabilizer.

As varicella vaccines are low on priority none is WHO prequalified. Variped is approved by US Food and Drug Administration (FDA) and EMA (European Medicine Agency) and Varilix is approved in Europe by EMA. Biovac-V and Nexipox are approved by Chinese health regulatory body but not US FDA or EMA.

TABLE 1: Stabilizers in varicella vaccines.

	Monosodium L-glutamate (MSG)—stabilizer	*Gelatin*	*Human serum albumin*	*Trehalose as a stabilizer*	*Stability at 2–8°C*
VARIAPED	Yes	Yes			24 months
VARILIX	Yes		Yes		24 months
BIOAC V	Yes	Yes	Yes		24 months
VARIVAX	Yes				24 months
NAXIPOX	Yes		Yes	Yes	36 months

IMMUNOGENICITY[10,11]

The gp-ELISA was the first test used to assess the immunogenicity of the vaccine. Prelicensure studies showed that seroconversion (any detectable varicella antibodies >0.3 gp-ELISA units/mL) was seen in 95–98% of susceptible children aged 1–12 years after a single dose of the vaccine. Later, a gp-ELISA cutoff of 5 units/mL was seen to correlate better with protection against clinical disease as compared to seroconversion and this level was achieved in 86% of children following a single dose. Subsequent studies used fluorescent antibody to membrane antigen (FAMA) titers of >1:4 at 16 weeks of vaccination as a correlate of protection; 76% children achieved this cutoff following receipt of single dose of the vaccine. Follow-up studies indicate persistence of antibodies for 7–10 years and even 20 years following vaccination. Since immunity to varicella is also cell-mediated, T lymphocyte proliferation responses have been studied and found to be present in 87–90% of children for up to 5 years postvaccination.

The immunogenicity improves with a second dose of the vaccine in all respects; percentage seroconversion and those with antibody levels above the serologic correlate of protection both by gp-ELISA and FAMA is higher (99.6% vs 85.7%), the geometric mean titers (GMTs) achieved are higher with two doses as compared to a single dose and the lymphocyte proliferation responses are better. The immunogenicity is similar whether the second dose is given 3 months or 4–6 years after the first dose. Immunogenicity is better when the second dose is given 8–12 weeks after the first dose as compared to 4 weeks.

The immunogenicity of the vaccine is lower in adolescents and adults and studies have demonstrated seroconversion rates of 72–94% following a single dose of the vaccine and 94–99% after two doses of the vaccine administered 4–8 weeks apart. However, other studies indicate that 25–31% of adults lose their detectable antibodies by FAMA at multiple intervals (1–11 years) following vaccination.

The immunogenicity of the MMR plus varicella (MMRV) vaccine is similar to that of MMR and varicella vaccine administered on the same day at different sites.

EFFICACY

Prelicensure efficacy and postlicensure effectiveness studies have shown the efficacy of a single dose of the vaccine to range from 70% to 90% against any disease and >95% against combined moderate and severe disease for 7–10 years after vaccination.[15–17] Administration of two doses 3 months/4–6 years apart improves seroprotection rates to 99% and results in higher GMTs 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 **(Table 2)**. A 10-year follow-up after vaccination comparing 1 versus 2 doses (2900–9000 PFUs) estimated vaccine efficacy to be 94.4% and 98.3% respectively ($p < 0.001$).There was no breakthrough varicella till 7–10 years after 2 doses.

Vaccine Effectiveness (Table 2)

Most postlicensure studies were done in the United States. Hence, most data are available for Variped. Varilrix, Okavax, and other vaccines were studied in other countries. SAGE Working Group of WHO did systemic review of both Variped and Varilrix with substantial data available. There have been few studies on Chinese vaccine. A systemic review concludes that vaccine efficacy appears similar across all products amounting to 80–92%.

INDIAN STUDIES

They are very few in number. Biovac-V study by Mitra M et al. was published in Human Vaccine Immunotherapy Journal in 2015. Nexipox trial was published in Chinese journal. Varilrix was used as a reference vaccine for trials of other vaccine in India. An Indian study

TABLE 2: Seroconversion and efficacy of one and two doses of varicella vaccine.

Parameter	*One dose*	*Two doses*
Seroconversion	86%	99%
Efficacy—mild disease	70–90%	98.3%
Efficacy—moderate to severe disease	>95%	100%

of combination of Varicella and MMR (Priorix Tetra) was published in BMJ (Lalwani) in 2015. There was a poster presentation in Pedicon 2015 about Variped. There has been no published Indian study about Varivax.

Population Impact Data

Till 2015, 24 countries have introduced Varicella in National Immunization Schedule (Europe 8, Americas 10, Eastern Mediterranean 4, and East Pacific 2). The impact studies have been published from seven countries, which are using either Variped, Varilrix, or both.

Breakthrough varicella: It is defined as varicella developing more than 42 days after immunization and usually occurs 2–5 years following vaccination. It occurs in about 1–4% of vaccines per year. This rate does not seem to increase with length of time after immunization.[9] 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.[18] 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.

Vaccine Failure and Breakthrough Varicella

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 one 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 gp-ELISA result but is inadequate to generate a sustained memory T-cell response leading to waning of immunity over a period of time. This logically explains that second dose given 3 months after the first dose is more protective to protect an individual against breakthrough varicella.

SAFETY

There is a strong evidence for safety of all varicella vaccines. Only minor adverse events are reported. Postmarketing survey and other data are available only for Variped and Varilrix.

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 vaccines. However, vaccine recipients who develop a rash should avoid contact with persons without "evidence of immunity" who are at high risk for severe complications. The side-effect profile is similar with the two-dose schedule. The attenuated viral vaccine carries little, if any, risk of development of zoster.

Contraindications

The vaccine is contraindicated during pregnancy, individuals with a history of anaphylactic reactions to any component of the vaccine (including neomycin), in those with clinically manifested human immunodeficiency virus (HIV) infection and in the immunocompromised (exceptions listed in the succeeding text). When used in adult females, pregnancy should be avoided for 3 months after vaccination.[18,19] Due to the risk of Reye syndrome, the use of salicylates is discouraged for 6 weeks following varicella vaccination.[17]

Risk of Herpes Zoster Among Immunized Individual

Herpes zoster in vaccine recipients is known to occur due to both the vaccine virus and the wild virus; however, the overall incidence of HZ in vaccinated children was noted to be much lower than unvaccinated children in prelicensure trials.

RECOMMENDATIONS FOR USE

Individual Use

Advisory Committee on Vaccines and Immunization Practices (ACVIP) 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 cutoff
- 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 setup, e.g. school teachers, daycare center workers, military personnel, and healthcare professionals.
- For postexposure prophylaxis in susceptible healthy nonpregnant contacts preferably within 3 days of exposure (efficacy 90%) and potentially up to 5 days of exposure (efficacy 70%, against severe disease 100%).

VACCINE STORAGE AND HANDLING

Vaccine is available in a lyophilized form. The vaccine should be reconstituted using the diluent provided and as per the instructions issued by the manufacturer in the product insert. Each 0.5 mL of

the reconstituted vaccine contains over 1,350–3,000 PFUs. It also contains hydrolyzed gelatin, trace amounts of neomycin and fetal bovine serum, sucrose, and trace residual components of MRC-5 cells (including DNA and protein). To maintain potency, the lyophilized vaccine must be stored frozen at 2–8°C in the refrigerator in the clinic. The diluent should be stored separately either at room temperature or in refrigerator at 2–8°C. The unreconstituted form of the vaccine has a shelf life of 2 years if stored as per manufacturer's guidelines. The reconstituted vaccine should be used immediately after reconstitution. It should be protected from light and needs to be used within 30 minutes of reconstitution.

DOSAGE AND SCHEDULE

The recommended dose is 0.5 mL to be administered subcutaneously. The vaccine may be given with all other childhood vaccines. It is to be given as two doses.

The vaccines are licensed for age 12 months and above. However, the risk of breakthrough varicella is lower if given 15 months onward. Hence, ACVIP 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 coinfected 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 ACVIP now recommends two doses of varicella vaccine for children of all age groups.

- For primary immunization, the first dose is best administered at 15 months and the second dose may be given any time 3 months after the first dose or at the time of school entry at 4–6 years. However, during an outbreak, the first dose may be administered at 12 months of age if it is ensured that the two-dose schedule will

be completed by the individual child. The second dose may be administered anytime 3 months after the first dose.

- For catch-up vaccination, children below the age of 13 years should receive two doses 3 months apart and those aged 13 years or more should receive two doses at an interval of 4–8 weeks.
- All high-risk children should, however, receive two doses 4–8 weeks apart irrespective of age.
- Susceptible household contacts of immunocompromised individuals can safely receive the varicella vaccine since there is no evidence of transmission of the vaccine virus from the vaccinee to the contact and even if it were to occur, the disease is likely to be very mild. If the vaccinee develops a vaccine-related rash, he/she should avoid contact with a susceptible immunocompromised contact.
- A live attenuated vaccine against HZ is now licensed and available in the United States but not in India.

THE NEED TO IMPLEMENT A TWO-DOSE VARICELLA SCHEDULE <13 YEARS

A two-dose schedule of varicella vaccination is now recommended along with a second-dose catch-up varicella vaccination for children and adolescents who previously had received only one dose. This is because vaccine failure has been seen to occur after a first dose. Outbreaks of varicella had been reported in populations with high coverage with one dose of vaccine.[18] A group of 148 children in the United States were tested for seroconversion after receiving one dose of the vaccine, using the FAMA assay, only 76% of these children seroconverted.[12] These results were one of the reasons why a second dose of varicella vaccine was mandated in 2006 by the Centers for Disease Control and Prevention (CDC) for all children.[2] In a recent publication, it has been shown that varicella incidence, hospitalizations, and outbreaks in two active surveillance are as declined substantially during the first 5 years of the two-dose varicella vaccination program.[20] In India also, breakthrough varicella has been observed in children immunized with one dose, in spite of the opportunities of natural boosting. Two doses of varicella will indeed work better than one dose for the individuals protection.

A single-dose varicella vaccine effectiveness (VE) against all grades of disease severity ranged from 20% to 100%, with an approximate mean VE of 80% against all grades of disease severity, irrespective of vaccine type. Single-dose varicella VE against moderate and severe disease ranged from 78% to 100%, with an approximate mean VE of 95%, irrespective of vaccine type. Whereas, the single-dose varicella VE against severe disease ranged from 85% to 100%. In a 10-year follow-up study, it was reported that children receiving two doses of vaccine developed no severe disease and additionally, were 3.3 times less likely to develop breakthrough disease of any severity,[21] and recipients of two doses did not develop any breakthrough infection 7–10 years postvaccination, whereas there were some breakthrough cases during this same timeframe in single-dose recipients.[21]

VARICELLA ZOSTER IMMUNOGLOBULIN

Varicella zoster immunoglobulin (VZIg) provided passive immunity against varicella and is indicated for postexposure prophylaxis in susceptible individuals with significant contact with varicella/HZ who are at high risk for severe disease. Susceptible individual is defined as:

- All unvaccinated children who do not have a clinical history of varicella in the past
- All unvaccinated adults who are seronegative for antivaricella 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 stays 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 HZ. 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 weightless than 1,000 g 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 antivaricella 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 intravenous immunoglobulin (IVIg) at the rate of 400 mg/kg in the past 3 weeks are deemed protected.

Dosage and Administration Schedule

Varicella zoster immunoglobulin 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 0.2–1 mL/kg diluted in normal saline over 1 hour.

Efficacy and Safety

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 nonaffordable/not available, other options with uncertain efficacy include IVIg at the rate of 200 mg/kg or oral acyclovir at the rate of 80 mg/kg/day beginning from the 7th day of exposure and given for 7–10 days.

PUBLIC HEALTH PERSPECTIVES

The varicella vaccine is not recommended for universal immunization in India in children as the disease is generally mild and as the vaccine is expensive at the current market prices and there are other health-related priorities that rank higher than varicella vaccine. WHO continues to mention that countries where varicella is an important public health burden could consider introducing varicella vaccination in the routine childhood immunization program. However, resources

should be sufficient to ensure reaching and sustaining vaccine coverage ≥80%. Vaccine coverage that remains <80% will result into shift in epidemiology.

Extensive use of varicella vaccine as a routine vaccine in children will have a significant impact on the epidemiology of the disease. If sustained high coverage can be achieved, the disease may virtually disappear. If only partial coverage can be obtained, the epidemiology may shift, leading to an increase in the number of cases in older children and adults. Hence, routine childhood varicella immunization programs should emphasize high, sustained coverage.

MMRV VACCINE

Measles, mumps, and rubella plus varicella (MMRV) is a live attenuated virus vaccine against measles, mumps, rubella, and varicella. It is a sterile lyophilized mixed preparation of the attenuated Schwarz measles, RIT 4385 mumps (derived from Jeryl Lynn strain), Wistar RA 27/3 rubella, and Oka varicella strains of viruses, separately produced in chick embryo cells (mumps and measles) or human diploid MRC5 cells (rubella and varicella). Neomycin sulfate is present as a residual from the manufacturing process.[22] It is marketed in India as PRIORIX-TETRA by GSK Vaccines Ltd. Each 0.5 mL dose of the reconstituted vaccine contains not less than 103.0 cell culture infectious dose 50% ($CCID_{50}$) of the Schwarz measles, not less than 104.4 $CCID_{50}$ of the RIT 4385 mumps, not less than 103.0 $CCID_{50}$ of the Wistar RA 27/3 rubella and not less than 103.3 PFU of the varicella virus strains.

CLINICAL STUDIES: IMMUNOGENICITY AND EFFICACY

Studies comparing two doses of MMR + V (MMR and varicella vaccine given separately) and MMRV have shown adequate seroconversion for all four antigens.[23-26]

In a large efficacy trial,[27] 2 years after vaccination with two doses of PRIORIX-TETRA; seropositivity rates for antivaricella antibodies were 99.4% (ELISA) and 99.2% immunofluorescence assay (IFA) and respectively 99.1%, 90.5%, and 100% for anti-MMR antibodies (ELISA). In children 9–10 months of age vaccinated with two doses of PRIORIX-TETRA, seroconversion rates after a first dose of PRIORIX-TETRA were comparable for all antigens except measles to those seen in 12- to

24-month-old children in other clinical studies. The immune response of PRIORIX-TETRA administered as a second dose of MMR vaccine in children 24 months to 6 years of age was evaluated in two clinical studies. Children were previously primed with respectively an MMR vaccine or with an MMR vaccine coadministered with a live attenuated varicella vaccine. Seropositivity rates for antivaricella antibodies were 98.1% (IFA) in children previously vaccinated with MMR and 100% in children previously vaccinated with an MMR vaccine coadministered with a live attenuated varicella vaccine. Seropositivity rates were 100% for anti-MMR antibodies in both studies. The immunogenicity and safety of PRIORIX-TETRA administered intramuscularly was evaluated in one comparative study conducted in 328 children who received PRIORIX-TETRA either by intramuscular or subcutaneous route. The study demonstrated similar immunogenicity and safety profiles for both administration routes.

In a large active controlled clinical trial in which children aged 12–22 months received two doses of PRIORIX-TETRA (N = 2,279) or one dose of VARILRIX (N = 2,263). The observed vaccine efficacy against confirmed varicella of any severity and against moderate or severe confirmed varicella after two doses of PRIORIX-TETRA and after one dose of VARILRIX (mean follow-up period 35 months) is studied.

Efficacy against confirmed varicella of any severity using two doses of PRIORIX-TETRA was 94.9% [confidence interval (CI) 92.4–96.6] as against 65.4% (CI 57.2–72.1) with one dose of Varilrix. Efficacy against confirmed moderate or severe varicella using two doses of PRIORIX-TETRA was 99.5% (CI 97.5–99.9) as against 90.7% (CI 85.9–93.9) with single dose of Varilrix.

SAFETY

In prelicensure clinical trials of combined MMRV vaccine, incidence of fever was reported at a significantly higher rate (0–42 days postvaccination) in children aged 12–23 months who received a first dose of MMRV vaccine than in children who received first doses of MMR and varicella vaccine as separate injections.[28]

A review of more recent postlicensure safety studies of the combination MMRV vaccine identified a new risk of febrile seizures

after vaccination among children aged 12–23 months, compared with children receiving separate MMR and varicella vaccinations.[29] The incidence rate of febrile seizures was twice as high in children receiving a first dose of MMRV compared to those receiving monovalent varicella vaccination and MMR at the same time, either 5–12 or 7–10 days postvaccination [relative risk (RR) 2.0; 95% CI: 1.4–2.9 and RR 2.2; 95% CI: 1.0–4.7], amounting to one extra febrile seizure for every 2,300–2,700 children vaccinated.[30–32]

As per Post-Marketing Observational Safety Surveillance Study,[27] the risk of febrile convulsions following PRIORIX-TETRA when used as the first measles-containing vaccination of children aged 9–30 months compared with a matched cohort who received either MMR or concomitant MMR and varicella vaccination was assessed in a retrospective database analysis. The study included 82,656 children immunized with MMRV, 149,259 with MMR, and 39,203 with separate MMR and varicella vaccines. The attributable risk of febrile convulsions on cohorts matched for confounding factors in the main risk period of 5–12 days following first dose of PRIORIX-TETRA was 3.64/10,000 (95% CI: 6.11–8.30).

The reports of higher incidence of adverse events following immunization with MMRV when compared to MMR+V, fever, and rash[19] and febrile seizures in the age group of 12–23 months of age,[33,34] prompted the US CDC Advisory Committee on Immunization Practices (ACIP) to suggest a "one-to-one discussion," unless the parent or caregiver expresses a preference for MMRV vaccine, CDC ACIP recommends that MMR+V separately be given for the first dose in this age group.[35] Even the immunogenicity and safety study of MMRV in India[36] has found approximately twofold higher incidence of grade 3 fever (>39.5°C) in subjects who received MMRV than those who received MMR.[36,37]

MMRV is thus far licensed till 12 years of age[25] and anyone 13 years or older who needs protection from these diseases should get MMR and varicella vaccines as separate shots.[35]

RECOMMENDATION FOR USE

- MMR+V at 15 months.
- At 5 years, MMRV or MMR+V as per parents' choice.

BOX 1: Varicella vaccines.

Routine vaccination:

- Minimum age: 12 months
- Administer the first dose at age 15 through 18 months and the second dose 3 months after the first dose or at age 4 through 6 years.
- If the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.
- The risk of breakthrough varicella is lower if given 15 months onward.

Catch-up vaccination:

- Ensure that all persons aged 7 through 18 years without "evidence of immunity" have two doses of the vaccine.
- "Evidence of immunity" to varicella includes any of the following:
  - Documentation of age-appropriate vaccination with a varicella vaccine
  - Laboratory evidence of immunity or laboratory confirmation of disease
  - Diagnosis or verification of a history of varicella disease by a healthcare provider
  - Diagnosis or verification of a history of HZ by a healthcare provider
- For children aged 12 months through 12 years, the recommended minimum interval between doses is 3 months. However, if the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.
- For persons aged 13 years and older, the minimum interval between doses is 4 weeks.
- For persons without evidence of immunity, administer two doses if not previously vaccinated or the second dose if only one dose has been administered.

REFERENCES

1. Varicella and herpes zoster vaccines: WHO position paper, June 2014. Wkly Epidemiol Rec. 2014;89:265-87.
2. CDC. Surveillance of Varicella. Manual for the Surveillance of Vaccine-Preventable Diseases (5th Edn, 2011). Available from http://www.cdc.gov/vaccines/pubs/surv-manual/chpt17-varicella.html. (Accessed on Dec 10, 2013)
3. Gershon A, Takahashi M, Seward JF, et al. Varicella vaccine. In: Plotkin S, Orenstein W, Offit P (Eds). Vaccines, 6th edn. Saunders Elsevier; 2013. pp. 836-69.
4. Background paper on varicella vaccines—SAGE working group. Available at http:// www.who.int/immunization/sage/meetings/2014/april/presentations_background_docs/en/. (Accessed on April, 2014).
5. WHO. Varicella Vaccine. Available from http://archives.who.int/vaccines/en/varicella.shtml. (Accessed on Dec 10, 2013).
6. Ooi PL, Goh KT, Doraisingham S, et al. Prevalence of varicella-zoster virus infection in Singapore. Southeast Asian J Trop Med Public Health. 1992;23:22-5.

7. Mandal BK, Mukherjee PP, Murphy C, et al. Adult susceptibility to varicella in the tropics is rural phenomenon due to lack of previous exposure. J Infect Dis. 1998;178 (Suppl 1): S52-54.
8. Richard VS, John TJ, Kenneth J, et al. Should health care workers in the tropics be immunized against varicella?. J Hosp Infect. 2001;47:243-5.
9. Varicella disease burden and varicella vaccine. Available at http://www.who.int/ immunization/sage/meetings/2014/april/2_SAGE_April_VZV_Seward_Varicella. pdf?ua=1. (Accessed on May, 2014).
10. Recommendations of Advisory Committee on Immunization Practices. Prevention of varicella. MMWR. 2007;56:1-40.
11. Chartrand SA. Varicella vaccine. Pediatr Clin North Am. 2000;47:373-95.
12. Lokeshvar MR, Tanu Singhal. Immunization against varicella. Immunization in clinical practice, 2nd edition; 2017.
13. Requirements for varicella vaccine (live), WHO Technical Report Series, No. 848, 1994 (http://www.who.int/biologicals/publications/trs/areas/vaccines/varicella/ WHO_TRS_848_A1.pdf).
14. Takahashi M. The varicella vaccine. Vaccine development. Infect Dis Clin North Am. 1996; 10(3): 469-88.
15. Kuter BJ, Weibel RE, Guess HA, et al. Oka/Merck varicella vaccine in healthy children: final report of a 2-year efficacy study and 7-year follow-up studies. Vaccine. 1991;9:643-7.
16. Skull SA, Wang EEL. Varicella vaccination—a critical review of the evidence. Arch Dis Child. 2001; 85:83-90.
17. Varicella vaccines. WHO Position Paper. Wkly Epidemiol Rec. 1998;73:241-8.
18. Pickering LK, Orenstein WO. Active Immunization. Principles and Practice of Pediatric Infectious Diseases Revised, 3rd edn. Churchill Livingstone; 2009.pp.48-71.
19. CDC. General recommendations on immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR; 2011.
20. Bialek SR, Perella D, Zhang J, et al. Impact of a routine two-dose varicella vaccination program on varicella epidemiology. Pediatrics. 2013;132: e1134-1140 .
21. Background Paper on Varicella Vaccine SAGE Working Group on Varicella and Herpes Zoster Vaccines https://www.who.int/immunization/sage/meetings/2014/april/1_SAGE_varicella_background_paper_FINAL.pdf.
22. PRIORIX-TETRA® PRODUCT INFORMATION-GSK Australia https://au.gsk.com/media/217228/priorix_tetra_pi_008_approved.pdf.
23. Czajka H, Schuster V, Zepp F, et al. A combined measles, mumps, rubella and varicella vaccine (Priorix-Tetra): immunogenicity and safety profile. Vaccine. 2009;27:6504-11.
24. Knuf M, Zepp F, Helm K, et al. Antibody persistence for 3 years following two doses of tetravalent measles-mumps-rubella-varicella vaccine in healthy children. Eur J Pediatr. 2012;171:463-70.

25. Lalwani S, Chatterjee S, Balasubramanian S, et al. Immunogenicity and safety of early vaccination with two doses of a combined measles-mumps-rubella-varicella vaccine in healthy Indian children from 9 months of age: A phase III, randomised, non-inferiority trial. BMJ Open. 2015;5:e007202.
26. Ma SJ, Li X, Xiong YQ, et al. Combination Measles-Mumps-Rubella-Varicella Vaccine in Healthy Children: A Systematic Review and Meta-analysis of Immunogenicity and Safety. Medicine (Baltimore). 2015;94:e1721.
27. Systematic review of available evidence on effectiveness and duration of protection of varicella vaccine www.who.int/.../sage/.../4_Systematic_review_on_effectiveness_and_duration_of_pro.
28. Varis T, Vesikari T. Efficacy of high-titer live attenuated varicella vaccine in healthy young children. J Infect Dis. 1996;174 (Suppl 3):S330-334.
29. Global Advisory Committee on Vaccine Safety, December 2012 (http://www.who. int/wer/2013/wer8806.pdf?ua=1; accessed February 2014).
30. Jacobsen SJ, Ackerson BK, Sy LS, et al. Observational safety study of febrile convulsion following first dose MMRV vaccination in a managed care setting. Vaccine. 2009;27(34):4656-61.
31. Klein NP, Fireman B, Yih WK, et al. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. Pediatrics. 2010;126(1):e1-8.
32. Grading of scientific evidence–table V: Safety of MMR plus varicella (MMRV) vaccine. Available at http://www.who.int/entity/immunization/position_ papers/mmrv_ grad_safety.pdf.
33. Leung JH, Hirai HW, Tsoi KK. Immunogenicity and reactogenicity of tetravalent vaccine for measles, mumps, rubella and varicella (MMRV) in healthy children: A meta-analysis of randomized controlled trials. Expert Rev Vaccines. 2015;14:1149-57.
34. Committee on Infectious Diseases. Policy statement—Prevention of varicella: update of recommendations for use of quadrivalent and monovalent varicella vaccines in children. Pediatrics. 2011;128:630-2.
35. Schink T, Holstiege J, Kowalzik F, et al. Risk of febrile convulsions after MMRV vaccination in comparison to MMR or MMR+V vaccination. Vaccine. 2014;32:645-50.
36. Marin M, Broder KR, Temte JL, et al; Centers for Disease Control and Prevention (CDC). Use of combination measles, mumps, rubella, and varicella vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rec. 2010;59(RR-3):1-12.
37. CDC fact sheet on MMRV. Available from: http://www.cdc.gov/vaccines/hcp/vis/visstatements/ mmrv.html. (Accessed on May 16, 2016)

3.10 HEPATITIS A VACCINES

Harish K Pemde

BACKGROUND

Hepatitis A virus (HAV) infection is a relatively benign infection in young children. As many as 85% of children below 2 years and 50% of those between 2 years and 5 years infected with HAV are anicteric and may have no symptoms at all or just have nonspecific symptoms like fever, malaise, diarrhea, vomiting, cough, etc. like any other viral infection. On the contrary, 70–95% of adults with hepatitis A are symptomatic with a mortality of 1%. The disease severity increases irrespective of age, in those with underlying chronic liver disease.

BURDEN OF DISEASE

Global Burden

Based on an ongoing reassessment of the global burden of hepatitis A, preliminary World Health Organization (WHO) estimates suggest an increase in the number of acute hepatitis A cases from 117 million in 1990 to 126 million in 2005 (and increase in deaths due to hepatitis A from 30,283 in 1990 to 35,245 in 2005).[1] Increased number of cases were estimated to occur in the age groups 2–14 years and more than 30 years. Hepatitis A cases increased 294% during 2016–2018 compared with 2013–2015 in USA.[2]

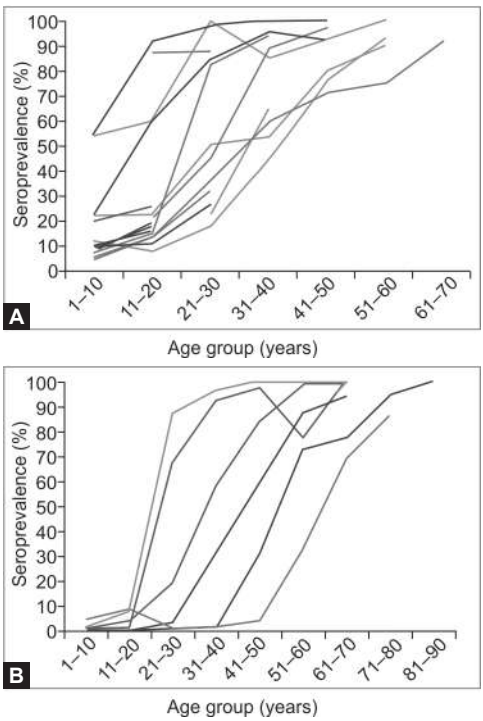
In high-income regions the prevalence of anti-HAV antibody is very low (<50% are immune by age 30 years), but there is almost no circulation of the virus and therefore the risk of acquiring HAV infection is low. In contrast, in countries with high endemicity, most individuals acquire natural infection in childhood and therefore burden of disease including incidence of outbreaks is also low. As a shift occurs toward intermediate endemicity due to improvements in hygiene and sanitation, the population stands at a higher risk because a certain proportion of children remains susceptible till adulthood and the risk of HAV transmission continues to be high due to overall suboptimal access to clean water and sanitation. Thus burden of

symptomatic disease and incidence of outbreaks paradoxically increase despite some improvements in socioeconomic indicators.

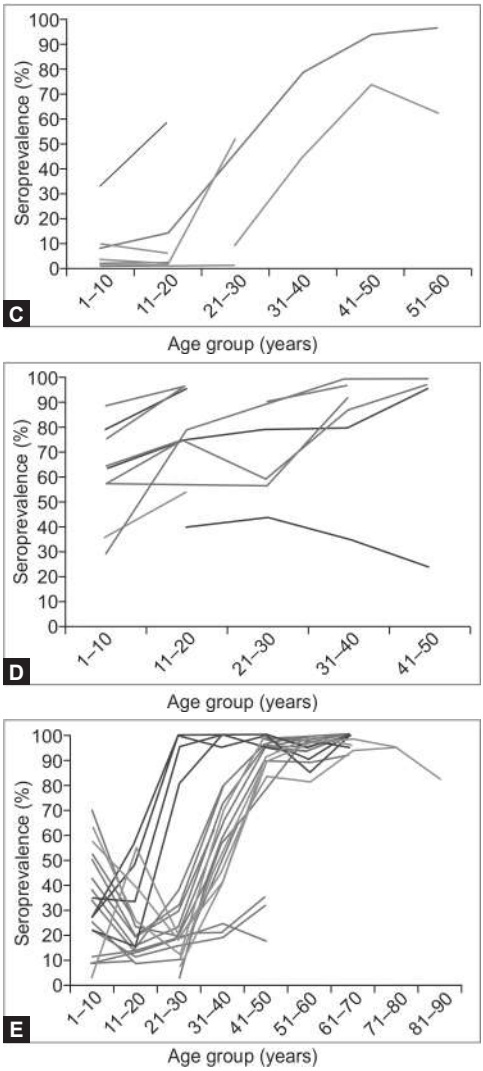
In several Asian countries, the age at first infection by hepatitis A seems to be increasing **(Figs. 1A to I)**.[3]

Indian Burden

India, earlier a highly endemic country, is now shifting to intermediate endemicity in some areas in cities and in higher socioeconomic strata of community.[4] 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 years.



Figs. 1A and B


C
Seroprevalence (%)
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21–30
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41–50
51–60
Age group (years)
D
Seroprevalence (%)
1–10
11–20
21–30
31–40
41–50
Age group (years)
E
Seroprevalence (%)
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71–80
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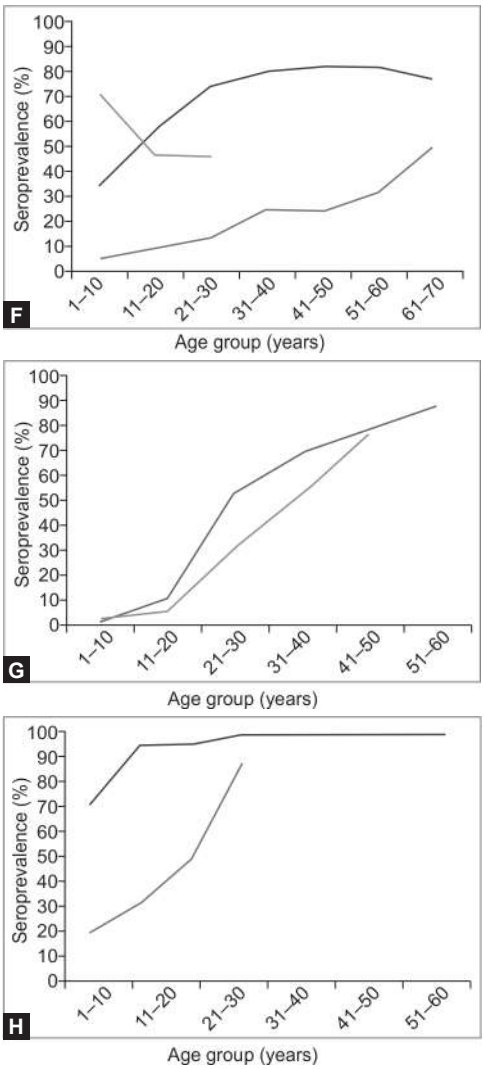
Age group (years)

Figs. 1C to E


Seroprevalence (%)
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Age group (years)
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Seroprevalence (%)
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Age group (years)
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Age group (years)
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Figs. 1F to H

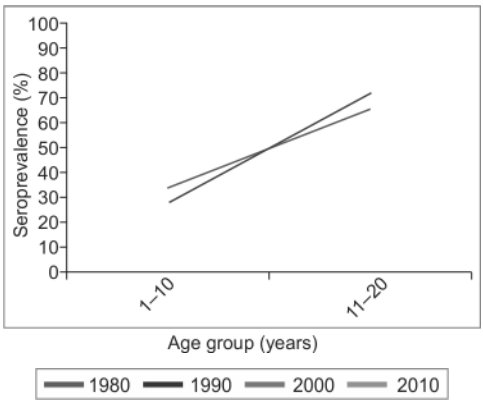


Fig. 1I

Figs. 1A to I: Age-specific hepatitis A seroprevalence in—(A) Thailand (n = 17); (B) Japan (n = 4); (C) Taiwan (n = 10); (D) India (n = 14); (E) Korea (n = 18); (F) China (n = 3); (G) Singapore (n = 2); (H) Indonesia (n = 2); (I) New Zealand (n = 1). N represents number of studies included in the review. Each line of the same color represents results from a single study.
Source: Gripenberg M, Aloysia D'Cor N, L'Azou M, et al. Changing sero-epidemiology of hepatitis A in Asia Pacific countries: A systematic review. Int J Infect Dis. 2018;68:13-17.

Several outbreaks of hepatitis A in various parts of India have been recorded in the past; children from rural and semiurban 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 (FHF) has also been noted, especially in children. In a study from Pune, 18–50% of pediatric patients admitted for FHF either had hepatitis A alone or along with other hepatitis viruses.[5] According to the academy's passive reporting system of 10 infectious diseases by the pediatricians (www.idsurv.org), a total of 1,690 (16%) cases of hepatitis A were reported out of total 10,554 cases from December 2010 to December 10, 2013.

The epidemiology of viral hepatitis A is changing in India too. Arankalle, et al. in their study on 928 children aged between 18 months and 10 years found that out of the 348 children who tested positive for anti-HAV, 50.3% were in the age group of 6–10 years and 30.3% were in the 18 months to 6 years age group **(Fig. 2)**. They also found linkages between the seropositivity of HAV and the educational and

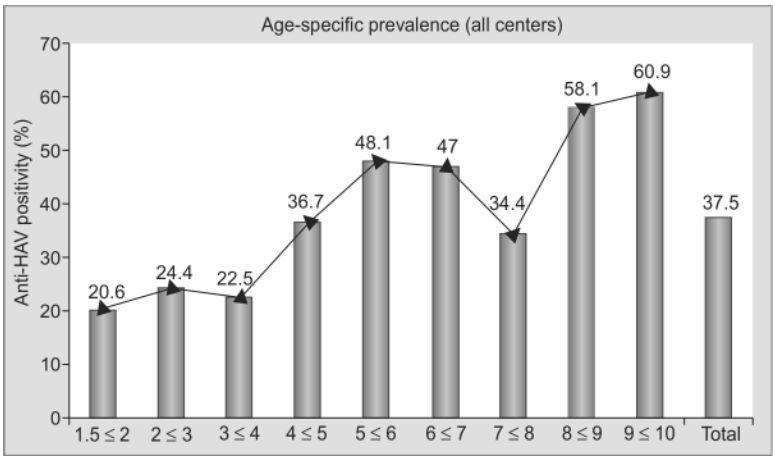


Fig. 2: Age-specific prevalence of hepatitis A in all centers in Kolkata, Pune, Chennai, and Delhi.
Source: Arankalle V, Mitra M, Bhave S, et al. Changing epidemiology of Hepatitis A virus in Indian children. Dovepress. 2014,4:7-13.

socioeconomic status of the parents. Children who used a private toilet within the house were less often seropositive (33.1%) when compared to the children and their parents who used an open field for excreta disposal (75%).[6]

VACCINES

Inactivated Vaccines

Most of the currently available vaccines are derived from HM 175/GBM strains and grown on MRC-5 human diploid cell lines. The virus is formalin inactivated and adjuvanted with aluminum hydroxide. The vaccine is stored at 2–8°C. The serologic correlate of protection is 20 mIU/mL. All hepatitis A vaccines are licensed for use in children aged 1 year or older.

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 of hepatitis A and hepatitis B vaccines is also available to be used in those who have not been vaccinated for hepatitis B previously. These are available in both adult and pediatric formulations and are discussed separately under combination vaccines. Similarly combinations of hepatitis A vaccine with Vi-polysaccharide vaccines are available internationally though not in India.

Efficacy and Effectiveness

In general, two doses of inactivated hepatitis A vaccine induce protective efficacies of 90–95%, or more. The median predicted duration of protection has been estimated at 45.0 years.[7] The vaccine efficacy is lower in the elderly, immunocompromised, those with chronic liver disease, in transplant recipients and those with pre-existing maternal antibodies. Immunity is life-long due to anamnestic response and no boosters are recommended at present in the immunocompetent.

A higher GMC of anti-HAV IgG was induced in the two-dose inactivated than in the one-dose inactivated and the attenuated vaccines at 12 months.[8] Compared to the classical two-dose schedule, one single dose of inactivated hepatitis A vaccines is similarly efficacious, less expensive and easier to implement. High efficacy of postexposure prophylaxis against hepatitis A using one single dose of inactivated vaccine within 2 weeks of exposure is also documented. However, in risk groups for hepatitis A, a two-dose vaccination schedule is preferred.[7]

Dosage Schedule

Indian Academy of Pediatrics (IAP) Advisory Committee on Vaccines and Immunization Practices (ACVIP) recommends two doses of inactivated hepatitis A vaccine given intramuscularly. Administer the second dose 6–18 months after the first.[9] Minimum age for giving hepatitis A vaccine is 12 months.

Safety

Adverse reactions are minor and usually include local pain and swelling. Cumulative global experience from the use of several hundred million doses of inactivated hepatitis A vaccines testify to

their excellent overall safety profile.[7] The vaccine may be safely given with other childhood vaccines and interchange of brands is permitted though not routinely recommended.

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 WHO requirements and is now licensed and available in India. Controlled trials conducted among large numbers of children 1–15 years of age have shown up to 100% efficacy for preexposure prophylaxis and 95% efficacy for postexposure prophylaxis. Anti-HAV antibodies were detected in 72–88% of the vaccines 15 years after vaccination.[7] However, live attenuated hepatitis A vaccine does not provide postexposure protection against HAV infection during the outbreak.[10]

LIVE HEPATITIS A VACCINE

Data on Immunogenicity and Safety of a Single Dose of this Vaccine

A study involving 11451 subjects was conducted to assess its immunogenicity. A seroprotection level of >20 mIU/mL was achieved in 92.9% of subjects within 2-5 weeks of vaccination.[11]

In a randomized controlled trial, Biovac-A was compared to inactivated international vaccine from GSK and also a domestic inactivated vaccine. The assessment was in terms of immunogenicity. There was a comparable immune response seen between Biovac-A and international inactivated hepatitis A vaccine within 7 to 28 days.[12]

In another study evaluating Biovac-A vaccine effectiveness and its long-term immunogenicity, there was a significant reduction in Hepatitis A cases reported (98%) in the vaccinated group. Additionally, there was reduction incidence of hepatitis A in the entire population by 90% because of herd immunity. Certain subjects in this group were regularly followed up for immunogenicity parameters up to 15 years. It was found that more than 80% subjects remain seroconverted above the protection criteria of 20 mIU/mL. The GMT graph also confirmed that the rate at which there is a fall in the titers over all these years is very slow.[13]

Indian Data

The vaccine was brought to India in 2004 and has undergone studies in Indian subjects as well.

- Of 143 children vaccinated in 2004, 121 children were evaluated in 2014, clinically and for anti-HAV antibodies. About 106 (98%) of 108 remaining children had seroprotective levels with a geometric mean titer of 100.5 mIU/mL. On analysis of all 121 children, the immunogenicity was 87.6%.[14]
- In a multicentric single arm study conducted in 4 metros of the country, children 18-60 months were followed up for 5 years. It was noted that the seroprotection criteria was maintained 97.3% in these 5 years of follow up with high GMT levels. While the GMT was 81.4 mIU/mL at 6 weeks, there was a rise in GMT seen at 6 months. This rise is attributed to the live-attenuated property of the vaccine. The seroconversion rates considering seroprotection levels of anti-HAV antibody titer >20 mIU/mL, following vaccination starting from 6 weeks, 6 months, 12 months, 24 months, 36 months, 48 months and 60 months were 95.1%, 97.9%, 98.3%, 96.2%, 97.8%, 92.6% and 97.3%, respectively. The geometric mean concentration (GMC) over the years increased from 64.9 mIU/mL at 6 weeks to 38.1 mIU/mL and 135.2 mIU/mL at 6 months and 12 months, respectively and was maintained at 127.1 mIU/mL at 60 months.[15]

In conclusion, the result of this 5-year follow up study showed that the single dose of live- attenuated vaccine is well tolerated and provides long-term immunogenicity in healthy Indian children. As per WHO position paper, both inactivated and live-attenuated hepatitis A vaccines are highly immunogenic and immunization will generate long-lasting, possibly life-long, protection against hepatitis A in children as well as in adults. Currently, inactivated HAV vaccines are licensed for intramuscular administration in a 2-dose schedule with the first dose given at the age 1 year, or older. The interval between the first (primary) dose and the second (booster) dose is flexible (from 6 months up to 4–5 years), but is usually 6–18 months. The live-attenuated vaccine is administered as a single subcutaneous dose.

The IAP ACVIP committee has already recommended a single dose of this vaccine at 12 months of age.[16]

IAP ACVIP (2018–19) also recommends a single dose of live Hepatitis A vaccine. Second dose of live-attenuated hepatitis A vaccine is not recommended.[17]

It is to be remembered that inactivated vaccine is preferred during outbreak situation.

Safety

No substantial safety concerns have been identified during vaccine trials[7] and no horizontal transmission or serious adverse effects have been noted with the live vaccine.

RECOMMENDATIONS FOR USE

Individual 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 hepatitis B and hepatitis 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 HAV 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.

Which Vaccine to Use?

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, immunocompromised patients where only inactivated vaccines may be used). WHO concludes that both inactivated and live attenuated hepatitis A vaccines are safe and highly immunogenic and that in most cases, these vaccines will generate long-lasting possibly life-long protection against hepatitis A both in children and adults.[7]

Age at Vaccination

Based on data suggesting a decline in the adult seropositivity rates especially in those belonging to the high socioeconomic status, it is likely that babies may be born with no maternal antibodies,

thereby making a case for vaccination for hepatitis A at an earlier age. Immunogenicity studies also show that antibody titers achieved with vaccination at 12 months are comparable to those achieved at 18 months to 2 years. In light of these facts, the IAP ACVIP recommends initiating hepatitis A vaccine at the age of 12 months.

Catch-up Vaccination and Screening for Hepatitis A Antibodies

In India, a very rapid socioeconomic development has taken place in the last years; many high endemicity areas for HAV infection coexist with others, making a transition to intermediate endemicity. Some studies have demonstrated an epidemiological shift of the age of acquisition of the HAV infection in the community, even if the current available data do not confirm a consistent decline in childhood HAV seroprevalence rates and increased susceptibility to HAV in young adults.[18] A study from Hyderabad observed that 25% of children less than 15 years remain susceptible to HAV infection.[19] Another study from Bijapur observed seropositivity in 54.4% children between 5 years and 15 years.[20] Since the cost of screening to identify those susceptible to get hepatitis A infection is lower than the cost of vaccine, IAP ACVIP recommends prevaccination screening for hepatitis A antibody in children more than 10 years of age.

PUBLIC HEALTH PERSPECTIVES

According to WHO, in countries transitioning from high to intermediate endemicity, as is the case in India, large-scale hepatitis A vaccination is likely to be cost-effective and is therefore encouraged. The effectiveness of vaccination of pediatric populations at risk of hepatitis A has been demonstrated in a number of geographic regions worldwide compared to the classical two-dose schedule, one single dose of inactivated hepatitis A vaccines is similarly efficacious, less expensive and easier to implement.[7]

Single-dose Immunization

Within 2–4 weeks of the first dose of inactivated hepatitis A vaccine, up to 100% of immunocompetent children and young adults achieve anti-HAV IgG titers over 20 mIU/mL.[21] Furthermore, a single dose

Hepatitis A (Hep A) vaccine schedule.

Routine vaccination:

- Minimum age: 12 months.
- Start the 2-doses of inactivated hepatitis A vaccine series for children aged 12 through 23 months; separate the two doses by 6–18 months.
- For inactivated vaccine 2 doses are recommended.
- A single dose is recommended for live hepatitis A vaccine after age of 12 months.

Catch-up vaccination:

- Administer two doses of inactivated vaccine at least 6 months apart to unvaccinated persons.
- Single dose for live hepatitis A vaccine.
- For catch-up vaccination, prevaccination screening for hepatitis A antibody is recommended in children older than 10 years, as at this age the estimated seropositive rates exceed 50%.
- Combination of hepatitis B and hepatitis A may be used in 0, 1, 6 schedule.

of this vaccine may successfully control outbreaks of hepatitis A.[7] In 2003, a randomized, double-blind trial of a single dose of inactivated hepatitis A vaccine was conducted in Nicaragua among 239 children. Protective efficacy within those 6 weeks was 85% (95% CI: 55–96%) and after 6 weeks, 100% (79.8–100%).[22]

Effectiveness of Single Dose in National Immunization Program

Argentina began a universal immunization program (UIP) in 12-month-old children based on a single dose schedule of inactivated hepatitis A vaccine in 2005. In 2007, with vaccination coverage of 95%, the incidence of symptomatic viral hepatitis A had dropped by more than 80% in all age groups.[23] Six years after implementation of this countrywide single-dose program, no hepatitis A cases have been detected among vaccinated individuals, whereas among the unvaccinated a number of cases have occurred, confirming continued circulation of hepatitis A virus in the Argentinian population.[7,23] The above studies demonstrate effectiveness of even a single dose of inactivated vaccine when used in large-scale programs.

Considering the uniformly high burden of the disease and effectiveness of hepatitis vaccine even in single dose, the IAP ACVIP recommends that vaccination against hepatitis A be integrated into the UIP for children aged more than or equal to 1 year. However, it should

be part of a comprehensive plan for the prevention and control of viral hepatitis including measures to improve hygiene and sanitation and measures for outbreak control.

REFERENCES

1. Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. Vaccine. 2010;28(41):6653-7.
2. Foster MA, Hofmeister MG, Kupronis BA, et al. Increase in hepatitis A virus infections—United States, 2013-2018. Morb Mortal Wkly Rep (MMWR). 2019;68(18):413-5.
3. Gripenberg M, Aloysia D'Cor N, L'Azou M, et al. Changing sero-epidemiology of hepatitis A in Asia Pacific countries: a systematic review. Int J Infect Dis. 2018;68:13-17.
4. Mathur P, Arora NK. Epidemiological transition of hepatitis A in India: issues for vaccination in developing countries. Indian J Med Res. 2008;128(6):699-704.
5. Bendre SV, Bavdekar AR, Bhave SA, et al. Fulminant hepatic failure: etiology, viral markers and outcome. Indian Pediatr. 1999;36(11): 1107-12.
6. Arankalle V, Mitra M, Bhave S, et al. Changing epidemiology of hepatitis A virus in Indian children. Dovepress. 2014,4:7-13.
7. Hepatitis A Vaccine—WHO Position Paper 2012. Wkly Epidemiol Rec. 2012;87:261-76.
8. Liu XE, Wushouer F, Gou A, et al. Comparison of immunogenicity between inactivated and live attenuated hepatitis A vaccines: a single-blind, randomized, parallel-group clinical trial among children in Xinjiang Uighur Autonomous Region, China. Hum Vaccine Immunother. 2013;9(7):1460-5.
9. Balasubramanian S, Shah A, Pemde HK, et al. Indian Academy of Pediatrics (IAP) Advisory Committee on Vaccines and Immunization Practices (ACVIP) recommended immunization schedule (2018-19) and update on immunization for children aged 0 through 18 years. Indian Pediatr. 2018;55(12):1066-74.
10. Wang X, Ma J, Xu Z, et al. Effectiveness of postexposure prophylaxis using live attenuated hepatitis Alpha vaccine (H(2) strain) among school children. Zhonghua Yi Xue Za Zhi. 2002;82(14):955-7.
11. Cheng NL, Zhonghua Yi Xue Za Zhi. Immunological effects of live attenuated hepatitis A vaccine. 1992;72(10):581-3, 638.
12. Zheng H, et al. Comparing live- attenuated and inactivated hepatitis A vaccines: An immunogenicity study after one single dose Vacc. 2011;29:9098-103.

13. Zhuang FC, Mao ZA, Jiang LM, Wu J, Chen YQ, Jiang Q, Chen NL, Chai SA, Mao JS. Long-term immunogencity and effectiveness of live attenuated hepatitis A vaccine (H2-strain): A study on the result of 15 years' follow up. Zhonghua LiuXing Bing Xue Za Zhi. 2010;31:1332-5.
14. Bhave S, et al. Long-term immunogenicity of single dose of live attenuated hepatitis A vaccine in Indian children. J Ind Ped. 2015;52: 687-90.
15. Monjori Mitra, Nitin Shah, MMA Faridi, Apurba Ghosh, VS Sankaranarayanan,Anju Aggarwal5, Suparna Chatterjee, Nisha Bhattacharyya, Ganesh Kadhe, Gaurav Vishnoi, and Amey. Long term follow-up study to evaluate immunogenicity and safety of a single dose of live attenuated hepatitis a vaccine in children Human Vaccines & Immunotherapeutics 2015;11(5):1147-52.
16. Vipin M Vashishtha, Panna Choudhury, Ajay Kalra, Anuradha Bose, Naveen Thacker, Vijay N Yewale, Cp Bansal, Pravin J Mehta. Indian Academy of Pediatrics (IAP) Recommended Immunization Schedule for Children Aged 0 through 18 years, India, 2014 and Updates on Immunization.
17. Balasubramanian S, Abhay Shah, Harish K Pemde, Pallab Chatterjee, Shivananda S, Vijay Kumar Guduru, Santosh Soans, Digant Shastri, Remesh Kumar. Immunization schedule (2018–19) for children birth through 18 years—Immunization Update Indian Pediatrics, volume 55, Dec 15, 2018.
18. Franco E, Meleleo C, Serino L, et al. Hepatitis A: epidemiology and prevention in developing countries. World J Hepatol. 2012;4(3):68-73.
19. Joshi N, Yr NK, Kumar A. Age related seroprevalence of antibodies to hepatitis A virus in Hyderabad, India. Trop Gastroenterol. 2000;21(2): 63-5.
20. Rath CP, Akki A, Patil SV, et al. Seroprevalence of hepatitis A virus antibody in Bijapur, Karnataka. Indian Pediatr. 2011;48(1):71-3.
21. Schmidtke P, Habermehl P, Knuf M, et al. Cell mediated and antibody immune response to inactivated hepatitis A vaccine. Vaccine. 2005;23(44):5127-32.
22. Mayorga Pérez O, Herzog C, Zellmeyer M, et al. Efficacy of virosome hepatitis A vaccine in young children in Nicaragua: randomized placebo-controlled trial. J Infect Dis. 2003;188(5):671-7.
23. Vacchino MN. Incidence of Hepatitis A in Argentina after vaccination. J Viral Hepat. 2008;15(Suppl 2):47-50.

3.11 TYPHOID VACCINES

Vijay Kumar Guduru

BACKGROUND

Typhoid fever is a disease of developing countries associated with poor public health and low socioeconomic indices. Cases of enteric fever occurring in travelers returning to the US and the UK suggest that it is present across the developing world but that the Indian subcontinent represents a hotspot of disease activity.

Typhoid fever is an acute generalized infection, caused by a highly virulent and invasive enteric bacterium, *Salmonella enterica serovar typhi*, generally termed *Salmonella typhi* (*S. typhi*). Typhoid fever primarily effects mononuclear phagocyte system, intestinal lymphoid tissue, and gallbladder. Typhoid fever is an important public health problem in many low- and middle-income countries (LMICs). The Indian subcontinent and recently Pakistan raising alarms of extensively drug-resistant (XDR) typhoid represent a hotspot of disease activity raising global concerns.

BURDEN OF DISEASE

Global

Global estimates of typhoid fever burden range between 11 million and 21 million cases and approximately 128,000 to 161,000 deaths annually.[1] Children are disproportionately affected by typhoid fever, with peak incidence known to occur in individuals aged 5 to <15 years of age.

According to 2004 estimates, the typhoid fever caused 21,650,974 illnesses and 216,510 deaths during the year 2000, and paratyphoid fever caused 5,412,744 illnesses.[2] This estimate was based on blood culture positive cases 22 in population-based studies. The best figures available for the global burden of enteric fever suggest that Africa (50/100,000) has a far lower burden of disease than Asia (274/100,000).[3] Typhoid fever is one of the most common etiological

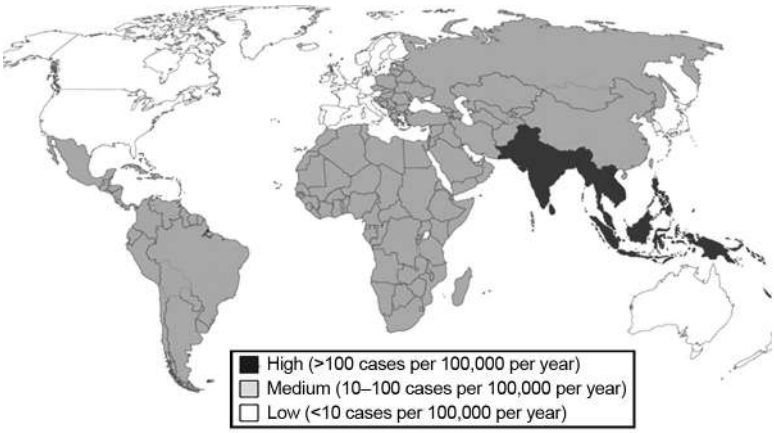


Fig. 1: Global burden of typhoid fever.[2]

sources of bacteremia in many developing countries, with most of the cases originating in the Indian subcontinent of South Asia **(Fig. 1)**.[3,4]

GEOGRAPHICAL DISTRIBUTION

Asia and the Indian Subcontinent

Typhoid fever incidence varies substantially in Asia. Very high typhoid fever incidence has been found in India and Pakistan. In comparison, typhoid fever frequency was moderate in Vietnam and China and intermediate in Indonesia.[4] However, it is the Indian subcontinent which has the highest incidence of the disease worldwide. A previous study from Pakistan in 2006 revealed an incidence rate (IR) of 170/100,000 (using blood culture), whereas a serology-based IR was 710/100,000 (using Typhidot).[5] Brooks et al. reported an overall IR of 3.9/1,000 person-years in an urban slum in Bangladesh.[6] In a multicentric study in five Asian countries—China, India, Indonesia, Pakistan, and Vietnam—it was estimated that the incidence of typhoid ranged from 15.3 per 100,000 persons/year in China to 451.7 per 100,000/year in Pakistan.[7]

The majority of cases occur in South/Southeast Asia, and sub-Saharan Africa. In addition, many island nations of Oceania experience high typhoid fever incidence and large outbreaks. Safe

water, adequate sanitation, appropriate personal and food hygiene, and vaccination are the most effective strategies for prevention and control of typhoid fever in areas where disease burden is high **(Fig. 2)**.[8]

John Crump et al. in 22 studies gave global burden of typhoid fever as high, medium, and low incidence and India falls in high incidence geography **(Table 1)**.[2]

Extensively drug-resistant typhoid fever in Pakistan 2016, resistant to five groups of antibiotics: An ongoing outbreak of XDR typhoid fever is reported by health officials in Karachi, Pakistan in November 2016. The strain of *S. typhi* resistant to five types of antibiotics is feared to disseminate globally. Several deaths have been reported. In 2018,

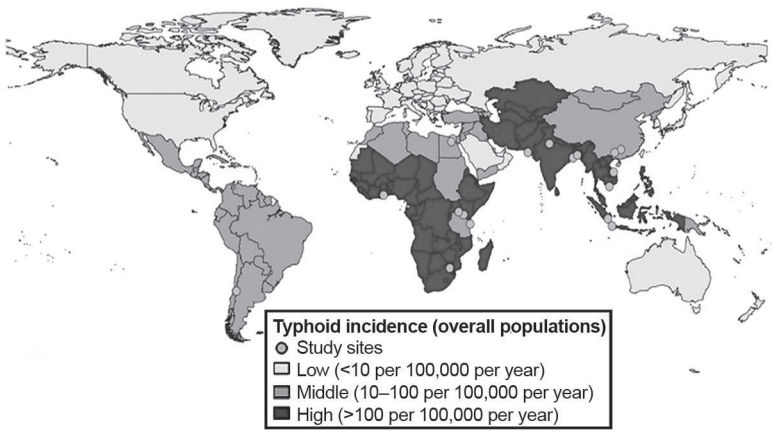


Fig. 2: Global burden with study sites.

TABLE 1: Global burden of typhoid fever as high, medium, and low incidence.

Region	*Incidence*	*No. of cases*
South central Asia, Southeast Asia	High	>100/100,000 cases per year
Rest of Asia, Africa, Latin America, Caribbean, and Oceania except New Zealand and Australia	Medium	10–100/100,000 cases per year
Europe, North America, and rest of the developed world	Low	<10/100,000 cases per year

three cases of XDR typhoid fever were reported in travelers—one who returned to the United Kingdom, and two who returned to the United States. Laboratory confirmation, identifying antimicrobial resistance patterns of typhoid fever cases, starting typhoid vaccination campaigns (from Bharat biotech, India) in the most affected districts, and spreading educational messages about proper hand washing and safe food and water practices is being carried out by health department in Pakistan.[9]

All travelers to Pakistan are at risk of getting XDR typhoid fever. Those who are visiting friends or relatives are at higher risk than are tourists and business travelers. Travelers to South Asia, including Pakistan, should get suitable typhoid vaccine and follow safe food and water as advised by WHO guidelines.

Age Distribution

Recent population-based studies from India, Indonesia, and Vietnam suggest that in some settings, typhoid fever is common in 1–5 years old children. Ochiai et al reported that the mean age of typhoid was significantly lower in the South Asian sites (Pakistan and India) than in the South East and North East Asian sites and suggested that there was an inverse correlation between typhoid incidence and mean age of cases.[7]

In a systematic review and meta-analysis on burden of typhoid and paratyphoid in India; from 1950 to 2015; 791 titles and abstracts, 37 studies of typhoid and 18 studies of paratyphoid were identified and analyzed. Pooled estimates of incidence were 377 (178–801) and 105 (74–148) per 100,000 person-years respectively, with significant heterogeneity between locations for typhoid ($p < 0.001$). Children 2–4 years old had the highest incidence.[10] In one multicenter study, the annual incidence of typhoid per 100,000 children aged 5–15 years was 180 in North Jakarta, Indonesia, 413 in Karachi, Pakistan and 494 in Kolkata, India.

In active search of febrile population in suburbs of Delhi, from 1,820 households; 63 culture-positive typhoid fever cases were detected. Of these, 28 (44%) were in children aged under 5 years. The IR of typhoid per 1,000 person-years was 27.3 at age under 5 years, 11.7

at 5–19 years, and 1.1 between 19 years and 40 years. The difference in the incidence of typhoid fever between those under 5 years and those aged 5–19 years [15.6 per 1,000 person-years (95% CI 4.7–26.5)], and those aged 19–40 years [26.2 (16.0–36.3)] was significant ($p < 0.001$ for both).[11]

Typhoid fever with severity sufficient for an outpatient visit or hospital admission is common in the 0–4 years age group with a large proportion of disease occurring between 6 months and 2 years of age. Among all age groups 27% of typhoid fever episodes are estimated to occur in children 0–4 years; including 29.7% of typhoid fever episodes in the <2 years age group, 9.9% in the <1 year age group, and 2.9% in infants <6 months.[12]

Children are disproportionately affected by typhoid fever, with peak incidence long known to occur in individuals aged 5 to <15 years of age. A recent systematic review and meta-analysis of studies on typhoid fever in children in Asia and Africa found that estimates of the proportion of typhoid fever cases in those aged <5 years ranged from 14% to 29%, compared with 30% to 44% in those aged 5–9 years and 28% to 52% in those aged 10–14 years.[13]

Data on the maternal and fetal morbidity and mortality associated with typhoid fever are limited and mostly based on small case series. Some published reports suggest that typhoid fever in pregnancy can result in a range of maternal complications as well as miscarriage, fetal death, and neonatal infection.[14] Conversely, a comparison of pregnant women with blood culture-confirmed typhoid and pregnant women without typhoid did not find a significant difference in maternal complications or pregnancy outcomes among the two groups.

Cross-sectional seroepidemiological surveys in some countries suggest that a substantial proportion of typhoid fever cases are undiagnosed (up to 80% in the Pacific region).

The DOMI project (Diseases of Most Impoverished) highlighted many epidemiological features of the disease in Asia, specifically showing the existence of a high burden of disease in both school-aged and preschool-aged children across sites.[18]

Prospective disease burden studies found annual IRs of blood culture-confirmed typhoid fever of 180–494 per 100,000 among 5–15

years old in three urban slums (North Jakarta, Indonesia; Kolkata, India; and Karachi, Pakistan). Preschool children aged 2–4 years were also shown to be highly vulnerable with IRs that were just as high, ranging from 149 to 573 per 100,000 in these same three settings. More recent studies from the region do not indicate any dramatic declines in the incidence of enteric fever, although there is increasing evidence of the burden of paratyphoid fever disease in Asia. In children <15 years, the seropositivity rates in 1998–2002 were 32.66% ± 13.79% which increased to 50.04% ± 9.61% in 2007–2011. Incidents occurring among children under 2–4 years of age were 478/100,000 annually.[15]

CASE FATALITY RATES

Estimates of case fatality rates in typhoid fever range from 1% to 4%; fatality rates in children younger than 4 years of age are 10 times higher than in older children. In untreated cases, the fatality rates may rise to 10–20%.[16]

PATHOGEN, ANTIGENS RELEVANT TO VACCINE

Salmonella is a genus of the family Enterobacteriaceae. *Salmonellae* are rod-shaped, gram-negative, facultative anaerobic bacteria, most of which are motile by peritrichous flagella which bear the H antigens. In addition to the H antigen(s), two polysaccharide surface antigens aid in the further characterization of *S. enterica*, namely the somatic O antigen and the capsular Vi (virulence) antigen. The Vi antigen is associated with resistance to complement-mediated bacterial lysis and resistance to complement activation by the alternate pathway.

Salmonella enterica serovars paratyphi A and *paratyphi B* (and uncommonly *paratyphi C*) cause a disease (paratyphoid fever) that is clinically indistinguishable from typhoid fever, particularly in parts of Asia. Typhoid fever and paratyphoid fever are collectively termed enteric fever. While *S. typhi* and *S. paratyphi C* express Vi, the Vi locus is absent from *S. paratyphi* A and B.

DISEASE

Ingested *S. typhi*, following a silent primary bacteremia, reaches the reticuloendothelial system and multiplies intracellularly within

macrophages. After an incubation period of 7–14 days on average (ranging from 3 days to 60 days), patients experience an illness with a wide range of clinical severity, more severe forms being characterized by persistent high fever, abdominal discomfort, malaise, and headache. Constipation or diarrhea may occur in older children and adults, and younger children more often suffer from diarrhea. Complications are estimated to occur in 10–15% of hospitalized patients and are more frequent among untreated patients whose illness has persisted for 2 weeks or more.[15] The most common life-threatening complications are intestinal hemorrhage, intestinal perforation, and encephalopathy with hemodynamic shock. Intestinal perforation has been reported in some outbreaks at unexpectedly high rates (>40%) and associated with high mortality (18–43%).

Seasonality

According to one Indian study, the incidence of typhoid fever in India varied seasonally. The maximum incidence occurred during the monsoon (July–October) of 18.8 cases per 1,000 person-years while lower rates of 5.4 and 4.7 per 1,000 person-years occurred during the summer and winter seasons respectively.

Paratyphoid Fever

While the 1997 Global Survey of *Salmonella* serotyping estimated an incidence of one case of paratyphoid fever for every four cases of typhoid fever, studies from India and Nepal suggest that in some settings, *S. paratyphi A* can contribute up to half of all cases of enteric fever.[18–21] Population surveillance had revealed an IR of *S. paratyphi A* of 42/100,000 persons in India, 72/100,000 in Pakistan, 13.7/100,000 in Indonesia, and 27/100,000 in China.[22] These figures may be due in part to the fact that current vaccines only offer protection against typhoid fever.

Infectious Disease Surveillance (ID_{surv}) Data

According to the Academy's passive reporting system of 10 infectious diseases by the pediatricians, a total of 2,302 (22%) cases of enteric fever were reported out of total 10,478 cases of 10 infectious diseases

from December 2010 to till December 6, 2013.[23] There were 2,261 cases of typhoid and 41 were paratyphoid cases, 10.7% were below 2 years of age and 44.6% were below 5 years, 20% cases were hospitalized, 17% were immunized with typhoid vaccine, and microbial diagnosis was established in 25% cases.[23]

VACCINES AGAINST TYPHOID FEVER

Typhoid vaccination was part of India's National Immunization Program till 1985 when measles vaccine was added by the Government as part of Universal Immunization Program (UIP). There have been several vaccines against typhoid till quite recently.

Historically different vaccine preparations have been developed against typhoid fever, many preparations are obsolete and not available now. Typhoid fever vaccines have been used for more than a century. Clinical trials, some conducted decades ago, have demonstrated efficacy of a range of typhoid vaccines which include:

- Whole cell inactivated vaccines
- Virulence capsular polysaccharide vaccines
- Live attenuated vaccines; and more recently
- Virulence conjugate vaccines (TCVs).

The World Health Organization (WHO) has recommended that countries consider the use of typhoid vaccines for high-risk groups and populations, and for outbreak control. Despite this, typhoid vaccines have not been widely applied in typhoid endemic areas or are often used in outbreaks.[17]

WHOLE CELL-INACTIVATED TYPHOID/PARATYPHOID

Heat-inactivated phenol-preserved whole-cell typhoid vaccines have been available since the 1890s. The vaccine was moderately efficacious (51–88%) in children and young adults in preventing typhoid fever, and the protection persisted for up to 7 years. However, their high levels of reactogenicity; fever (up to 30% of the vaccines), headache (up to 10%), and severe local pain (up to 35%), led to the removal from public health programs in most countries.[3]

NEW GENERATION TYPHOID VACCINES

The new generation current typhoid fever vaccines include oral live attenuated Ty21a vaccine, parenteral Vi polysaccharide and Vi polysaccharide capsular conjugate vaccines (Vi-PS). Oral live attenuated Ty21a vaccine is not available in the country, hence will not be discussed further.

Vi Capsular Polysaccharide Vaccine

The vaccine contains highly purified antigenic fraction of Vi-PS antigen of *S. typhi*, which is a virulence factor of the bacteria. Each dose contains 25 μg 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.

A single dose of Vi polysaccharide vaccine prevents around two-third of typhoid cases in the first year after vaccination (year 1: 69%, 95% CI 63–74%; 3 trials, 99,979 participants; high-certainty evidence). The 3 years cumulative efficacy of the vaccine may be around 55% (95% CI 30–70%; 11,384 participants, 1 trial; low-certainty evidence).[16]

Field effectiveness trials of Vi-PS in Kolkata, India, and Karachi, Pakistan showed moderate protection (56–59%) of older children 5–16 years old while there was variable protection of preschool children 2–4 years of age in the two settings. Indirect protection was shown in the Kolkata trial but not in the Karachi trial. In a postlicensure cluster randomized trial in Kolkata, vaccine effectiveness was 56% (95% CI, 18,77) in the older children 5–14 years of age, and 80% (95% CI 53,91) in children under 5 years of age.[12] This finding of a higher level of protection in younger children was unusual among field trials of typhoid vaccines.

Administering a booster dose of Vi-PS, one or two months later is not helpful, since unconjugated Vi-PS is a T-independent antigen that does not confer immunological memory.

Though there are no issues with hyporesponsiveness with repeat doses, Vi-PS vaccines are advised every 3 years till recently. With more safe, stable and effective conjugate vaccines with long-term protection potential, Advisory Committee on Vaccines and Immunization Practices (ACVIP) is of opinion that Vi-PS use may in future shift to catch-up immunization or to handle special situations like outbreak control.

Efficacy

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%.[24] Interestingly the herd protection of 44% was noted in unvaccinated children in the vaccinated cluster as compared to the control cluster.

Safety

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 human immunodeficiency virus (HIV) infected.

Dosage

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.

Currently there are at least three manufacturers exporting the vaccine [Sanofi Pasteur, GlaxoSmithKline Biologicals, and Bharat Biotech (India)] and many other companies producing for local use [e.g. Lanzhou Institute (China), Chengdu Institute (China), Finlay

Institute (Cuba), DAVAC (Vietnam)]. Out of these vaccines, the one from Sanofi Pasteur is now prequalified by WHO.

Vi Capsular Polysaccharide Conjugate Vaccines

Vi-PS Conjugate Vaccine Conjugated with Pseudomonas aeruginosa Exotoxin A

Unconjugated, polysaccharide typhoid vaccines have the disadvantage of noneffectiveness 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. Oral typhoid vaccines have the limitations of administration, age stability, and availability issues.

Conjugation of the Vi antigen with a protein carrier is hence desirable as it would induce a T-cell dependent immune response.

The scientists at the US National Institute of Child Health and Disease (NICHD) have developed an improved Vi-PS conjugate typhoid vaccine by using exotoxin A of *Pseudomonas aeruginosa* as a carrier protein. This vaccine candidate underwent many human clinical trials in Vietnam. The safety and immunogenicity was evaluated in adults, 5–14 years old children, and 2–4 years old children. None of the recipients experienced a temperature of >38.5°C or significant local reactions after receiving an injection.[25]

A double-blind, placebo-controlled, and randomized efficacy study was conducted in 2–5 years old children in Vietnam. 11,091 children were injected twice, 6 weeks apart, with the Vi conjugate vaccine or saline. The overall efficacy after 27 months of active surveillance followed by 19 months of passive surveillance was 89%.[26]

Lanzhou Institute in China has received this technology from US National Institutes of Health (NIH) and is developing this vaccine candidate, although further details are not currently available.

Vi-PS Conjugate Typhoid Vaccines in India

Different Vi-PS conjugate vaccines have been licensed in India in last 8 years. Conjugate vaccines have solved the issue of able to administer below 2 years, incorporate in programmatic schedules of nations with high endemicity and high incidence of typhoid fever below 4 years of

TABLE 2: Licensed typhoid conjugate vaccines (TCVs) in India.

Name	*Manufacturer*	*Composition*	*Comments*
Typbar-TCV	Bharat Biotech International Ltd	25 µg purified Vi-PS of *S. typhi* (strain 2) to tetanus toxoid	Literature plenty robust evidence regarding safety, VE
Zyvac TCV	Cadila Healthcare Pvt Ltd	25 µg purified Vi-PS of *S. typhi*, tetanus toxoid, 2-phenoxy ethanol as preservative	Few trials, DCGI approved
PedaTyph	Bio-Med	5 µg purified Vi-PS of *S. typhi*, tetanus toxoid	Claim usefulness in <6 months also dose schedule not clear
Vac-T	Zuventus Healthcare Ltd	5 µg purified Vi-PS of *S. typhi*, tetanus toxoid	Limited use
Typbar	Bharat Biotech	Vi-PS 25 µg purified Vi-PS of *S. typhi* (strain 2) to tetanus	Above 2 years 0–adults, recommended every 3 years
Enteroshield	Abbott	Vi-PS 25 µg of *S. typhi* to tetanus toxoid	Human challenge study proved efficacy, long-term efficacy and safety data up to 5 years available
Zyvac	Cadila Healthcare Pvt Ltd	Vi-PS unconjugated	Few studies

(DCGI: Drug Controller General of India; Vi-PS: virulence capsular polysaccharide vaccine)

age. India fits in to this situation along with Southeast Asia and parts of Africa.

VI-PS CONJUGATE VACCINE CONJUGATED WITH TETANUS TOXOID (PEDATYPH®) BY BIO-MED PVT LTD

After the initial attempt (described above) at making a conjugated typhoid vaccine, there have been many efforts to develop a conjugate typhoid vaccine by using different carrier proteins. With the technology initially transferred from US NIH, Bio-Med Pvt. Ltd. in India developed a conjugate vaccine using tetanus toxoid (TT) as the carrier protein

with a dose of 5 μg of Vi-PS antigen. This product was tested in a clinical trial in 169 subjects >12 weeks with a comparison group (Vi) of 37 children >2 years. The results from this study were compared with the NIH study in Vietnam and it was reported that there was four-fold or greater rise in antibody titer [or an enzyme-linked immunosorbent assay (ELISA) level higher than the threshold 1 μg/mL] of each group on ELISA which was statistically equivalent to Vi-rEPA. The vaccine was well-tolerated with no major local or systemic side effects. No data on duration of immunity and efficacy is available.

Based on the results of this study, this product was submitted for licensure and was licensed for more than 3 months of age in 2008 in India. This vaccine is licensed in India as two injections of 0.5 mL each at interval of 4–8 weeks in 3 months to 2 years old children; followed by booster at 2–2.5 years age; and as two injections at interval of 4–8 weeks in children older than 2 years of age. Booster vaccination is recommended every 10 years thereafter. The lack of detailed data before licensure was an issue.[27]

In a school based open label, cluster randomized, controlled, postmarketing surveillance in Indian children aged 6 months to 12 years in Kolkata, India, safety and efficacy of PedaTyph were studied 1 year postvaccination. Children from 6 months to 3 years of age in the study were younger siblings at home of study or control group. Of 905 children in test group, all received first dose of PedaTyph vaccine and 765, second dose after 6 weeks interval. Control group received regular National Immunization Schedule (NIS) vaccines.[15]

Fever without focus for more than 3 days was reported in 7.14%, 42.86%, and 50% of subjects aged 6 months to 2 years, >2–5 years and >5 years, respectively in the test group. In the control group, 27.66%, 38.30%, and 34.04% of children belonging to age groups 6 months to 2 years, 2–5 years, and >5 years, respectively had fever without focus for more than 3 days. Overall, febrile episodes in all subjects were 19% from vaccinated group and 24% in the unvaccinated group. About 1.27% from control group and none from vaccine group suffered from culture positive typhoid fever.

A final subgroup of only 62 children at third follow-up after 1 year among 76 children who received second dose of vaccine after 6 weeks were estimated for protective antibodies titers. An antibody

titer value of 1.8 ELISA (EU)/mL (95% CI: 1.5 EU/mL, 2.2 EU/mL), 32 EU/mL (95% CI: 27 EU/mL, 39 EU/mL) and 14 EU/mL (95% CI: 12 EU/mL, 17 EU/mL) at baseline, 6 weeks and 12 months, respectively was observed.[15]

Cochrane database of systematic reviews, in a review on effects of vaccines in preventing typhoid fever is uncertain of the efficacy of administration of two doses of Vi-TT (PedaTyph) in typhoid cases in children during the 1st year after vaccination (year 1: 94%, 95% CI–1% to 100%, 1 trial, 1,625 participants; very low-certainty evidence). These data come from a single cluster-randomized trial in children aged 6 months to 12 years and conducted in India.[16]

VI-POLYSACCHARIDE CONJUGATE VACCINE CONJUGATED WITH TETANUS TOXOID FROM BHARAT BIOTECH (TYPBAR-TCV®)

Typbar-TCV was first licensed in India in 2013 for intramuscular administration of a single dose (0.5 mL) in children aged 6 months and older and in adults up to 45 years of age. It is available in single-dose vials or prefilled syringes, and five-dose vials.

Each vaccine dose comprises 25 μg of purified Vi-PS conjugated to TT. In the multidose formulation each dose also contains 5 mg of 2-phenoxyethanol as preservative. The manufacturer-recommended storage temperature is 2–8°C. The vaccine has a vaccine vial monitor (VVM30).

Typbar-TCV® is a Vi-PS conjugate typhoid vaccine conjugated with TT. The manufacturer has used a dose of 25 μg/0.5 mL of conjugate Vi content polysaccharide which is the highest having been used in other trials as well on conjugate vaccine the world over.[28]

Phase IIa/IIb study revealed no difference in the geometric mean titers (GMTs) between two doses (15 μg/0.5 mL) and single (25 μg/0.5 mL) dose cohorts, and a single dose of 25 μg/0.5 mL showed excellent immune response (100% seroconversion). A phase III, randomized, multicentric, controlled trial was conducted to evaluate the immunogenicity and safety of this vaccine, Typbar-TCV® in a total of 981 healthy subjects and compared with the typhoid Vi-PS vaccine of the same manufacturer (Typbar) having similar amount of antigen per dose.

The study group receiving the test vaccine (Typbar-TCV) was divided into two cohorts, i.e. ≥6 months to ≤2 years (327 subjects) and >2 years to <45 years (654 subjects). Cohort-I was single arm open label and all the 327 subjects received single dose of the test vaccine. Cohort-II was randomized double blind trial and the subjects were recruited into two groups—one who received single dose of either test vaccine (340 subjects) or reference vaccine (314 subjects).

There is moderate-certainty evidence that Typbar-TCV results in improved GMTs and seroconversion rates compared to Vi-PS vaccine. Among subjects 2–45 years of age, Typbar-TCV elicits significantly higher titers of immunoglobulin (IgG) Vi antibody than unconjugated Typbar at 6 weeks after a primary immunization [1292.5 (95% CI 1152.9, 1448.9), N = 332 vs. 411.1 (95% CI 358.9, 470.9), N = 305] and 6 weeks after a second immunization [1680.6 (95% CI 1498.3, 1885.1), N = 174 vs. 475.0 (95% CI 339.9, 663.6)], N = 50. At 3 and 5 years after a single immunization, the antiVi GMTs and the proportion of individuals with titers more than four-fold over their baseline were significantly higher among recipients of the TCV.[1] In infants 6–11 months old and toddlers 12–23 months old, a single dose of Typbar-TCV elicited high titers of IgG antiVi antibody [1937.4 (95% CI 1785.0, 2102.9), N = 307] that endured up to 5 years in a proportion of young children.

Data on antibody avidity and IgG subclasses provide further confidence in the quality of the antibody response, and that the vaccine-induced immune response is boostable.

Coadministration with Other Vaccines Measles and MMR

Compatibility and efficacy of Typbar-TCV with measles vaccine alone at 9 months and measles, mumps, and rubella (MMR) at 15 months were studied. Measles vaccine with Typbar-TCV at ~9 months of age vs. either vaccine alone and of Typbar-TCV coadministered with MMR vaccine at 15 months of age conducted by manufacturer and results are published.

- Group 1A Typbar-TCV + Measles (N = 98)
- Group 1B Typbar-TCV + Measles (N = 99)
- Group 2 measles (N = 98)
- Group 3 Typbar-TCV (N = 98)
- Group 4 measles (N = 100)

No significant differences were detected among the groups at any time relevant points including days 56, 180, 360, and 720. The antiVi GMT and antimeasles antibodies were similar in all five groups. The antiVi antibodies and IgG antimeasles antibodies were similar when the vaccines were given either in combination or alone.

Human Challenge Model Trial

When Typbar-TCV was evaluated in a human challenge model in a population of immunologically naïve adult volunteers (16–80 years of age), efficacy of 87.1% (95% CI 47.2–96.9%) was estimated based on an endpoint of persistent fever followed by positive blood culture, thus reflecting clinical and surveillance parameters under which a typhoid fever case would be confirmed.[1]

Background paper to SAGE on Typhoid Vaccine Policy Recommendation 2017, conclusions regarding Typbar TCV: Based on the data available for review, the SAGE Working Group concluded that there is moderate-certainty evidence that at least one licensed Vi-TT vaccine (Typbar-TCV™ manufactured by Bharat Biotech International Ltd) results in improved GMTs and seroconversion rates compared to Vi-PS vaccine (there are no comparative data with Ty21a). Further the data on coadministration of Typbar-TCV with measles-containing vaccines (measles and MMR) do not show evidence of interference with the immune responses to either vaccine. Data from a human challenge study using Typbar-TCV in a population of immunologically naïve adult volunteers produced an estimate of efficacy of 87.1% (95% CI 47.2–96.9%) based on an endpoint of persistent fever followed by positive blood culture. This was considered as good supporting evidence for the vaccine.

Immunogenicity Results

In cohort-I, 98.05% subjects showed seroconversion (more than or equal to four-fold titer rise) on day 42, and the GMTs on day 0 and 42 were 9.44 U/mL and 1,952.03 U/mL respectively. The GMTs were slightly higher in the >1–2 years than in 6 months to <1 year age group while no difference was seen in seroconversion rates. In cohort-II, 97.29% and 93.11% subjects of test and reference vaccine groups respectively, were seroconverted (more than or equal to four-fold

titer rise) on day 42, whereas the GMTs on day 42 in the test and reference vaccine groups were 1,301.44 U and 411.11 U, respectively (p = 0.00001). Both seroconversion and GMTs were higher in younger (>2 to <15 years) than older (15–45 years) age groups.

Long-term Immunogenicity

The manufacturer has planned a 3-year follow-up for seroconversion data of phase III. So far, they have shared 18 months follow-up data which show significant waning of GMTs and seroconversion levels in both the cohorts from day 42 levels while 100% of subjects of test vaccine subjects were still seroprotected (the protective level: Vi antibody >7.4 ELISA unit/mL). Similar trend was observed in the subgroup of cohort-II that received reference vaccine.

Safety Issues

Comparative assessment of safety and tolerability of the vaccine in all subjects up to 12 weeks postvaccination. The most common local and systemic events reported were pain at injection site and fever, respectively in both the cohorts. Fever was noticed in 10%, 4.28%, and 2.75% in cohort-I, test and reference vaccine groups of cohort-II, respectively. None of the enrolled subjects were withdrawn from study for vaccine-related adverse reaction. The vaccine has been licensed by the Drug Controller General of India (DCGI) in August, 2013 for clinical use in India.

The Indian Academy of Pediatrics (IAP) ACVIP has reviewed the pivotal trial of this new vaccine and considers it to be a promising vaccine, fulfilling the critical gap of providing protection under 2 years of age. However, before a slot is created for the vaccine in the existing IAP immunization timetable, the committee has shortlisted a few key issues that need to be addressed by the manufacturers.[28]

A field effectiveness trial is in progress at Navi Mumbai and results awaited.[31]

VAC-T FROM ZUVENTUS HEALTHCARE PVT LTD

Purified Vi polysaccharide of *S. typhi* (strain Ty2) 5 μg/0.5 mL conjugated to TT protein 5 μg in isotonic saline. Indicated for infants

aged >3 months, children and adults appear similar to the brand with similar dose. Manufacturer recommends a booster dose at 3 years after single primary dose. Open, controlled, and comparative phase III clinical trial was conducted at three centers to assess safety, immunogenicity in 206 subjects aged 3 months to 2 years. This well-designed small study elicited protective antibodies at 4 weeks postvaccination. Authors claim protective antibodies 5 years after single dose, however recommend a booster at 3 years.[32]

ZYVAC TYPHOID CONJUGATE VACCINE

Single dose: 0.5 mL vial; Vi polysaccharide of *S. typhi* 25 μg, 2-phenoxy ethanol 2.50 mg as preservative and buffer solution.

ENTEROSHIELD

Large phase III, trial for long-term follow-up for up to 720 days, avidity index, a controlled human infection model is carried out. Recommended.

SEROLOGIC CORRELATES OF PROTECTION

Unlike many vaccine preventable diseases, serologic correlates of protection are not available for typhoid disease or typhoid vaccines. Hence, even though typically more than 90% of vaccines achieve seroconversion after unconjugated Vi vaccine, efficacy is actually 50–70% in field efficacy trials. Different researchers have used different levels. For example, NIH estimated around 7 EU/mL as protective level of Vi antibody[18] and same group of researchers have estimated 3.52 EU/mL as protective level.[29]

RECOMMENDATIONS FOR USE

Individual Use

IAP/ACVIP Recommendation Typhoid Vaccines[33]

Primary schedule

- A single dose of TCV 25 μg is recommended from the age of 6 months onwards routinely.

- An interval of at least 4 weeks is not mandatory between TCV and measles-containing vaccine when it is offered at age of 9 months or beyond.
- For a child who has received only typhoid polysaccharide vaccine, a single dose of TCV is recommended at least 4 weeks following the receipt of polysaccharide vaccine. Routine booster for TCV at 2 years is not recommended as of now.

Currently, three products of TCV are licensed in India. Two of them contain 25 μg of purified Vi-PS of *S. typhi*, and one of them containing 5 μg purified Vi-PS of *S. typhi*. The WHO position paper in 2018 has remarked that the body of evidence for the 5 μg vaccine is very limited.

Vi-PS vaccine: IAP ACVIP recommends the administration of the currently available Vi polysaccharide vaccine 0.5 mL intramuscularly (IM) every 3 years beginning at the age of 2 years. A child with history of suspected or confirmed enteric fever may be vaccinated 4 weeks after recovery if he/she has not received the vaccine in the past 3 years.

As availability of conjugate vaccines is steadily increasing, usage of Vi-PS for individual protection may decrease. However for control of epidemics, in high endemic places and in humanitarian emergencies Vi-PS has a role.

Vi-PS TT conjugate (PedaTyph®) by Bio-Med: IAP believes that since the immunogenicity trial assessed response to only single dose and 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. Subsequent Vietnamese trials have shown better antibody levels when the strength of the dose was increased to 12.5 μg and 25 μg per dose (0.5 mL).[29]

In view of these issues, the committee does not recommend the use of this conjugated vaccine at present.

In a large cluster randomized study involving 1,765 children from municipal schools of Kolkata, two doses of PedaTyph with 6 weeks interval was administered to test group. Results show the vaccine elicits protective antibodies. Number of doses to be recommended

need for a booster dose is unanswered. More studies are required before a recommendation can be made.

The SAGE Working Group on Typhoid Vaccines was unable to conclude on the potential benefits for PedaTyph in order to make a policy recommendation.

Vi polysaccharide conjugate vaccine conjugated with TT from Bharat Biotech (Typbar-TCV®):[30] considering the typhoid epidemiology in the country and analyzing the available data of the vaccine, IAP recommends the use of new Vi-PS conjugate vaccine below 1 year of age, preferably between 9 months and 12 months (minimum age 6 months).

Among the available typhoid vaccines, TCV is preferred at all ages in view of its improved immunological properties, use in younger children and expected longer duration of protection. Countries may also consider the routine use of Vi-PS vaccine in individuals aged 2 years and older.

PUBLIC HEALTH PERSPECTIVES

Despite the substantial and recognized disease burden, typhoid fever remains a neglected disease in both the Southeast Asia and Western Pacific regions. Coordinated action involving key stakeholders and partners at the regional and national levels is needed to create appropriate typhoid fever prevention and control policies and strategies, especially in settings with high incidence of disease.

Emerging threats, including multidrug resistance and increasing urbanization warrant focused attention to shorter term interventions including programmatic vaccination, with the new typhoid conjugate vaccines.

There is a huge burden of the disease in almost every state of the country. Improvement in sanitary infrastructures and implementation of hygienic practices can reduce the disease burden as seen in most developed countries. However, the development of an adequate infrastructure for improved water and sanitation requires large investments, and is therefore a distant goal for the impoverished populations in the developing world including India. Basic health education such as hand washing and food handling is also known

to be effective in reducing typhoid fever. Furthermore, there are licensed vaccines to prevent typhoid fever. Although typhoid fever can be effectively treated with antibiotics, growing rates of antibiotic resistance in many countries are making this treatment option increasingly more difficult and costly.

As recent evidence based on systematic collection of blood cultures in febrile, children during active household surveillance in multiple vaccine efficacy trials or in children seeking ambulatory healthcare services, bacteremic *S. typhi* infection in children 1–4 years of age is much more common than previously thought and with the availability of indigenous, new generation Vi-PS conjugate vaccines and a healthy pipeline of new generation conjugate typhoid vaccines, universal typhoid vaccination of Indian children must be prioritized without further delay **(Box 1)**. A few cost-effectiveness studies in the past have demonstrated that administration of even a single dose of the polysaccharide vaccine in the age group of 2–15 years would be highly cost-effective. The Academy strongly urges the Government to include typhoid vaccination in the UIP considering the enormous burden of the disease.

BOX 1: Typhoid vaccines.

- Both Vi-PS (polysaccharide) and Vi-PS conjugate vaccines are available.
- *Minimum ages*:
  - *Vi-PS (Typbar-TCV®)*: 6 months.
  - *Vi-PS (polysaccharide) vaccines*: 2 years.
- *Vaccination schedule*:
  - *Vi-PS (polysaccharide) vaccines*: Single dose at 2 years; revaccination every 3 years (no evidence of hyporesponsiveness on repeated revaccination so far).
  - *Vi-PS conjugate (Typbar-TCV®)*: Single dose at 6-9 months. The need for boosters is not certain.
  - *Vi-PS conjugate vaccine (PedaTyph®)*: There are study design issues with a single large study done. Further data needed specially on number of doses. Available data not sufficient and does not justify recommendation for routine use.

Catch-up vaccination:

- Recommended throughout the adolescent period, i.e. till 18 years.

REFERENCES

1. World Health Organization. 153 Typhoid vaccines: WHO position paper, March 2018. Vaccine. 2018;93:153-72.
2. Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. Bull World Health Organ. 2004;82:346-53.
3. Kothari A, Pruthi A, Chugh TD. The burden of enteric fever. J Infect Dev Ctries. 2008;2:253-9.
4. Kanungo S, Dutta S, Sur D. Epidemiology of typhoid and paratyphoid fever in India. J Infect Dev Ctries. 2008;2:454-60.
5. Siddiqui FJ, Rabbani F, Hasan R, et al. Typhoid fever in children: some epidemiological considerations from Karachi, Pakistan. Int J Infect Dis. 2006;10:215-22.
6. Brooks WA, Hossain A, Goswami D, et al. Bacteremic typhoid fever in children in an urban slum, Bangladesh. Emerg Infect Dis. 2005;11:326-9.
7. Ochiai RL, Acosta CJ, Danovaro-Holliday MC, et al. A study of typhoid fever in five Asian countries: disease burden and implications for controls. Bull World Health Organ. 2008;86:260-8.
8. Date KA, Bentsi-Enchill AD, Fox KK, et al. Typhoid Fever surveillance and vaccine use—South-East Asia and Western Pacific regions, 2009-2013. MMWR Morb Mortal Wkly Rep. 2014;63:855-60.
9. Qamar FN, Yousafzai MT, Khalid M, et al. Outbreak investigation of ceftriaxone-resistant Salmonella enterica serotype Typhi and its risk factors among the general population in Hyderabad, Pakistan: a matched case-control study. Lancet Infect Dis. 2018;18:1368-76.
10. John J, Van Aart CJ, Grassly NC. The Burden of Typhoid and Paratyphoid in India: Systematic Review and Meta-analysis. PLoS Negl Trop Dis. 2016;10(4):e0004616.
11. Sinha A, Sazawal S, Kumar R, et al. Typhoid fever in children aged less than 5 years. Lancet. 1999;354:734-7.
12. WHO. (2017). Background Paper on Typhoid Vaccines for SAGE Meeting (October 2017). [online] Available from https://www.who.int/immunization/sage/meetings/2017/october/1_Typhoid_SAGE_background_paper_Final_v3B.pdf. [Accessed October 2019].
13. Luthra K, Watts E, Debellut F, et al. A Review of the Economic Evidence of Typhoid Fever and Typhoid Vaccines. Clin Infect Dis. 2019;68:S83-95.
14. Touchan F, Hall JD, Lee RV, et al. Obstet Med. 2009;2:161-3.
15. Mitra M, Shah N, Ghosh A, et al. Efficacy and safety of Vi-tetanus toxoid conjugated typhoid vaccine (PedaTyph™) in Indian children: School based cluster randomized study. Hum Vaccin Immunother. 2016;12:939-45.
16. Milligan R, Paul M, Richardson M, et al. Vaccines for preventing typhoid fever. Cochrane Database Syst Rev. 2018;5:CD001261.
17. Crump JA. Building the case for wider use of typhoid vaccines. Vaccine. 2015;33:C1-C2.

18. Ochiai RL, Wang XY, von Seidlein L, et al. Salmonella paratyphi A rates, Asia. Emerg Infect Dis. 2005;11:1764-6.
19. Shlim DR, Schwartz E, Eaton M. Clinical Importance of Salmonella Paratyphi A Infection to Enteric Fever in Nepal. J Travel Med. 1995;2:165-8.
20. Sood S, Kapil A, Dash N, et al. Paratyphoid fever in India: An emerging problem. Emerg Infect Dis. 1999;5:483-4.
21. Tankhiwale SS, Agrawal G, Jalgaonkar SV. An unusually high occurrence of Salmonella enterica serotype paratyphi A in patients with enteric fever. Indian J Med Res. 2003;117:10-2.
22. Bhan MK, Bahl R, Bhatnagar S. Typhoid and paratyphoid fever. Lancet. 2005;366:749-62.
23. IAP. (2019). Infectious disease surveillance. [online] Available from www.idsurv.org. [Accessed October 2019].
24. Sur D, Ochiai RL, Bhattacharya SK, et al. A cluster-randomized effectiveness trial of Vi typhoid vaccine in India. N Engl J Med. 2009;361:335-44.
25. Kossaczka Z, Lin FY, Ho VA, et al. Safety and immunogenicity of Vi conjugate vaccines for typhoid fever in adults, teenagers, and 2- to 4-year-old children in Vietnam. Infect Immun. 1999;67:5806-10.
26. Lin FY, Ho VA, Khiem HB, et al. The efficacy of a Salmonella typhi Vi conjugate vaccine in two-to-five-year-old children. N Engl J Med. 2001;344:1263-9.
27. Shah NK. Indian conjugate Vi typhoid vaccine: do we have enough evidence?. Indian Pediatr. 2009;46:181-2.
28. Vashishtha VM, Kalra A, Bose A, et al. Indian Academy of Pediatrics (IAP) recommended immunization schedule for children aged 0 through 18 years—India, 2013 and updates on immunization. Indian Pediatr. 2013;50:1095-108.
29. Canh DG, Lin FY, Thiem VD, et al. Effect of dosage on immunogenicity of a Vi conjugate vaccine injected twice into 2- to 5-year-old Vietnamese children. Infect Immun. 2004;72:6586-8.
30. Mohan VK, Varanasi V, Singh A, et al. Safety and immunogenicity of a Vi polysaccharide-tetanus toxoid conjugate vaccine (Typbar-TCV) in healthy infants, children, and adults in typhoid endemic areas: a multicenter, 2-cohort, open-label, double-blind, randomized controlled phase 3 study. Clin Infect Dis. 2015;61:393-402.
31. US National Institute of Health. (2019). Typhoid Conjuagte Vaccine Introduction in Navi Mumbai, India. [online] Available from https://clinicaltrials.gov/ct2/show/NCT03554213. [Accessed October 2019].
32. Marchello CS, Hong CY, Crump JA. Global Typhoid Fever Incidence: A Systematic Review and Meta-analysis. Clin Infect Dis. 2019;68:S105-S116.
33. Balasubramanian S, Shah A, Pemde HK, et al. Indian Academy of Pediatrics (IAP) Advisory Committee on Vaccines and Immunization Practices (ACVIP) Recommended Immunization Schedule (2018-19) and Update on Immunization for Children Aged 0 Through 18 Years. Indian Pediatr. 2018;55:1066-74.

3.12 HUMAN PAPILLOMA VIRUS VACCINES

Harish K Pemde

EPIDEMIOLOGY

Human papillomavirus (HPV) infections are highly transmissible and are primarily transmitted by sexual contact. Whereas most HPV infections are transient, self-regressing and benign, persistent genital infection with certain viral genotypes can lead to the development of anogenital precancers and cancers. Presence of oncogenic HPV-DNA has been demonstrated in 99.7% of all cervical cancer cases, the highest attributable fraction so far reported for a specific cause of major human cancer. The lag period between infection with oncogenic HPV and invasive cervical cancer is 15–20 years.[1]

CERVICAL CANCER MORBIDITY AND MORTALITY IN INDIA

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.[2] In many countries in sub-Saharan Africa, Central and South America, South and South-East Asia, age-standardized incidence rates of cervix cancer exceed 25 per 100,000.[3] In India, cancer of the cervix uteri is the second most important cancer in women.[4] Globally Age Adjusted Incidence Rate (AAR) of cervical cancer is 15.3 per 100000, and for Indian women it is 14.9 per 100,000. It is estimated that 96,922 cases of cervical cancer cases occur in India and of these 60,078 die every year[4] and this has come down from earlier very high rates even without a control program.[5] The urban population-based cancer registries (PBCRs) at Bengaluru, Bhopal, Chennai, Delhi and Mumbai have shown a significant decrease in the AARs of cervical cancer (16.9 in 2001 to 15.3 in 2012 in Bengaluru, 18.6 to 13.8 in Bhopal, 29.1 to 15.7 in Chennai, 19.7 to 15.5 in Delhi and 14.1 to 9 in Mumbai)[6] **(Fig. 1)**.

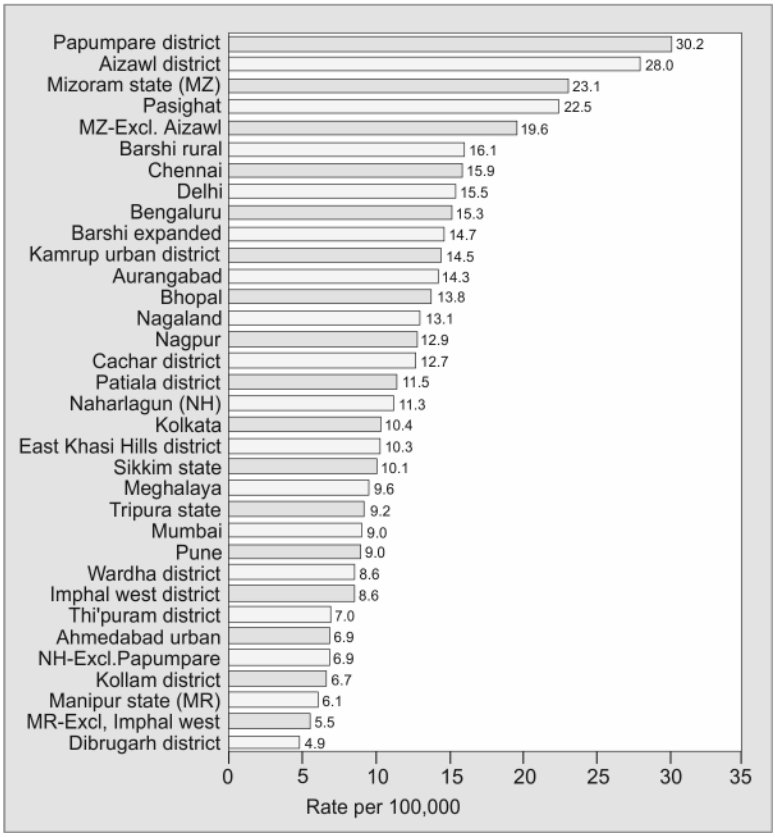


Fig. 1: Age adjusted incidence rate of cervical cancer from population-based cancer registries in India.[7]

PREVENTION OF CERVICAL CANCER: SCREENING OR VACCINATION

Cervical cancer is essentially a preventable cancer as it has a long preinvasive stage. Countries with well-organized programs to detect and treat precancerous abnormalities and early stage cervical cancer can prevent up to 80% of these cancers.[8] It has been shown that it is possible to screen and treat cervical cancer in early stages with high success even in rural India.[9] However, information on screening behaviors of Indian women related to cervical cancer is very little. In a

study from Kolkata, most women reported "limited" to "no" knowledge of cervical cancer (84%) and the Pap smear test (95%).[10] Further, to implement national screening program, large investment has to be made in terms of logistics and training of healthcare personnel.

Realistically, we would need HPV vaccines to significantly reduce the health care burden currently required for cervical cancer prevention. But we also would need screening because of the limitations of current HPV vaccines both in their lack of therapeutic effect (thus not protecting women with an ongoing neoplastic processes) and in their limited number of HPV types. Thus it is imperative that we would need both vaccination as well as efficient screening schemes and rapid intervention like "screen and treat" protocol.[11]

PATHOGEN

Human papillomaviruses are nonenveloped, double-stranded deoxyribonucleic acid (DNA) viruses in the family of *Papillomaviridae*. The HPV genome is enclosed in a capsid shell comprising major (L1) and minor (L2) structural proteins. More than 100 HPV genotypes are known. Certain HPV genotypes are associated with cell immortalization and transformation related to carcinogenesis. Of these, at least 13 may cause cervical cancer or are associated with other anogenital and oropharyngeal cancers. HPV types 16 and 18 cause about 70% of all cases of invasive cervical cancer worldwide, with type 16 having the greatest oncogenic potential. The distribution of HPV types varies among geographical regions, but the dominant oncogenic type in all regions is HPV-16.[12] The low-risk HPV types 6 and 11 are responsible for about 90% of anogenital warts and almost all recurrent respiratory papillomatosis.

In India high-risk HPV types were found in 97% of cervical cancers.[13] A meta-analysis of HPV type-distribution from India showed that in invasive cervical carcinoma (ICC), HPV-16 was the predominant type (64.8%), followed by HPV 18, 45, 33, 35, 58, 59 and 31. The estimated HPV-16/18 positive fraction was 78.9% in women with ICC 61.5% with high squamous intraepithelial lesion, 30.8% with low squamous intraepithelial lesion and 3.9% in women with normal

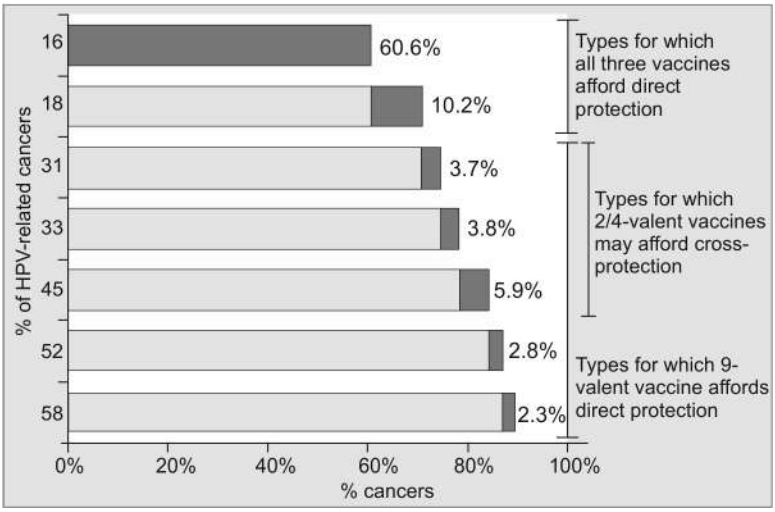


Fig. 2: Relative contribution of different HPV types to cervical cancer—World, 2012.[16]

cytology/histology. There was no difference in overall HPV prevalence in cervical cancer between North and South India. However, HPV-16 and HPV-45 appeared to be more prevalent in North India while HPV-35 appeared to be more prevalent in South India. It is estimated that HPV-16/18 vaccines will provide over 76.7% protection against ICC in South Asia.[14]

Globally, 60.6% [95% confidence interval (CI): 59.6–61.6] of cases are attributed to HPV-16 and 10.2% (95% CI: 9.6–10.9) to HPV-18.[15] HPV-31 accounts for 3.7%, HPV-33 for 3.8%, HPV-45 for 5.9%, HPV-52 for 2.8% and HPV-58 for 2.3% of cervical cancer cases. Approximately 90% of the squamous cell carcinomas which are positive for HPV DNA are related to HPV types 16, 18, 45, 31, 33, 52, and 58[15] **(Fig. 2)**.

PROTECTIVE IMMUNITY

Natural HPV infections do not induce a vigorous immune response as they are restricted to the intraepithelial basement layers of the mucosa. 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. They are

known as "nonneutralizing" antibodies. The neutralizing antibodies are best characterized and most type-specific HPV antibodies which are those directed against the L1 protein of the virus, which is the main capsid protein. The other L2 protein is minor and is responsible for nononcogenic genital warts.

HPV Vaccines

Two vaccines have been licensed globally; a quadrivalent and a bivalent vaccine. Both are manufactured by recombinant DNA technology that produces noninfectious VLPs comprising of the HPV L1 protein. 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 (CIN-2/3) 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. Higher immune response is seen in preadolescents through 9–13 years as compared to adolescents and young adults. Both vaccines have been licensed in several countries world over. These vaccines are equally safe and both have shown nearly complete protection against precancerous and other anogenital lesions caused by the respective vaccine-related HPV-types during the 10–12 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. However, the immune protective correlates are not known and the level of antibody titers which will be translated into clinical efficacy are ill understood.

Quadrivalent Vaccine

Quadrivalent vaccine (HPV4) 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 AlOH.

Efficacy

The safety and efficacy of quadrivalent vaccine was assessed in a large study named FUTURE (Females United to Unilaterally Reduce Endo/Ectocervical Disease). This analysis studied 17,622 women aged 15–26 years who were enrolled in one of two randomized, placebo-controlled, efficacy trials for the HPV6/11/16/18 vaccine (first patient on December 28, 2001, and studies completed July 31, 2007). Clinical trials with three doses at 0, 2 and 6 months have shown 99% efficacy at a median follow-up of 1.9 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). Reduction in HPV-16 related lesions and HPV-18 related lesions are 98% and 100%, respectively when CIN-2/3 is taken into consideration and AIS as end points. Data from two international, double blind, placebo-controlled, randomized efficacy trials of quadrivalent HPV vaccine (FUTURE I) and (FUTURE II) showed persistent protection in participants over 5 years.[17,18] The studies for 126 months (10.5 years) are still to be published and targeted studies for 14 years are being processed.

Bivalent Vaccine

The bivalent vaccine (HPV2) is a mixture of L1 proteins of HPV serotypes 16 and 18 with AS04 as an adjuvant.

Efficacy and Safety

The safety and efficacy of the bivalent HPV vaccine was assessed in a large study named PATRICIA (Papilloma Trial against Cancer in Young Adults). In this phase III study, prevention of vaccine-related HPV types CIN-2/3 was assessed that included 18,644 healthy women

aged 15–25 years at the time of first vaccination. Women were enrolled between May 2004 and June 2005. The trial was carried out at 135 centers across 14 countries worldwide, as previously described.[19]

In women with no evidence of current or previous HPV-16/18 infection (DNA negative and seronegative), vaccine efficacy (VE) was 90.3% (96.1% CI: 87.3–92.6) against 6-month persistent infection (PI), 91.9% (84.6–96.2) against CIN-11 and 94.6% (86.3–98.4) against CIN-21 [97.7% (91.1–99.8)]. In women HPV-16/18 DNA negative but with serological evidence of previous HPV-16/18 infection (seropositive), VE was 72.3% (53.0–84.5) against 6-month PI, 67.2% (10.9–89.9) against CIN-11, and 68.8% (228.3–95.0) against CIN-21 [88.5% (10.8–99.8)]. In women with no evidence of current HPV-16/18 infection (DNA negative), regardless of their baseline HPV-16/18 serological status, VE was 88.7% (85.7–91.1) against 6-month PI, 89.1% (81.6–94.0) against CIN-11 and 92.4% (84.0–97.0) against CIN-21 [97.0% (90.6–99.5)]. In women who were DNA positive for one vaccine type, the vaccine was efficacious against the other vaccine type. The vaccine did not impact the outcome of HPV-16/18 infections present at the time of vaccination. Vaccination was generally well tolerated regardless of the woman's HPV-16/18 DNA or serological status at entry.[20] Follow-up studies in a subset of participants over 8.4 years shows no evidence of waning immunity for bivalent vaccine.

Efficacy against Genital Warts

Conventionally, it is believed that HPV4 having ST 6 and 11 will prevent good efficacy against genital warts. In the FUTURE trial, 99–100% efficacy was seen against vaccine type related genital warts. In countries where this vaccine was introduced in NIP like US, reductions in HPV vaccine type prevalence of genital warts have been reported in young females. Surprisingly, in UK where bivalent vaccine was introduced in 2008, a 13.3–20.8% reduction among women aged <19 years in new diagnoses of external genital warts among since the vaccine was introduced in national vaccination program.[21] Later a post hoc analysis of the phase III PATRICIA trial found efficacy against low-risk HPV types 6, 11, 74 ranged from 30.3% to 49.5%.[22]

The HPV4 vaccine was found to have good efficacy against genital warts in males also. Having an efficacy of 65% (intention to treat)

and 90.4% (per protocol) against external genital lesions caused by vaccine-type in 16–26 years old males in 18 countries.[23]

Cross-protection against Nonvaccine Serotypes

The other serotypes phylogenetically aligned to serotypes 16 and 18 which are responsible for about 20% of lesions are cross-protected to some extent by both the vaccines.

However, the immunity is not robust. In PATRICIA study phase three trial in 4 years follow-up against 6 months persistent infections cross-protection for nonvaccine ST-33, 31, 45 were seen to be 43%, 77% and 79%, respectively. However, in long-term follow-up (LTFU) study for 9 years failed to demonstrate efficacy for 6 months against persistent infection by the bivalent vaccine. The true cross-protection for lesions non-coinfected with ST-16/18 were found to be 46% for quadrivalent vaccine in FUTURE II study and 36% for bivalent vaccine in PATRICIA study. Whatever the cross-protection concurred was less robust and less consistent.

Nine Valent HPV Vaccine

Nine valent HPV (9vHPV) vaccine contains HPV-6, 11, 16, 18, 31, 33, 45, 52, and 58 virus like particles (VLPs). Studies have found that 9vHPV is an efficacious vaccine. A phase III efficacy trial compared 9vHPV with 4vHPV among approximately 14,000 females aged 16 through 26 years. The 9vHPV efficacy for prevention of ≥CIN-2, vulvar intraepithelial neoplasia grade 2 or 3, and vaginal intraepithelial neoplasia grade 2 or 3 caused by HPV-31, 33, 45, 52, or 58 was 96.7%.[24,25] The efficacy for prevention of ≥CIN-2 caused by HPV-31, 33, 45, 52, or 58 was 96.3% and for 6-month persistent infection was 96.0%.[25] There were only few cases caused by HPV-6, 11, 16, or 18 in either vaccine group. The 9vHPV was not inferior to 4vHPV as the geometric mean antibody titers (GMTs) 1 month after the third dose were noninferior for HPV-6, 11, 16, and 18; and in the 9vHPV group, >99% seroconverted to all nine HPV vaccine types.[25]

The schedule of administration is same as 4vHPV vaccine and reactogenicity is also similar to 4vHPV vaccine. However, 9vHPV vaccine is yet not available for use in India.

Safety of HPV Vaccines

Local adverse effects with quadrivalent vaccines reported were pain at the injection site in 83% of vaccines (mainly mild and moderate intensity) and swelling and erythema in 25%. Systemic adverse effects such as fever reported in 4% of vaccines. They are all minor adverse effects and no serious vaccine-related adverse events have been reported either in trials or post-marketing surveillance studies.

Local side-effects with bivalent vaccines 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. Both the vaccines have very good safety record. More than 175 million doses have been distributed worldwide and more countries offering the vaccine through national immunization programs. WHO's Global Advisory Committee on Vaccine Safety (GACVS) continues to be reassured by the safety profile of the available products.[26] Centers for Disease Control and Prevention (CDC) monitors HPV vaccine safety and states that there are no new or unusual patterns of adverse events to suggest a HPV vaccine safety concern. However, CDC states that syncope (fainting) can occur among adolescents following vaccination. To decrease the risk of falls and other injuries that might follow syncope, CDC's Advisory Committee on Immunization Practices (ACIP) recommends that clinicians consider observing patients for 15 minutes after vaccination.[27]

RECOMMENDATIONS FOR USE

Public Health Perspectives

The HPV vaccines are of public health importance. WHO states that HPV vaccine should be included in national immunization programs.[28] This is especially so in countries like India having considerable disease burden but without a screening program. All three licensed HPV vaccines (bivalent, quadrivalent and nonavalent) have excellent safety, efficacy and effectiveness profiles.[28]

However, introduction of vaccine in program need to take into account public awareness and programmatic feasibility. The production capacity of HPV vaccine is also limited and may not serve

the need of India, if it decides to give it to all eligible girls during adolescence. WHO recommends introduction of HPV vaccine in national immunization programs.[28]

Individual Use

The ACVIP 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. The 3rd dose may be considered as booster. 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.

Currently both the vaccines are not licensed in India for use in the males. However, they are licensed to be used in males in some countries like Australia, New Zealand, and Austria.

DOSE AND SCHEDULE

The vaccines should be stored at 2–8°C and must not be frozen. The dose is 0.5 mL intramuscular in deltoid. The recommended age for initiation of vaccination is 9 years. As of current licensing regulations in India, catch-up vaccination is permitted up to the age of 45 years. However, preadolescent vaccination is immunologically superior to the postadolescent vaccination. Three doses at 0, 2 and 6 months are recommended with the quadrivalent and 9-valent vaccine, 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 postvaccination.

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.

Human papillomavirus (HPV) vaccines routine.

9–14 years: 2 doses at 0–6 months.

- Interval between doses should not be <5 months.
- The minimum interval is 5 months between the first and second dose.
- If the second dose is administered after a shorter interval, a third dose should be administered a minimum of 5 months after the first dose and a minimum of 12 weeks after the second dose.
- If the vaccination schedule is interrupted, vaccine doses do not need to be repeated (no maximum interval).

15 years and older:

- 3 doses at 0–1–6 months for BHPV and 0–2–6 months for QHPV.
- Interval between dose 1st and 2nd dose should not be less than 4 weeks and between 2nd and 3rd does not less than 12 weeks.
- All immunocompromised, irrespective of age should receive the 3-dose schedule.

REFERENCES

1. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999;189(1):12-9.
2. Ferlay J, Shin HR, Bray F, et al (Eds). GLOBOCAN 2008: Cancer Incidence and Mortality Worldwide. IARC Cancer Base No. 10. IARC Press: Lyon; 2010.
3. Curado MP, Edwards B, Shin HR, et al. (Eds). Cancer incidence in five continents, Vol. IX. IARC Scientific Publications No. 160. Lyon: IARC; 2007.
4. Bruni L, Albero G, Serrano B, et al. ICO/IARC; Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in India. Summary Report 10. Barcelona: HPV Information Centre; 2019.
5. Nandakumar A, Ramnath T, Chaturvedi M. The magnitude of cancer cervix in India. Indian J Med Res. 2009;130(3):219-21.
6. Takiar R. Status of breast and cervix cancer in selected registries of India. Ann Women's Health. 2018;2(1):1012.

7. ICMR, NCDIR. National Cancer Registry Program. Three-year report of population based cancer registries: 2012–14. Available from: http://ncdirindia.org/NCRP/all_ncrp_reports/pbcr_report_2012_2014/all_content/Printed_Version.htm [Last Accessed on June, 2019].
8. Human Papillomavirus Vaccines: WHO position paper. Wkly Epidemiol Rec. 2017;92(9):241-68.
9. Bhatla N, Gulati A, Mathur SR, Rani S, Anand K, Muwonge R, et al. Evaluation of cervical screening in rural North India. Int J Gynecol Obstet. 2009;105(2):145-9.
10. Roy B, Tang TS. Cervical cancer screening in Kolkata, India: beliefs and predictors of cervical cancer screening among women attending a women's health clinic in Kolkata, India. J Cancer Educ. 2008;23(4):253-9.
11. Bosch FX, Castellsague X, Sanjose SD. HPV and cervical cancer: screening or vaccination? Br J Cancer. 2008;98(1):15-21.
12. Smith JS, Melendy A, Rana RK, et al. Age-specific prevalence of infection with human papillomavirus in females: a global review. J Adolesc Health. 2008;43(4 Suppl):S5-25, S25.e1-41.
13. Sankaranarayanan R, Bhatla N, Gravitt PE, Basu P, Esmy PO, Ashrafunnessa KS, et al. Human papillomavirus infection and cervical cancer prevention in India, Bangladesh, Sri Lanka and Nepal. Vaccine. 2008;26(Suppl 12):M43-52.
14. Bhatla N, Lal N, Bao YP, et al. A meta-analysis of human papillomavirus type-distribution in women from South Asia: Implications for vaccination. Vaccine. 2008;26(23):2811-7.
15. Serrano B, de Sanjose S, Tous S, et al. Human papillomavirus genotype attribution for HPVs 6,11,16,18,31,33,45,52 and 58 in female anogenital lesions. Eur J Cancer. 2015;51(13):1732-41.
16. WHO (2016). HPV vaccine background document. Available from: http://www.who.int/immunization/sage/meetings/2016/october/1_HPV_vaccine_background_ document_27Sept2016.pdf?ua=1 [Last Accessed on June, 2019].
17. Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med. 2007;356(19):1928-43.
18. Dillner J, Kjaer SK, Wheeler CM, et al. Four year efficacy of prophylactic human papillomavirus quadrivalent vaccine against low grade cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital warts: Randomized controlled trial. BMJ. 2010;341:c3493.
19. Paavonen J, Naud P, Salmeron J, Wheeler CM, Chow SN, Apter D, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomized study in young women. Lancet. 2009;374(9686):301-14.

20. Szarewski A, Poppe WA, Skinner SR, et al. Efficacy of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine in women aged 15–25 years with and without serological evidence of previous exposure to HPV-16/18. Int J Cancer. 2012;131(1):106-16.
21. Howell-Jones R, Soldan K, Wetten S, et al. Declining genital Warts in young women in England associated with HPV 16/18 vaccination: An ecological study. J Infect Dis. 2013;208(9):1397-403.
22. Szarewski A, Skinner SR, Graland SM, et al. Efficacy of the HPV-16/18 AS04-adjuvanted vaccine against low-risk HPV types (PATRICIA randomized trial): an unexpected observation. J Infect Dis. 2013;208(9):1391-6.
23. Giuliano AR, Palefsky JM, Goldstone S, et al. Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males. N Engl J Med. 2011;364(5):401-11.
24. Food and Drug Administration. Highlights of prescribing information. Gardasil 9 (human papillomavirus 9-valent vaccine, recombinant). Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2014. Available from: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf [Last Accessed on June, 2019].
25. Joura EA, Giuliano AR, Iversen OE, et al.; Broad Spectrum HPV Vaccine Study. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med. 2015;372(8):711-23.
26. WHO. Global Advisory Committee on Vaccine Safety, 12–13 June 2013. Weekly Epidemiol Rec. 2013;88(29):301-12. Available from: http://www.who.int/wer/2013/wer8829.pdf [Last Accessed on October, 2019].
27. Human Papillomavirus (HPV) Vaccine safety. Centers for Disease Control and Prevention. Available from: http://www.cdc.gov/vaccinesafety/vaccines/HPV/Index.html [Last Accessed on Oct, 2019].
28. Human papillomavirus vaccines: WHO position paper. Weekly Epidemiological Record. 2017;92(9):241-68. Available from: https://apps.who.int/iris/bitstream/handle/10665/255353/WER9219.pdf?sequence=1 [Last Accessed on November, 2019].

3.13 INFLUENZA VACCINES

Harish K Pemde, Sujeet Kumar Singh, Pradeep Khasnobis, Sanket V Kulkarni, Ranjeet Prasad

BACKGROUND

Pathogen

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, and C. The subtypes of type A influenza virus is determined by hemagglutinin (HA) 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 number, year of isolation, and virus subtype. Therefore, the nomenclature of the pandemic influenza virus is A/California/7/2009/H1N1.

Influenza virus is characterized by frequent mutations—antigenic drifts (minor antigenic change, both A and B) and antigenic shifts (major antigenic change, only A). The 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. To ensure optimal vaccine efficacy against prevailing strains in both the northern and southern hemispheres, the antigenic composition of the vaccines is revised twice annually and adjusted to the antigenic characteristics of circulating influenza viruses obtained within the World Health Organization (WHO) global influenza surveillance and response system (GISRS). This gives the vaccine

manufacturer's 4–6 months to manufacture the vaccine in time for the flu season for the respective hemisphere.[1]

HISTORICAL PERSPECTIVES

The 20th century pandemics were in 1918 due to H1N1 (Spanish flu), 1957 due to H2N2 (Asian flu), and 1968 due to H3N2 (Hong Kong flu). Of these pandemics, the 1918 pandemic was the most severe causing an estimated 20–40 million or more deaths worldwide.

The new virus tends to replace endemic/seasonal influenza viruses and postpandemic, 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 to 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. In 2009, global outbreaks caused by the A (H1N1) strain designated as A (H1N1) pdm09 attained pandemic proportions although it gradually evolved into a seasonal pattern in 2010.

In India, the first positive case of pdm H1N1 was reported in May 2009 and by end of the year 2010, 20,604 cases with 1,763 deaths were reported. The country experienced three waves during the period of pandemic of 2009–2010, first one in 2009 September, followed by second wave in December, and the third peak in August 2010 when the end of pandemic was declared. The year-wise number of cases and deaths since May 2009 to till date is given in **Figure 1**.

DISEASE BURDEN

Global: Influenza occurs globally with an annual attack rate estimated at 5–10% in adults and 20–30% in children.[1] Children, particularly below 2 years of age, have a high burden of influenza. In 2008, there were 90 million [95% confidence interval (CI), 49–162 million] new cases of seasonal influenza, 20 million (95% CI, 13–32 million) cases

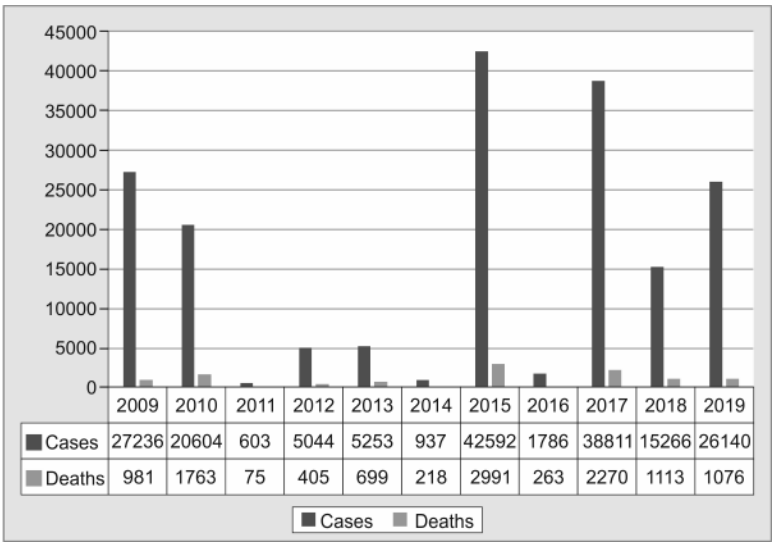


Fig. 1: Yearwise laboratory confirmed cases and death since May, 2019–23rd June, 2019.

of influenza-associated acute lower respiratory infections (ALRIs), and 1–2 million cases of influenza-associated severe ALRI, including 28,000–111,500 deaths.[2]

The incidence of influenza episodes and associated ALRI is significantly higher in developing countries as compared to developed countries.[2] A systematic review of seasonal influenza epidemiology in sub-Saharan Africa showed that influenza accounted for about 10% of all outpatient visits and for about 6.5% of hospital admissions for acute respiratory infections (ARIs) in children.[3] A recent systemic review[4] found that the influenza was associated with 10% (95% CI, 8–11%) of respiratory hospitalizations in children <18 years worldwide and it ranged from 5% (95% CI, 3–7%) among children <6 months to 16% (95% CI, 14–20%) among children 5–17 years. According to the authors' estimates, influenza results in approximately 374,000 (95% CI, 264,000–539,000) hospitalizations in children <1 year of which 228,000 (95% CI, 150,000–344,000) occur in children <6 months and 870,000 (95% CI, 610,000–1,237,000) hospitalizations in children <5 years annually. They also found influenza-associated hospitalization

rates more than three times higher in developing countries than in industrialized countries (150/100,000 children/year versus 48/100,000 children/year).

Recently, a multicenter, case–control study[5] by Global Approach to Biological Research, Infectious diseases and Epidemics in Low-income countries (GABRIEL) network in Cambodia, China, Haiti, India (Lucknow and Pune), Madagascar, Mali, Mongolia, and Paraguay on hospitalized children (up to 60 months of age) with radiologically confirmed pneumonia (cases 888, and healthy children as controls 870) collected nasopharyngeal swabs for identifying 19 viruses and 5 bacteria by reverse transcription-polymerase chain reaction. More than one microorganism was detected in respiratory samples in 93.0% of cases and 74.4% of controls ($P < 0.001$). *Streptococcus pneumoniae (S. pneumoniae)*, *Mycoplasma pneumoniae*, human metapneumovirus, rhinovirus, respiratory syncytial virus (RSV), parainfluenza virus 1, 3, and 4, and influenza virus A and B were independently associated with pneumonia; the adjusted population attributable fraction (aPAF) was 42.2% (95% CI, 35.5–48.2%) for *S. pneumoniae*, 18.2% (95% CI, 17.4–19.0%) for RSV, 11.2% (95% CI, 7.5–14.7%) for rhinovirus, and 6.5% (6.4–6.7%) for influenza virus A, and 2.1% (1.3–2.8%) for influenza virus B.

India: Adequate data on the prevalence and burden of influenza in India is lacking. According to published data, it contributes to around 5–10% of all ARIs. The reported incidence of influenza upper respiratory infection (URI) was found to be 10/100 child years and that of ALRI to be only 0.4/100 child years. According to an Indian review, influenza virus was responsible for about 1.5–14.5% of all ARIs episodes.[6] A community-based study from north India estimated incidence of influenza episodes among children with ARI around 180 and 178 per 1,000 children per year, among children below 1 and 2 years, respectively. Similarly, the incidence of influenza-associated ALRI was calculated as 33 and 44 per 1,000 children per year.[2,7] It is estimated that around 24,179 influenza-associated ALRI mean deaths are occurring per year based on verbal autopsy confirmed ALRI deaths in the community in children younger than 5 years.[8] Though burden of influenza-like illness (ILI) was highest in children <5 years, the isolation rate for laboratory confirmed influenza was highest for

individuals aged >46 years.[8] Various studies from India[6] have shown that viruses are responsible for a minority of respiratory tract infections and out of that influenza is responsible for a small proportion of patients. RSV is the most frequently isolated virus from patients having respiratory tract infections. The author further concluded that influenza is responsible for a minority of lower respiratory tract infections in children in India. In contrast, in developed countries, influenza is a major cause of respiratory tract infections.

A recent study[9] (2018) from rural North India reported ILI among children <5 years 13 (95% CI, 4–29%) per 1,000 person years.

SWINE FLU OR A H1N1

Globally, between 151,700 people and 575,400 people died from 2009 H1N1 virus infection during the 1st year, the virus was circulated according to a new study from the Centers for Disease Control and Prevention (CDC) Influenza Division. A disproportionate number of deaths occurred in Southeast Asia and Africa, where access to prevention and treatment resources are more likely to be limited.[10] According to the data from Government of India, 22.8% of the samples out of the total samples from 202,790 persons who had been tested have been found positive for A (H1N1). In the majority, the illness was self-limited with recovery within a week. Among those tested, 94% cases were recovered and 2,728 deaths were reported till December 2010.[11] In India in 2015 (up to March 17), 30,766 patients were reported to have H1N1 influenza and out of which 1,809 died; 17% of deaths occurred in the age group of 18–30 years while 12% of deaths were in the 60 and above age category, 4% in 0–12 years and 1% in 12–18 years of age.[12] In 2015, outbreak of influenza A (H1N1) pdm09 occurred in India causing 42,592 laboratory confirmed cases with 2,991 deaths. Rajasthan, Gujarat, Delhi, Jammu and Kashmir, Maharashtra, Madhya Pradesh, Telangana, Karnataka, and Tamil Nadu reported most cases.[13]

INDIAN SCENARIO

The following is the status of influenza cases in all age group patients as reported to the National Centre for Disease Control (NCDC), New

Delhi, India, the nodal agency to manage reporting of cases of diseases on national importance in India.

For year 2015, the maximum number of seasonal influenza A (H1N1) cases and deaths were recorded from 1st January to 31st March with peak in month of February, 2015. The cases and deaths were reported primarily from the States of Rajasthan, Gujarat, Maharashtra, Delhi, Karnataka, Madhya Pradesh, Telangana, and Uttar Pradesh. In 2015, till 31st December, 2015, 42,592 cases were reported from all States/Union Territories (UTs), out of which 2,991 died. In 2016, upsurge of seasonal influenza (H1N1) cases was not observed and 1,786 cases were reported from all States/UTs, out of which 263 died.

In 2017, the increase in cases was observed from 1st January, 2017 to 12th March, 2017. Again increasing trend was observed from 12th June, 2017 to 3rd September, 2017. In 2017, total 38,811 cases (highest number of cases in the month of August) of seasonal influenza (H1N1) and 2,270 deaths were reported and most affected States/UTs were Gujarat, Maharashtra, Uttar Pradesh, Tamil Nadu, Rajasthan, Karnataka, Delhi, Telangana, Kerala, Madhya Pradesh, West Bengal, Andhra Pradesh, Odisha, Chhattisgarh, Punjab, Haryana, Goa, Assam, Uttarakhand, Puducherry, and Jammu and Kashmir. However, again increasing trend of cases was observed from Rajasthan from 49 weeks ending on 10th December, 2017.

In 2018, total 15,266 cases and 1,113 deaths have been reported. Majority of the cases and deaths were reported from Rajasthan during month from January to April and again upsurge was observed from week 30th ending on 29th July, 2018, most of the cases and deaths being reported from Maharashtra, Gujarat followed by Rajasthan, Karnataka, Kerala, Tamil Nadu, Telangana, Andhra Pradesh, West Bengal, and Puducherry. Again, increasing trend of cases has been observed from States of Rajasthan, Gujarat, Delhi, and Haryana.

In 2019 (till 23.06.2019), total 26,140 cases and 1,076 deaths have been reported. Majority of cases and deaths were reported from Rajasthan, Gujarat, Delhi, Punjab, and Haryana followed by Himachal Pradesh, Uttar Pradesh, Telangana, Kerala, Kashmir (J&K), Karnataka, Maharashtra, Madhya Pradesh, Tamil Nadu, and West Bengal. The declined trend of cases and deaths was observed since 8th week ending on 24th February, 2019 in country.

SEASONALITY OF INFLUENZA

Influenza occurs throughout the year, but its incidence has distinct peaks in most geographical areas. Every season's epidemic or outbreak lasts for 6–8 weeks or longer. Reasons for seasonality are not well-known. Effects of humidity and temperature on virus survival and crowding inside home in winters are attributed for seasonality. The start, peak, duration, and size of outbreak in a season cannot be predicted. Virus's antigenic variation, virulence, and transmissibility make the outbreaks vary each year. Population immunity also affects the severity of outbreak.

In temperate climates, influenza activity occurs in late autumn and winter months, i.e. October to April in Northern hemisphere countries and May to September in Southern hemisphere tropical countries. Tropical countries experience influenza transmission year round and some peaks do occur in a year.

In India, influenza season differs in various parts of country. In India, the disease is observed to have two peaks; overall major peak one during the winter (January to March) and a minor peak during the postmonsoon season (August to October). However, it may vary from state to state. The monthwise trend of Pan India for year 2014–2019 is described in **Figure 2**.

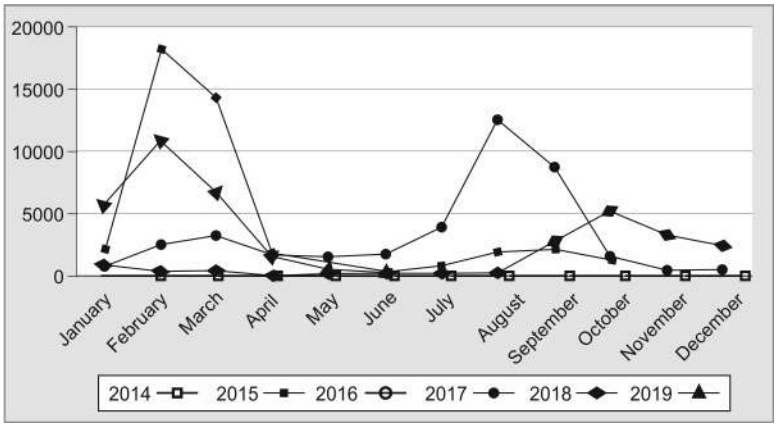
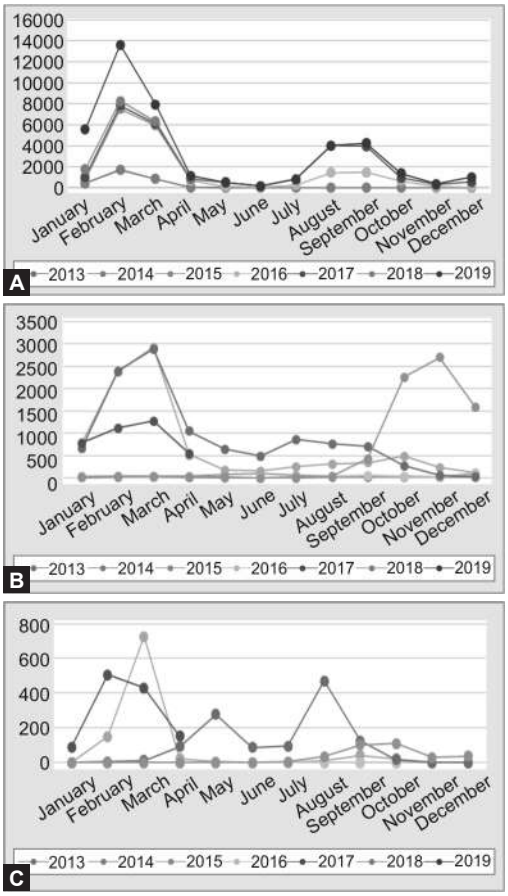


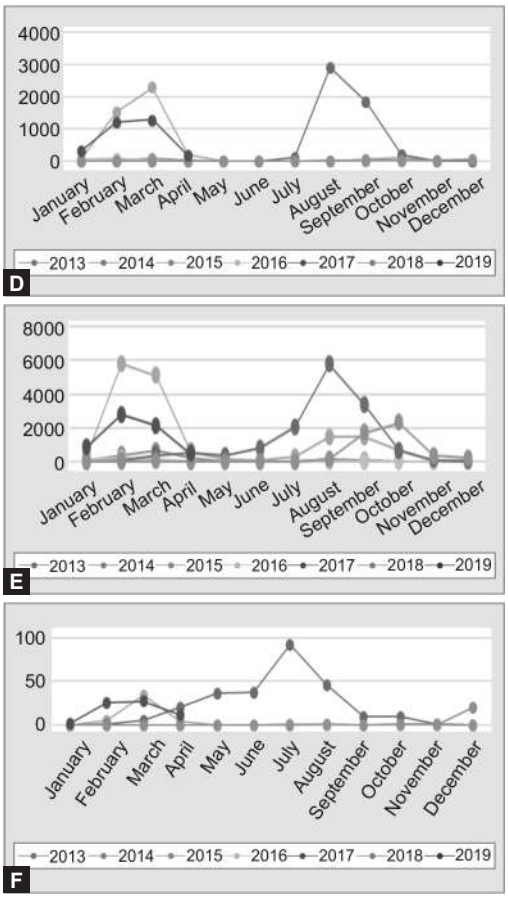
Fig. 2: Monthwise trend of cases reported in India since 2014–2019 (data up to 23rd June, 2019).

The seasonality in India on zonal basis may be observed from following trend (data from NCDC) is illustrated in **Figures 3A to F**.

- *North Zone States/UTs*: Chandigarh, Delhi, Haryana, Himachal Pradesh, Jammu and Kashmir, Punjab, and Rajasthan



Figs. 3A to C



Figs. 3D to F

Figs. 3A to F: (A) *North Zone States*: Monthwise trend of laboratory confirmed cases of seasonal influenza A (H1N1) for year 2013–2019 (till 30th April, 2019); (B) *South Zone States*: Monthwise trend of laboratory confirmed cases of seasonal influenza A (H1N1) for year 2013–2019 (till 30th April, 2019); (C) *East Zone States*: Monthwise trend of laboratory confirmed cases of seasonal influenza A (H1N1) for year 2013–2019 (till 30th April, 2019); (D) *Central Zone States*: Monthwise trend of laboratory confirmed cases of seasonal influenza A (H1N1) for year 2013–2019 (till 30th April, 2019); (E) *Western Zone States*: Monthwise trend of laboratory confirmed cases of seasonal influenza A (H1N1) for year 2013–2019 (till 30th April, 2019); and (F) *Northeast Zone States*: Monthwise trend of laboratory confirmed cases of seasonal influenza A (H1N1) for year 2013–2019 (till 30th April, 2019).

- *South Zone States/UTs*: Andhra Pradesh, Karnataka, Kerala, Lakshadweep, Puducherry, Tamil Nadu, and Telangana
- *East Zone States/UTs*: Bihar, Jharkhand, Odisha, and West Bengal
- *West Zone States/UTs*: Dadra and Nagar Haveli, Daman and Diu, Goa, Gujarat, and Maharashtra
- *Central Zone States/UTs*: Uttarakhand, Uttar Pradesh, Madhya Pradesh, and Chhattisgarh
- *Northeast Zone States/UTs*: Arunachal Pradesh, Assam, Manipur, Meghalaya, Mizoram, Nagaland, Sikkim, and Tripura.

In northern part of India, influenza peak is in January to March which is similar to Northern hemisphere. In central India (e.g. Delhi, Lucknow, Nagpur, and Pune), influenza peak is in July to September and in southern part of India (e.g. Chennai, Vellore), it occurs in September to November. Thus, it is a mixture of both Northern and Southern hemisphere seasons.

A recent analysis[14] found a 3–8% year round incidence of influenza A and B in India with peaks of influenza A in monsoon season June to December. An India-specific study[8] found co-circulation of seasonal influenza A (H1N1, H3N2) and type B. These viruses circulated throughout year (2004–2008) with peaks during rains. However, in Delhi, peak of influenza activity was observed in winters also. The authors suggested a staggered policy on timing of vaccination in large country like India.

INFLUENZA VACCINES

Most of the current seasonal influenza vaccines include two influenza A strains and one influenza B strain. Globally, trivalent inactivated vaccines (TIVs3) and live attenuated influenza vaccines (LAIVs) are available. In order to enhance immunogenicity, some current formulations of trivalent vaccines include adjuvants such as oil-in-water adjuvants or virosomes. Adjuvanted trivalent influenza vaccines (aTIVs3) show enhanced priming and boosting, as well as efficacy in infants, although need for two doses remains. The development of quadrivalent inactivated influenza vaccine (QIIV4) formulation for seasonal influenza is of interest in providing comprehensive protection against influenza B viruses.

Inactivated Influenza Vaccines

The IIVs are produced from virus growth in embryonated hen's eggs and are of three types: (1) Whole virus, (2) Split product, and (3) 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 HA and neuraminidase. **Table 1** provides a list of available influenza vaccines in Indian market. All currently available trivalent vaccines now have the influenza strain that is antigenically similar to 2009 pandemic swine flu strain, i.e. A (H1N1) pdm09. Hence, there is no need to

TABLE 1: Influenza vaccines licensed in India.

Brand names	*Manufacturer*	*Types of vaccine*	*Valent*	*Composition*
Vaxigrip	Sanofi Pasteur India Pvt. Ltd.	Split virion, inactivated	Trivalent	TIV (both SH and NH)*
Agrippal	Chiron Panacea (Panacea Biotec Ltd.)	Surface antigen, inactivated	Trivalent	TIV (NH)
Influgen	Lupin Laboratories Ltd.	Split virion, inactivated	Trivalent	TIV (NH)
Influvac Tetra	Abbott India Ltd	Surface antigen, inactivated	Quadrivalent	QIV
Fluarix	GlaxoSmithKline Pharmaceuticals Ltd.	Split virion, inactivated	Trivalent	TIV (NH)
VaxiFlu	Zydus Cadila	Purified H1N1, monovalent inactivated	Trivalent	TIV (NH)
Nasovac	Serum Institute of India Pvt. Ltd.	Live attenuated, monovalent	Trivalent	LAIV (A/H1N1pdm)
FluQuadri	Sanofi Pasteur India Pvt. Ltd.	Split virion, inactivated	Quadrivalent	QIV (NH)
VaxiFlu 4	Zydus Cadila	Split virion, inactivated	Quadrivalent	QIV (NH)

(*SH: Southern hemisphere; NH: Northern hemisphere; LAIV: live attenuated influenza vaccine; TIV: trivalent inactivated vaccine; QIV: quadrivalent influenza vaccine)

TABLE 2: Dosage and schedule of inactivated vaccines (IIV).

Age	*6–35 months*	*3–8 years*	*From 9 years of age*
Dose	0.25 mL	0.5 mL	0.5 mL
Number 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.*

Note: In February 2020, the DCGI approved the 0.5 mL dose of Influvac Tetra, for administration from 6 months of age.

go for separate "swine flu" vaccine. The trivalent and quadrivalent vaccines contain 15 µg HA of each of WHO recommended two influenza A strains (H1N1 and H3N2) and one/two influenza B strain. Quadrivalent vaccines contain two influenza B strains. Vaccines are licensed for use in children aged 6 months and older.

The WHO recommendations on composition of influenza vaccines:

- For the 2019–2020 influenza season (Northern hemisphere),[15] it is recommended that trivalent vaccines for use contain the following: an A/Brisbane/02/2018 (H1N1) pdm09-like virus; an A/Kansas/14/2017 (H3N2)-like virus; and a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage). For quadrivalent vaccine, add a B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage).
- For the Southern hemisphere,[16] trivalent vaccines for use in 2019 will contain the following: an A/Michigan/45/2015 (H1N1)pdm09-like virus; an A/Switzerland/8060/2017 (H3N2)-like virus; and a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage). For quadrivalent vaccine, add a B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage).

Dosage and schedule: The dosage schedule is provided in **Table 2**. Revaccination is recommended with a single annual dose irrespective of age.

DCGI has recently approved 0.5 mL Influvec Tetra flu vaccine in India for use in children below 3 years.

Efficacy and Effectiveness of Trivalent Influenza Vaccines

The reported efficacy/effectiveness of influenza vaccines varies substantially with factors such as the case definition

(e.g. laboratory-confirmed influenza disease or the less specific ILI), the "match" between the vaccine strains and prevailing influenza strains, vaccine preparation, dose, prior antigenic experience, and age or underlying disease conditions of an individual.[1] There is no published data on efficacy/effectiveness of influenza vaccines from India.

Duration of protection: Following vaccination, anti-HA antibody titers peak 2–4 weeks postvaccination in primed individuals but may peak 4 weeks or later in unprimed individuals or older adults. Serum antibody titers may fall by 50% or more by 6 months after vaccination, with the degree of reduction being proportional to the peak titers achieved. Vaccine induced serum antibody titers and then remains stable for 2–3 years. Evidence from clinical trials suggests that protection against viruses that are similar antigenically to those contained in the vaccine extends for at least 6–8 months.[17]

Safety of Trivalent Influenza Vaccines

Transient local reactions at the injection site occur frequently (>1/100), and fever, malaise, myalgia, and other systemic adverse events may affect persons without previous exposure to the influenza vaccine antigens, trivalent influenza vaccines are generally considered safe.[1] During some influenza seasons, IIV3 has been associated with a slight increase in the risk of Guillain–Barré syndrome (GBS). However, time-series analysis demonstrated no evidence of seasonality and revealed no statistically significant increase in hospital admissions because of GBS after the introduction of the universal influenza immunization program.[18]

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

Live attenuated influenza vaccine provides broader and higher levels of protection than trivalent inactivated vaccines in healthy children aged 2–5 years of age. A Cochrane review of randomized controlled trials (RCTs) evaluating live vaccines in healthy children

aged >2 years found an overall efficacy against laboratory confirmed influenza of 82% (95%, CI 71–89%) and an effectiveness against ILI of 33% (95% CI, 28–38%). Inactivated vaccines had a lower efficacy of 59% (95% CI, 41–71%) but similar effectiveness at 36% (95% CI, 24–46%).[19] A quadrivalent live attenuated vaccine for intranasal application containing two influenza A strains and two influenza B strains was licensed in the USA in 2012.[1] Live attenuated vaccine is not recommended below 2 years of age, in high-risk individuals, and in pregnant women. Nonpregnant individuals aged 2–49 years may receive either TIV or LAIV in accordance with national policy.

RECOMMENDATIONS FOR USE

Individual Use

Whom to Give?

Influenza vaccines are recommended for:

- Children 6 months to 5 years of age.
- The "high-risk children" aged >5 years[13] including the following:
  - Chronic cardiac, pulmonary (excluding asthma), hematologic and renal (including nephritic syndrome) condition, chronic liver diseases, and diabetes mellitus
  - Congenital or acquired immunodeficiency [including human immunodeficiency virus (HIV) infection]
  - Children on long-term salicylates therapy
  - Laboratory personnel and healthcare workers.

Target group prioritization for seasonal influenza vaccination: The prioritization is based on following attributes: Contribution of risk group to the overall influenza disease burden in population, disease severity within individual risk group, and vaccine effectiveness in different age groups and categories. The WHO position paper states that pregnant women have increased risk of severe disease and death from influenza; the infection may also lead to complications such as stillbirth, neonatal death, preterm delivery, and decreased birth weight.[1] Pregnant women should be vaccinated with IIV at any stage of pregnancy. This recommendation is based on evidence of a substantial risk of severe disease in this group and evidence that seasonal influenza vaccine is safe throughout pregnancy and effective

in preventing influenza in the women as well as in their young infants, in whom the disease burden is also high.

Elderly people, individuals with chronic medical conditions, and healthcare providers should receive influenza vaccine on priority.

Which Vaccine to Give?

In those who with underlying risk factors, only the inactivated vaccines should be used. In healthy individuals aged 2–49 years, either the inactivated or live attenuated vaccines may be used. In India, since the LAIV is currently not available, hence only IIVs should be used. Both IIV3 and IIV4 are available in India.

When to Give?

As far as the influenza virus circulation in India is concerned, influenza viruses remain active throughout the year in a low grade (3–8%). The peaks have been noted during rainy seasons throughout India. In northern India (Delhi), peaks have also been noted during winters.

The evidence of antigenic drifts of circulating influenza viruses in India, together with the temporal peaks in seasonality of influenza in different parts of the country, illustrate the need for a staggered approach in vaccination timing. This is to be noted that the WHO convenes two meetings to provide recommendations for the usage of influenza vaccine in February and September each year. The vaccine for the February recommendations (Northern hemisphere) and September recommendations (Southern hemisphere) becomes available after 6 months of each recommendation. In addition to this, the WHO classifies India under the "South Asia" transmission zone of influenza circulation. This strongly points India's alignment with the availability of Southern hemisphere vaccine (March–April) to ensure that we have the latest available strains for early vaccination to prevent the peak of circulation of influenza in the rainy season across the country.[20]

To summarize, influenza season should ideally be recognized in every area, and when possible, the latest available vaccines should be offered about 2 weeks before beginning of the season.

BOX 1: Routine vaccination for influenza vaccine.

INFLUENZA VACCINE

Routine vaccination:

- *Minimum age*: 6 months for trivalent inactivated influenza vaccine (IIV3)
- Recommended for the vaccination of children 6 months to 5 years of age and the persons with certain high-risk conditions
- *First time vaccination*: 6 months to below 9 years: Two doses 1 month apart; 9 years and above: Single dose
- Annual revaccination with single dose
- *Dosage (IIVs): Aged 6–35 months: 0.25 mL; 3 years and above: 0.5 mL*
- All the currently available IIVs in the country contain the "swine flu" or "A (H1N1)" antigen; no need to vaccinate separately
- *Best time to vaccinate*:
  - As soon as the new vaccine is released and available in the market, preferably 2 weeks before the onset of influenza season in the area.

PUBLIC HEALTH PERSPECTIVES

Influenza vaccine has now been recommended for routine use in children 6 months to 5 years of age **(Box 1)**.

One estimate shows 6.5% of all pediatric ALRI deaths in India were associated with influenza in 2006–2008 and also showed substantial yearly variation in magnitude of influenza epidemic activity and associated ALRI deaths.[6] Recent multicenter studies also show similar trend. However, there are issues related to vaccine availability, timing, and suitability (of strains) in India.

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REFERENCES

1. Vaccines against influenza WHO position paper—November 2012. Wkly Epidemiol Rec. 2012;87(47):461-76.
2. Nair H, Brooks WA, Katz M, et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. Lancet. 2011;378(9807):1917-30.
3. Gessner BD, Shindo N, Briand S. Seasonal influenza epidemiology in sub-Saharan Africa: a systematic review. Lancet Infect Dis. 2011;11(3): 223-35.
4. Lafond KE, Nair H, Rasooly MH, et al. Global Role and Burden of Influenza in Pediatric Respiratory Hospitalizations, 1982-2012: A Systematic Analysis. PLoS Med. 2016;13(3):e1001977.
5. Bénet T, Sánchez Picot V, Messaoudi M, et al. Microorganisms Associated With Pneumonia in Children <5 Years of Age in Developing and Emerging Countries: The GABRIEL Pneumonia Multicenter, Prospective, Case-Control Study. Clin Infect Dis. 2017;65(4):604-12.
6. Mathew JL. Influenza vaccination of children in India. Indian Pediatr. 2009;46(4):304-7.
7. Broor S, Parveen S, Bharaj P, et al. A Prospective Three-year Cohort Study of the Epidemiology and Virology of Acute Respiratory Infections of Children in Rural India. PLoS One. 2007;2(6):e491.
8. Chadha MS, Broor S, Gunasekaran P, et al. Multisite virological influenza surveillance in India: 2004-2008. Influenza Other Respir Viruses. 2012;6(3):196-203.
9. Saha S, Gupta V, Dawood FS, et al. Estimation of community-level influenza-associated illness in a low resource rural setting in India. PLoS One. 2018;13(4):e0196495.
10. Centers for Disease Control and Prevention (CDC). (2012). First Global Estimates of 2009 H1N1 Pandemic Mortality Released by CDC-Led Collaboration. [online] Available from http://www.cdc.gov/flu/spotlights/pandemic-global-estimates.htm. [Last accessed September, 2019].
11. Ministry of Health and Family Welfare. (2013). Pandemic influenza A H1N1: Clinical Management Protocols and Infection Control Guidelines. [online] Available from https://mohfw.gov.in/sites/default/files/2366426352.pdf. [Last accessed September, 2019].
12. The New Indian Express. (2015). People in 30-45 Age Group Worst Affected by Swine Flu. [online] Available from http://www.newindianexpress.com/nation/People-in-30-45-Age-Group-Worst-Affected-by-Swine-Flu/2015/03/18/article2719779.ece. [Last accessed September, 2019].

13. Press Information Bureau (PIB). (2015). [online] Available from https://pib.gov.in/newsite/PrintRelease.aspx?relid=115710 [Last accessed September, 2019].
14. Saha S, Chadha M, Shu Y, et al. Divergent seasonal patterns of influenza types A and B across latitude gradient in Tropical Asia. Influenza Other Respir Viruses. 2016;10(3):176-84.
15. World Health Organization (WHO). (2019). Recommended composition of influenza virus vaccines for use in the 2019–2020 northern hemisphere influenza season. [online] Available from https://www.who.int/influenza/vaccines/virus/recommendations/2019_20_north/en/. [Last accessed September, 2019].
16. World Health Organization (WHO). (2018). Recommended composition of influenza virus vaccines for use in the 2019 southern hemisphere influenza season. [online] Available from https://www.who.int/influenza/vaccines/virus/recommendations/2019_south/en/. [Last accessed September, 2019].
17. Fiore AE, Uyeki TM, Broder K, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. MMWR Recomm Rep. 2010;59(RR-8):1-62.
18. Juurlink DN, Stukel TA, Kwong J, et al. Guillain-Barré syndrome after influenza vaccination in adults: a population-based study. Arch Intern Med. 2006;166(20):2217-21.
19. Jefferson T, Rivetti A, Harnden A, et al. Vaccines for preventing influenza in healthy children. Cochrane Database Syst Rev. 2008;(16):CD004879.
20. Vashishtha VM, Kalra A, Choudhury P. Influenza vaccination in India: position paper of Indian Academy of Pediatrics, 2013. Indian Pediatr. 2013;50(9):867-74.

3.14 JAPANESE ENCEPHALITIS VACCINES

Vijay Kumar Guduru

BACKGROUND

Japanese encephalitis (JE), a mosquito borne flavivirus disease, is a leading form of viral encephalitis in Asia in children below 15 years of age. The Japanese encephalitis virus (JEV) has shown a tendency to extend to other geographic regions. Case fatality averages 30% and a high percentage of the survivors are left with permanent neuropsychiatric sequelae.[1]

Japanese encephalitis occurs in nearly all Asian countries, whether temperate, subtropical, or tropical, and has intruded into new areas through importation of infected vectors. Currently, an estimated 3 billion people live in the 24 countries, mainly in the World Health Organization (WHO) South-East Asia and Western Pacific Regions, considered at risk of JE.[2]

ACUTE ENCEPHALITIS SYNDROME

Clinically, a case of acute encephalitis syndrome (AES) is defined as a person of any age, at any time of year with the acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk) and/or new onset of seizures (excluding simple febrile seizures). Other early clinical findings may include an increase in irritability, somnolence or abnormal behavior greater than that seen with usual febrile illness.[3]

Acute encephalitis syndrome has heterogeneous etiology and JE remains an important contributing agent (5–40%) to AES in our country.

GLOBAL BURDEN

Japanese encephalitis is one of the most important causes of viral encephalitis in Asia. High case fatality rates (CFR), significant, long-term neurological sequelae among survivors make this otherwise geographically defined focal disease a public health problem. The

WHO recommends integration of JE vaccination into national immunization schedules in all areas where the disease is public health priority.

According to WHO, nearly 50,000 cases of JE occur worldwide per year and 15,000 of them die.[4] In endemic areas, the annual incidence of disease ranges from 10–100 per 1,00,000 population. Japan, South Korea, North Korea, Taiwan, Vietnam, Thailand, and the People's Republic of China (PRC) practice routine childhood immunization against JE. The results suggest that the actual incidence of JE is nearly 10 times higher than reflected in recent reports to WHO.[5]

Over the past 60 years, it has been estimated that JE has infected ~10 million children globally, killing 3 million and causing long-term disability in 4 million. Countries have not been able to generate adequate JE surveillance data because of the difficulty in making a clinical recognition of the disease. Reporting and the lack of sufficient laboratory support has also been a problem. Despite the fact that 68% of the babies born in Asia are at risk for JE, there remain major gaps on JE reporting, effecting decision making purposes.

In 2016, 22 (92%) of 24 countries with JEV transmission risk conducted JE surveillance, an increase from 18 (75%) countries in 2012, and 12 (50%) countries had a JE immunization program, compared with 11 (46%) countries in 2012. Strengthened JE surveillance, continued commitment, and adequate resources for JE vaccination should help maintain progress toward prevention and control of JE.[6]

A recent systematic review of the literature estimates 67,900 cases of JE each year, with approximately 13,600 to 20,400 deaths, and an overall incidence rate of 1.8/100,000. More than 3 billion persons live in 24 countries that have JEV transmission risk areas. The majority (75%) of JE cases occur in children aged <15 years. Although most JE cases are asymptomatic, the CFR among patients with encephalitis approaches 30%, and approximately 30–50% of survivors have long-term neurologic sequelae. Vaccination is the cornerstone of JE control and prevention measures. A 2011 systematic review of JE disease burden estimated that approximately 68,000 cases occur globally each year; only about 10% of these cases are reported to WHO.

INDIAN BURDEN

Japanese encephalitis or AES has been reported from 231 districts of 23 states. 37 more districts have been added in 2018 taking the total to 268. The JEV has shown a tendency to extend to other geographic regions. Inapparent infections tend to outnumber the clinical cases with a ratio ranging from 1:250 to 1:1000. Inapparent infections confer lifelong immunity. Spread of JE is documented in newer states, newer districts in endemic states due to increased surveillance efforts including laboratory confirmation by national agencies.[7] The risk is highest in children aged 1–15 years in rural areas and in the monsoon or postmonsoon season.

SEASONALITY

Patterns of JE transmission vary within individual countries and from year to year. In endemic areas, sporadic cases occur throughout the year. In North temperate area (Japan, Taiwan, Nepal, Northern India), large epidemics occur from May to October. In Southern tropical areas (South India, Indonesia, Sri Lanka), the disease is endemic but peak starts after rains, i.e. from July to December.

AGE DISTRIBUTION

Annual incidences vary by age group and have been estimated to be in the range of 5.4 per 100,000 in the 0–14 years' age group, and 0.6 per 100,000 in the ≥15 years' age group. While traditionally considered a childhood disease, available data suggest that in many areas of the world it is a disease of all ages. As the number of cases in children decreases due to successful vaccination programs, there is frequently a shift to a greater proportion of cases in older, unvaccinated age groups. But even in some areas without vaccination programs, such as Bangladesh, over 50% of cases are in the adult age groups.[8]

Indian Council of Medical Research (ICMR) National Institute of Virology (NIV), Pune investigated adult AES epidemic in West Bengal and Assam in 2014. The study revealed in 49.4%, JE, as causative agent in investigation of 398 cases of AES for viral etiology. About 398 line-listed AES cases, mostly (70.8%, 282/398) adults, with case fatality ratio

of 28.9% (115/398). JEV infection was detected in 134 (49.4%) among 271 AES cases tested and most of them (79.1%, 106/134) were adults.[9]

OUTBREAKS OF JAPANESE ENCEPHALITIS IN INDIA

In India, Japanese encephalitis (JE) was first diagnosed in Vellore in 1955 and the first major outbreak took place in West Bengal in 1973. Presently highly endemic areas are Andhra Pradesh, Tamil Nadu, Karnataka, and Uttar Pradesh.[10]

In 2005, Uttar Pradesh faced a devastating epidemic of JE mostly confined to Gorakhpur district affecting 6,061 cases with 1,500 deaths followed by another outbreak in 2006 with 2,320 cases and 528 deaths. Similarly, JE cases in Uttar Pradesh were confined predominantly in Gorakhpur during 2007 reporting 3,024 cases and 645 deaths.[11] The reported mortality rate varies between 8.5% and 72%.[12,13]

The CFR due to AES or JE in India has been around 17% with wide variations in states **(Fig. 1)**.

Acute encephalitis syndrome or encephalitis contributed to 11% of mortality due to communicable diseases in 2017 **(Fig. 2)**.[14]

Reasons for increase in JE cases while major epidemics are not reported since 2015 are presumably due to spread of JE to previously

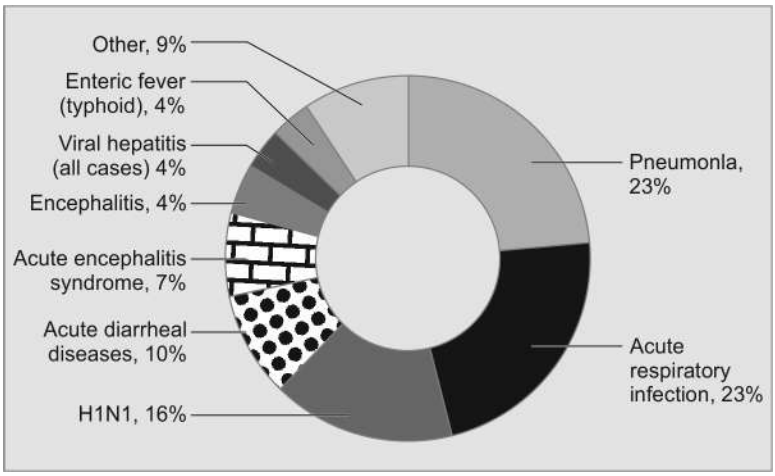

Fig. 1: Percentage distribution of mortality reported in communicable diseases in 2017.
Source: National Health Profile 2018 13th issue, Central Bureau of Health Intelligence, DGHS, MoH and FW,GOI, p.75

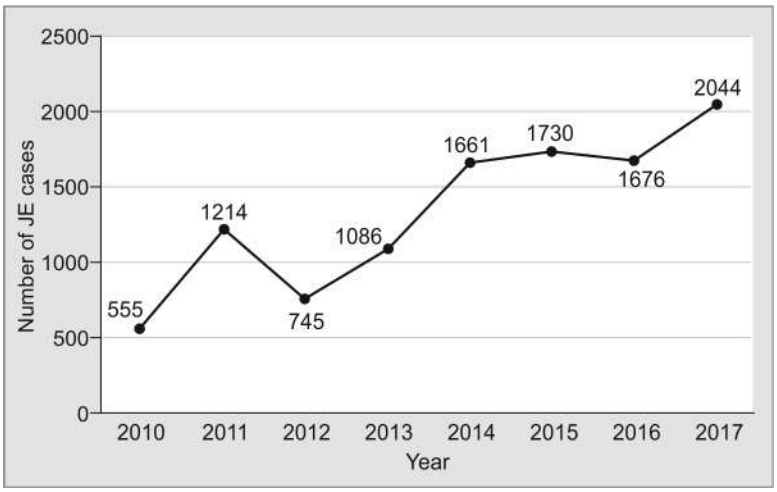

Fig. 2: Confirmed cases of Japanese encephalitis (JE) in India.
Source: Directorate of National Vector Borne Disease Control Programme, Delhi. http://nvbdcp.gov.in/Doc/je-aes.pdf. [Accessed October 2019].

nonendemic states and spread to new districts within endemic states, increase in adult cases, and increased surveillance efforts.

VACCINES

World over, following vaccines are available for use against JE **(Fig. 3)**:

- Mouse brain-derived inactivated JE vaccine (JE-VAX).
- Inactivated primary hamster kidney cells with P3—China.
- Live attenuated, cell culture-derived SA 14-14-2.
- *Newer JE vaccines*:
  - Inactivated SA 14-14-2 vaccine (IC51; IXIARO® by Intercell and JEEV® by Biological Evans India Ltd.) **(Table 1)**.
  - Inactivated Vero cell culture-derived Kolar strain, 821564XY, JE vaccine (JENVAC® by Bharat Biotech).
  - Live attenuated recombinant SA 14-14-2 chimeric vaccine (JE-CV, IMOJEV® by Sanofi Pasteur).
  - Inactivated vero cell-derived JE vaccine (Beijing-1 JE strain by Biken and Kaketsuken, Japan) not available in India.

Owing to many drawbacks (high cost, complicated dosing schedule, requirement of numerous doses and boosters, concerns

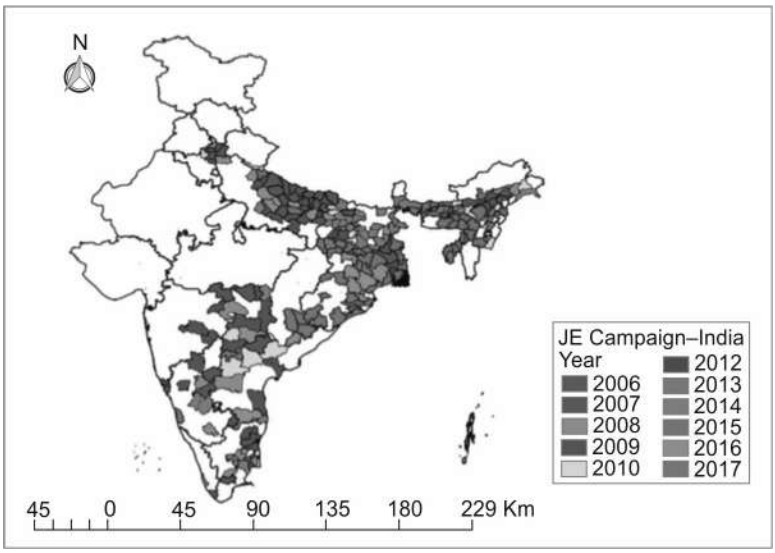

Fig. 3: Operational Guide, Japanese encephalitis vaccination in India.

about side effects and reliance neurological tissue for production) and availability of better vaccines, the first two vaccines, i.e. mouse brain-derived and primary hamster kidney cells with P3 are no longer being produced, hence will not be discussed further.

LIVE ATTENUATED CELL CULTURE-DERIVED SA 14-14-2 VACCINE

This vaccine is based on the genetically stable, neuroattenuated SA 14-14-2 strain of the JEV, which elicits broad immunity against heterologous JEVs. Reversion to neurovirulence is considered highly unlikely. WHO technical specifications have been established for the vaccine production.[15] Chengdu Institute of Biological Products is the only manufacturer authorized to export this vaccine from China.

The live attenuated vaccine was licensed in China in 1989. Since then, more than 300 million doses have been produced and more than 200 million children have been vaccinated. Currently, more than 50 million doses of this vaccine are produced annually.[10] Extensive use of this and other vaccines has significantly contributed to reducing

TABLE 1: Japanese encephalitis (JE) vaccines available in India.

Vaccine type	*Manufacturer (country)*	*Commercial name*	*Pharmaceutical form*	*Presentation*	*No of doses*
JE vaccine (inactivated)	Biological E. Limited (India)	JEEV	Liquid: ready to use	Vial	1
JE vaccine (inactivated)	Biological E. Limited (India)	JEEV Pediatric	Liquid: ready to use	Vial	1
JE vaccine (live, attenuated)	Chengdu Institute of Biological Products Co., Ltd. (People's Republic of China)	JE Live attenuated (SA14-14–2) Public sector only	Lyophilized active component to be reconstituted with excipient diluent before use	Two vial set (active + excipient) Two vial set (active + excipient)	1 5
JE vaccine (live, attenuated)	GPO-MBP Co., Ltd. (Thailand)	IMOJEV MD	Lyophilized active component to be reconstituted with excipient diluent before use	Two vial set (active + excipient)	4
JE vaccine (inactivated)	Bharat Biotech	JENVAC	Liquid: ready to use	Vial	1

the burden of JE in China from 2.5/100,000 in 1990 to <0.5/100,000 in 2004. This vaccine is also licensed for use in Nepal (since 1999); South Korea (since 2001); India (since 2006); Thailand (since 2007); and Sri Lanka.[10] The price per dose of the vaccine is comparable to the Expanded Program On Immunization (EPI) measles vaccine.

Dosage and Administration

In China, the vaccine is licensed for 0.5 mL dose to be administered subcutaneously to children at 8 months of age and a second opportunity again at 2 years. In some areas, a booster dose is given at 7 years. Measles has been given concurrently.[16] It should not be used as an "outbreak response vaccine". It can also be offered to all susceptible children up to 15 years as catch-up vaccination.[11]

Stability

The infectious titer of the vaccine is not appreciably changed after storage at 37°C for 7–10 days, at room temperature for 4 months, or at 2–8°C for at least 1.5 years.[16]

Immunogenicity and Correlate of Protection

After a single dose, antibody responses are produced in 85–100% of nonimmune 1–12 years old children. A neutralization antibody titer of more than 1:10 is generally accepted as evidence of protection and postvaccination seroconversion.[16]

Efficacy and Effectiveness

Efficacy in China

A case-control study performed in 1993 in Sichuan Province China in children <15 years measured effectiveness of routinely delivered SA 14-14-2 vaccine at 80% [confidence interval (CI) 44–93%] for a single dose and 97.5% (CI 86–99.6%) for two doses given at a 1 year interval.[17]

Five major efficacy trials of SA 14-14-2 vaccine, completed in China from 1988 to 1999 in 1–10 years old, consistently yielded high protection rates, above 98%.[16] Case control studies and numerous large-scale field trials in China have consistently shown an efficacy of at least 95% following two doses administered at an interval of 1 year.[5]

Efficacy in Nepal

In a field trial in Nepal in 1999, involving more than 160,000 subjects 1–15 years of age, reported efficacy of a single dose of 99.3% in the same year and 98.5% one year later.[18,19] At 5 years the protective efficacy was 96.2%.[20] Vaccine in this study contained 105.8 plaque-forming unit (PFU) per 0.5 mL. The study provides evidence that SA 14-14-2 will be useful to combat epidemics.

Indian Experience

In India, one dose of SA 14-14-2 imported from China is being used since 2006 and children between the age group of 1 and 15 years

were vaccinated with a single dose of the vaccine.[21] Following the campaigns targeting all children in the age group of 1–15 years in the high-risk districts, the vaccine is integrated into the UIP of endemic districts. Children at 16–24 months of age [with diphtheria, pertussis and tetanus/oral poliovirus vaccine (DPT/OPV) booster] are targeted for one dose of this vaccine in selected endemic districts after the campaign.[22]

A small case-control study from Lucknow, India found an efficacy of 94.5% (95% CI, 81.5-98.9) after a single dose of this vaccine within 6 months after its administration.[23] However, data from postmarketing surveillance (PMS) in India showed that protective efficacy of the vaccine in India is not as high as that seen in Nepal. PMS study showed that virus neutralizing antibodies were seen in 45.7% of children before vaccination. Seroconversion against Indian strains 28 days after vaccination was 73.9% and 67.2% in all individuals and in those who were nonimmune prevaccination, respectively. The protective efficacy of the vaccine at 1 year was 43.1% overall and 35% for those who were nonimmune prevaccination, respectively.[24]

Preliminary results of a recent case control study carried out by ICMR on impact of JE vaccine shows an unadjusted protective effect of 62.5% in those with any report of vaccination. According to this report, the JE vaccine efficacy has been around 60% in Uttar Pradesh and around 70% in Assam. Following this report, the ICMR has recommended a study on the impact of two doses vs. single dose of SA 14-14-2 vaccine in Assam.[24]

Boosters

Government of India has also recommended two doses of the vaccine to be used in UIP since 2013.

Safety

An estimated 300 million children have been immunized with this vaccine without apparent complication.[16] WHO's Global Advisory Committee on Vaccine Safety acknowledged the vaccine's "excellent" safety profile. Transient fever may occur in 5–10%, local reactions, rash, or irritability in 1–3%. Neither acute encephalitis nor hypersensitivity reactions have been associated with the use of this vaccine.[25]

INACTIVATED VERO CELL CULTURE-DERIVED SA 14-14-2 JE VACCINE (JE-VC), IXIARO® BY INTERCELL AND JEEV® BY BIOLOGICAL E LTD

IXIARO® by Intercell AG

This is an inactivated vaccine (JE-VC) derived from the attenuated SA 14-14-2 JEV strain propagated in Vero cells. This vaccine has been evaluated in several clinical trials conducted in India and abroad in both adults and children.[26-28] IXIARO® has now been approved by the US Food and Drug Administration (FDA) and European Union (EU) for use in children from the age of 2 months onwards.[29,30] There is no efficacy data for IXIARO®, and the vaccine has been licensed in pediatric age group especially for travelers to Asian countries on the basis of a phase III randomized controlled trials (RCT) conducted in the Philippines,[31] and favorable interim data from a second Phase III trial in EU, US, and Australia.[32] The safety profile of the test vaccine was good, and its local tolerability profile was more favorable than that of the mouse brain vaccines.

Indian Trial

A half-dose given to young children (1–3 years of age) has the excellent immunogenicity and the safety profile comparable to that of adults taking the full adult dosage. A phase II trial investigated the safety and immunogenicity of JE-VC in healthy children aged 1 and 2 years in India, using a standard (6 μg) or half (3 μg) dose.[26] Children in both groups received two doses of JE-VC administered 28 days apart. A third group of children received three doses of a JE-MB vaccine (JenceVac) on days 0, 7, and 28. At 56 days after the vaccination series was complete, seroconversion rates in the 6 μg (n = 21) and 3 μg (n = 23) JE-VC recipient groups and the JE-MB vaccine group (n = 11) were 95%, 96%, and 91%, and plaque reduction neutralization test (PRNT50) geometric mean titers (GMTs) were 218 (95% CI, 121–395), 201 (CI 106–380), and 230 (CI 68–784), respectively. The corresponding figures at 28 days were 71.4% (15/21), 65.2% (15/23), and 63.6% (7/11). None of the differences in seroconversion rates or GMTs was statistically significant.[26]

JEEV®—the Indian Variant of IC51, IXIARO by Biological E Ltd

Biological E Ltd has launched a vaccine for the endemic markets under the trade name JEEV® based on Intercell's technology and has already been WHO prequalified. In 2011, the Biological E Ltd India, conducted a multicentric open label randomized controlled phase II/III study to evaluate safety and immunogenicity of JEEV® vaccine in ~450 children (≥1 to <3 years old) and compared to control Korean Green Cross Mouse Brain Inactivated (KGCC) vaccine.[33] This study demonstrated seroconversion (SCR) of 56.28% on day 28 and 92.42% on day 56 in JEEV® vaccinated group. Noninferiority of JEEV® established against control in terms of proportion of subjects seroconverted. GMTs in JEEV® group were significantly higher than GMTs achieved in KGCC-JE vaccine group (218 vs. 126). There was no significant difference between the groups in proportion of subjects' seroprotected, and in proportion of subjects reporting adverse events between groups. JEEV® has been licensed by drug controller general of India (DCGI) for use in prevention of JEV infection in children and adult population on the basis of its ability to induce JEV neutralizing antibodies as a surrogate for protection.[33]

INACTIVATED VERO CELL CULTURE-DERIVED KOLAR STRAIN, 821564XY, JE VACCINE (JENVAC®)

JENVAC® is a Vero cell culture derived, inactivated, adjuvanted and thiomersal-containing vaccine developed by Bharat Biotech International Ltd (BBIL). The original virus strain used in the vaccine was isolated from a patient in the endemic zone in Kolar, Karnataka, India by National Institute of Virology (NIV), Pune, and later transferred to BBIL for vaccine development.

A phase II/III, randomized, single-blinded, active controlled study to evaluate the immunogenicity and safety of the vaccine was conducted among 644 healthy subjects. Out of 644 subjects, 212 were between the age of ≤50 years and >18 years, 201 subjects were between the age of ≤18 years and >6 years and 231 subjects were between the age of ≤6 years and >1 years. Subjects received two doses of the test vaccine or a single dose of a reference vaccine (live attenuated, SA 14-14-2 Chinese vaccine) as the first dose and a placebo as the second dose.

The results revealed that even a single dose of the test vaccine was sufficient to elicit the immune response. On 28th day, the subjects who had received a single dose were 98.67% seroprotected and 93.14% seroconverted (four fold) for ≤50 to ≥1 years, whereas the corresponding figures for the reference vaccine were 77.56% and 57.69%, respectively (p-value <0.001). There was no statistically significant difference in all the three groups. The seroconversion (93.14% and 96.90%) and seroprotection (98.67% and 99.78%) percentages on the 28th and 56th day were not significantly different and similarly, no statistically significant difference in these rates was noted amongst different age groups. Higher GMTs were achieved in younger age groups. After the second dose of the test vaccine, the GMTs increased exponentially from day 28 (145) to day 56 (460.5) in ≤50 to ≥1 years. However, there was waning of both seroconversion and GMTs in both the test vaccine and reference vaccine groups at 18 months. All the subjects were followed up for 56 ± 2 days. There was no serious adverse event or adverse event of any special interest noted in the study.

LIVE ATTENUATED RECOMBINANT SA 14-14-2 CHIMERIC VACCINE (JE-CV, IMOJEV® BY SANOFI PASTEUR)

A promising new genetic approach is adopted in the construction of a chimeric live attenuated vaccine comprising neutralizing antigen-coding sequences of the SA 14-14-2 strain of the JEV inserted into the genome of the 17D yellow fever vaccine strain. The resulting recombinant virus is cultivated on Vero cells.[27] This novel, live, recombinant vaccine, was previously known as ChimeriVax-JE and developed initially by Acambis. It is a safe, highly immunogenic and capable of inducing long-lasting immunity in both preclinical and clinical trials.[34] A single dose was sufficient to induce protective immunity, similar to that induced in adults by three doses of JE-VAX® with a seroconversion rate of >97% (after single dose).[5] This vaccine has been licensed in Australia and is under review in Thailand.[35] The clinical development of this vaccine (IMOJEV) is currently on hold in India due to severe delays in authorization of the Phase III study.

RECOMMENDATIONS FOR USE

Individual Use

The vaccination against JE is not recommended for routine use, but only for individuals living in endemic areas. Though occasional cases have been reported from urban areas in a few districts, JE is predominantly a disease of rural areas. Government of India has identified around 231 districts to be endemic for JE in India so far. 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.

Live Attenuated SA 14-14-2 Vaccine

Two doses are given in UIP in endemic districts of India. First dose of the vaccine can be administered at 9 months along with measles and rubella (MR) vaccine and second at 16–18 months at the time of 1st booster of DTP vaccine.

JEEV® by Biological E Ltd

The committee believes that although Biological E India Ltd has used the same strain, adjuvant and technology in production of JEEV® as used by Intercell AG in development of IXIARO®, the two vaccines cannot be treated as the same product. Considering the proven efficacy and safety profile of its parent vaccine in many countries over past many years, and demonstration of good seroprotection in Indian trial, the committee endorses use of this vaccine in India and recommends a primary schedule of two doses of 0.25 mL for children aged ≥1 to ≤3 years and two doses of 0.5 mL for children >3 years, adolescents and adults administered intramuscularly on days 0 and 28. However, the long-term persistence of protective efficacy and need of boosters are still undetermined.[33] In February 2011, Advisory Committee on Immunization Practices (ACIP) approved recommendations for a booster dose of JE-VC (IXIARO®) in adults.

JENVAC® by BBIL

The committee reviewed the data provided by the manufacturer on the clinical trials of JENVAC® in India. Although it lacks the

experience of multinational trials of IXIARO® in different countries, nevertheless the results of a pivotal phase II/III study conducted in India appear satisfactory for issuing recommendations for clinical use. The committee recommends two doses of the vaccine (0.5 mL each) administered intramuscularly at 4 weeks interval for the primary immunization series for office practice starting from 1 year of age. Since appreciable waning was noted in both seroconversion and seroprotection rates, and GMTs were also waned significantly, there is definitely a need of booster dose at later stage. The exact timing of the booster along with feasibility of single dose for primary series can be determined only after obtaining the long-term follow-up data.[33]

PUBLIC HEALTH PERSPECTIVES

Vaccination of humans is the method of choice for prevention of JE. The consensus statement from all the Global JE meetings over the years (1995, 1998, and 2002) has been that human vaccination is the only effective long-term control measure against JE. All at-risk population should receive a safe and efficacious vaccine as part of their national immunization program.

Advisory Committee on Vaccine and Immunization Practices (ACVIP) supports the government's decision to include JE vaccine in its UIP program in endemic districts only. Large scale JE vaccination is required because there is a large population which is susceptible to JE, ratio of asymptomatic to symptomatic infection is high, disease has a high mortality and morbidity and other control measures are not effective. Vaccination of the susceptible population has been demonstrated to be cost–effective strategy in China, Nepal, Japan, and Thailand. After introduction of mass vaccination in high-risk areas of Andhra Pradesh (population of 75 million) cases of JE decreased from 300 cases in 2002 to 25 in 2003.[26] However, there is need to undertake periodic assessment of the effectiveness of the employed JE vaccine.

JE Campaigns in India

In India though JE is primarily a disease that affects children living in rural areas, there have also been reports of cases from urban areas.

Therefore, a decision has been made to vaccinate all target children in both rural and urban areas of the operational districts to have the maximum impact of the program.

Following the massive outbreak of JE in 2005 in the districts of Eastern Uttar Pradesh and the adjoining districts of Bihar and Telangana districts of erstwhile Andhra Pradesh, vaccination campaigns were carried out in 11 of the highest risk districts of the country in 2006, 27 districts in 2007, 22 districts in 2008, and 30 districts in 2009. Children between the age group of 1 year and 15 years were vaccinated with a single dose of SA 14-14-2 vaccine. Mass vaccinations will continue to cover all the 109 endemic districts. Following the mass campaign, the vaccination will continue in the routine immunization program to cover the new cohort. As mentioned above, Government of India has identified around 231 districts to be endemic for JE. More districts are identified in 2018 and 268 districts are considered JE endemic.

Campaigns in Adults

Following mass vaccination of campaigns with Chinese SA 14-14-2 vaccine among pediatric age group, adult JE cases have outnumbered pediatric cases in some JE endemic states including Assam. This has become a cause of concern for public health program, researchers, and medical practitioners in India. This led Government of Assam to conduct supplementary immunization activities (SIAs) of JE vaccines in adults (>15 years) in the most affected districts like Sivasagar in Assam. The exact reason behind this shift in age group is not well–understood.

Japanese encephalitis vaccine should not be used as an "outbreak response vaccine". With the availability of two quality inactivated vaccines in India, the academy urges the government to introduce one of these products in the UIP program of affected districts based on cost-effective analysis. The performance of the current live attenuated Chinese vaccine, SA 14-14-2 has not been very satisfactory in high burden states.

BOX 1: Japanese encephalitis (JE) vaccines.

Routine vaccination:

- Recommended only for individuals living in endemic districts. Both rural and urban children in a district should be vaccinated.
- Three types of new generation JE vaccines are licensed in India: One, live attenuated, cell culture-derived SA 14-14-2, two inactivated JE vaccines, namely "vero cell culture-derived SA 14-14-2 JE vaccine" (JEEV® by BE India) and three "vero cell culture-derived, 821564XY, JE vaccine" (JENVAC® by Bharat Biotech).
- Live attenuated, cell culture-derived SA-14-14-2:
  - *Minimum age*: 8 months.
  - Two-dose schedule, first dose at 9 months along with measles and rubella (MR) vaccine and second at 16–18 months along with diphtheria, tetanus toxoids and pertussis (DTP) booster.
  - Not available in private market for office use.
- Inactivated cell culture-derived SA 14-14-2 (JEEV® by BE India):
  - *Minimum age*: 1 year [US Food and Drug Administration (FDA): 2 months].
  - *Primary immunization schedule*: Two doses of 0.25 mL each administered intramuscularly on days 0 and 28 for children aged ≥ 1 to ≤ 3 years.
  - Two doses of 0.5 mL for children >3 years and adults aged ≥18 years.
  - Need of boosters still undetermined.
- Inactivated Vero cell culture-derived Kolar strain, 821564XY, JE vaccine (JENVAC® by Bharat Biotech):
  - *Minimum age*: 1 year.
  - *Primary immunization schedule*: Two doses of 0.5 mL each administered intramuscularly at 4 weeks interval.
  - Need of boosters still undetermined.

Catch-up vaccination:

All susceptible children up to 15 years should be administered during disease outbreak or ahead of anticipated outbreak in campaigns.

REFERENCES

1. Tiwari S, Singh RK, Tiwari R, et al. Japanese encephalitis: A review of the Indian perspective. Braz J Infect Dis. 2012;16:564-73.
2. WHO. Japanese Encephalitis Vaccines: WHO position paper February 2015—Recommendations. Vaccine. 2016;34:302-3.
3. National Vector Borne Control Program, GOI. Acute encephalitis syndrome. [online] Available from nvbdcp.gov.in/WriteReadData/l892s/25510462041546326501.pdf. [Accessed October, 2019].
4. World Health Organization. Japanese encephalitis vaccines. Wkly Epidemiol Rec. 2006;81:331-40.
5. Campbell GL, Hills SL, Fischer M, et al. Estimated global incidence of Japanese encephalitis: a systematic review. Bull World Health Organ. 2011;89:766-74.

6. Heffelfinger JD, Li X, Batmunkh N, et al. Japanese Encephalitis Surveillance and Immunization—Asia and Western Pacific Regions, 2016. MMWR Morb Mortal Wkly Rep. 2017;66:579-83.
7. http://nvbdcp.gov.in/Doc/je-aes-cd-Jan17.pdf. [Accessed October, 2019].
8. Background Paper on Japanese Encephalitis vaccines. (2014). SAGE Working Group on Japanese encephalitis vaccines. [online] Available from http://www.who.int/immunization/sage/meetings/2014/october/1_JE_Vaccine_Background_Paper.pdf.
9. Gurav YK, Bondre VP, Tandale BV, et al. A large outbreak of Japanese encephalitis predominantly among adults in northern region of West Bengal, India. J Med Virol. 2016;88(11):2004-11.
10. Tiroumourougane SV, Raghava P, Srinivasan S. Japanese viral encephalitis. Postgrad Med J. 2002;78:205-15.
11. Arunachalam N, Samuel PP, Paramasivan R, et al. Japanese encephalitis in Gorakhpur Division, Uttar Pradesh. Indian J Med Res. 2008;128:775-7.
12. Gourie-Devi M. Clinical aspects and experience in the management of Japanese encephalitis patients. Proceedings of the National Conference on Japanese Encephalitis. New Delhi: Indian Council of Medical Research; 1984:25-9.
13. Kumar R, Mathur A, Kumar A. Clinical features and prognostic indicators of Japanese encephalitis in children in Lucknow (India). Indian J Med Res. 1990;91:321-7.
14. National Health Profile. (2018). Health status indicators in India 3.1.4(B) state/UT wise cases and deaths due to Japanese encephalitis, 2013-2017. [online] Available from http://www.cbhidghs.nic.in/WriteReadData/l892s/Chapter%203.pdf. [Accessed October, 2019].
15. World Health Organization. (2002). WHO Expert Committee on Biological Standardization. Fifty-first report. WHO Technical Report Series No. 910. [online] Available from http://www.who.int/biologicals/publications/trs/51/en/index.html. [Accessed October, 2019].
16. Halstead SB, Jacobson J. Japanese encephalitis vaccines. In: Plotkins SA, Orenstein WA, Offit PA (Eds). Vaccines, 5th edition. Philadelphia: Saunders Elsevier; 2008. pp. 311-52.
17. Hennessy S, Zhengle L, Tsai TF, et al. Effectiveness of live-attenuated Japanese encephalitis vaccine (SA 14-14-2): a case control study. Lancet. 1996;347:1583-671.
18. Bista MB, Banerjee MK, Shin SH, et al. Efficacy of single-dose SA 14-14-2 vaccine against Japanese encephalitis: a case control study. Lancet. 2001;358:791-5.
19. Ohrr H, Tandan JB, Sohn YM, et al. Effect of single dose of SA 14-14-2 vaccine 1 year after immunisation in Nepalese children with Japanese encephalitis: a case-control study. Lancet. 2005;366:1375-8.

20. Andan JB, Ohrr HC, Sohn YM, et al. Single dose of SA14-14-2 vaccine provides long-term protection against Japanese encephalitis: a case-control study in Nepalese children five years after immunization. Vaccine. 2007;25:5041-5.
21. Immunization Division Department of Family Welfare Ministry of Health and Family Welfare, Government of India. Control of Japanese Encephalitis. Operational Guide Japanese Encephalitis Vaccination in India. 2010. pp. 13-5.
22. Ministry of Health and Family Welfare, Government of India. (2011). Immunization Handbook for Medical Officers. [online] Available from http://www.searo.who.int/india/topics/routine_immunization/Immunization_Handbook_for_Health_Workers_English_2011.pdf. [Accessed August 2013].
23. Kumar R, Tripathi P, Rizvi A. Effectiveness of one dose of SA 14-14-2 vaccine against Japanese encephalitis. N Engl J Med. 2009;360:1465-6.
24. Indian Council of Medical Research. Minutes of the meeting of the Core Committee on Vaccines. [online] Available from http://www.icmr.nic.in/minutes/Minutes%20Core%20Committee%20on%20Vaccines.pdf. [Accessed October, 2019].
25. WHO. Global Advisory Committee on Vaccine Safety, 9-10 June 2005. Wkly Epidemiol Rec. 2005;80:242-3.
26. Kaltenbock A, Dubischar-Kastner K, Schuller E, et al. Immunogenicity and safety of IXIARO (IC51) in a Phase II study in healthy Indian children between 1 and 3 years of age. Vaccine. 2010;28:834-9.
27. Schuller E, Jilma B, Voicu V, et al. Long-term immunogenicity of the new Vero cell-derived, inactivated Japanese encephalitis virus vaccine IC51 Six and 12 month results of a multicenter follow-up phase 3 study. Vaccine. 2008;26:4382-6.
28. Dubischar-Kastner K, Eder S, Kaltenboeck A, et al. Long-term immunity following vaccination with the inactivated Japanese encephalitis vaccine IXIARO and neutralizing antibody response to a booster dose. 11th Conference of the International Society of Travel Medicine; May 24–28, 2009, Budapest, Hungary.
29. Intercell announces pediatric approval of its Japanese encephalitis vaccine in the US. [online] Available from http://www.vaccines.mil/documents/1624_2013-05-21_JEV_pediatric_US_ENG_final.pdf. [Accessed October 2019].
30. ACIP unanimously votes to extend the recommendations for use of IXIARO(R) vaccine. [online] Available from http://www.reuters.com/article/2013/06/21/idUSnHUGd8N0+72+ONE201306. [Accessed October 2019].
31. Dubischar-Kastner K, Eder S, Kaltenboeck A, et al. (2012). Safety and immunogenicity of the inactivated Japanese encephalitis vaccine

IXIARO®, IC51, in Filipino children aged 2 months to <18 years. Presented at the 4th Northern European Conference on Travel Medicine. [online] Available from http://nectm.com/wp-content/uploads/BookofAbstracts.pdf. [Accessed October 2019].
32. Dubischar-Kastner K, Eder S, Kaltenboeck A, et al. (2012). Interim safety and immunogenicity data for the inactivated Japanese encephalitis vaccine IXIARO®, IC51, in children from JE non-endemic countries. Presented at the 4th Northern European Conference on Travel Medicine. [online] Available from http://nectm.com/wp-content/uploads/BookofAbstracts.pdf. [Accessed October 2019].
33. Vashishtha VM, Kalra A, Bose A, et al. Indian Academy of Pediatrics (IAP) recommended immunization schedule for children aged 0 through 18 years—India, 2013 and updates on immunization. Indian Pediatr. 2013;50:1095-108.
34. Appaiahgari MB, Vrati S. IMOJEV®: a Yellow fever virus-based novel Japanese encephalitis vaccine. Expert Rev Vaccines. 2010;9:1371-84.
35. Halstead SB, Thomas SJ. New Japanese encephalitis vaccines: Alternatives to production in mouse brain. Expert Rev Vaccines. 2011;10:355-64.

3.15 MENINGOCOCCAL VACCINES

Harish K Pemde

BACKGROUND

Meningococcal disease is caused by Gram-negative bacterium *Neisseria meningitidis*, which is a diplococcus and appears bean-shaped lying with flat surfaces adjacent to each other in a polysaccharide capsule. The meningococci are usually found as commensal organisms in the upper respiratory tract of about 10% of the population at any one time. Humans are the only natural reservoir. Meningococcal disease generally manifests as acute illness but chronic course with a mean duration of 6–8 weeks is also known.[1] The disease spectrum includes meningitis, septicemia, pneumonia, myocarditis, pericarditis, arthritis, and conjunctivitis, and occasionally may present as shock referred to as Waterhouse-Friderichsen syndrome with high risk of mortality.

There are 13 known serogroups but 90% of the disease causing isolates belongs 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 *Hajj* pilgrims have been attributed to A and W-135. Disease in industrialized countries is primarily due to B, C and Y.[2] There is lack of information of serogroup responsible for endemic meningococcal disease in India. In one study from Postgraduate 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 *Meningococcus* is the cause of all the major investigated epidemics.

EPIDEMIOLOGY OF MENINGOCOCCAL DISEASE

Global

In most countries, *Neisseria meningitidis* is recognized as a leading cause of meningitis and fulminant septicemia and a significant public

health problem. Endemic disease mostly afflicts young children; older children, adolescents and young adults mainly suffer during epidemics. In developing countries the background incidence of meningococcal disease is 15–20 cases per 100,000 peoples per year. When three or more cases of meningococcal disease occur in a 3-month period in the same locality, amounting to at least 10 cases per 100,000 persons suffering from the disease, the situation is referred as outbreak. However, in sub-Saharan Africa disease is hyperendemic due to unknown reasons and is considered to have the highest annual incidence (10–25/100,000 population) of meningococcal disease in the world. In the African meningitis belt, the World Health Organization (WHO) definition of a meningococcal epidemic is >100 cases/100,000 population/year. In endemic regions, an incidence of >10 cases, 2–10 cases, and <2 cases per 100,000 population in a year characterizes high, moderate, and low endemicity, respectively.[3] However, the situation has changed after the introduction of monovalent MenA vaccine in the year 2010, and meningococcal group A disease has reduced sharply. However, the meningococcal disease by strains with other capsular groups such as C, W or X has emerged (Fig. 1). A low-cost pentavalent vaccine MenACWXY is under development and may replace the monovalent vaccine.

A recent global systemic review and survey found that different serotypes are prevalent in different parts of the world **(Fig. 1)**.[4] In India, serotype A has been reported in studies.

India

The data available on the background incidence of meningococcal disease in India are suggestive of low incidence of meningococcal disease. Hence routine childhood vaccination with meningococcal vaccine is unlikely to be a priority. As per the review by Sinclair et al.[4] 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. *N. meningitidis* is the third most common cause of bacterial meningitis in India in children less than 5 years of age and is responsible for an estimated 1.9% of all cases regardless of age.[5] Prevalence of septicemia according to one study is 2.8% of all hospital admissions.

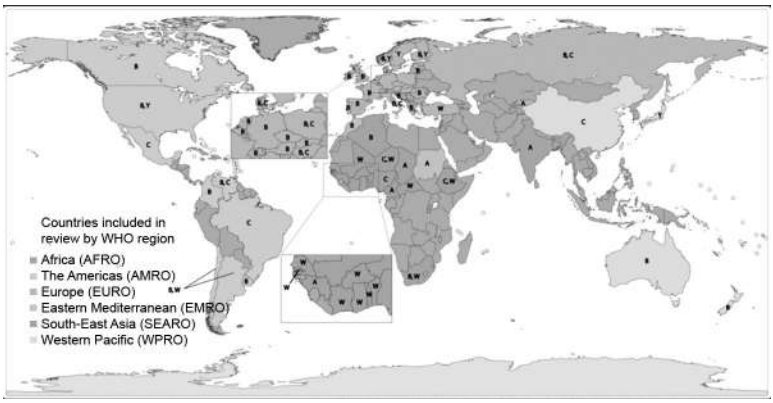

Fig. 1: Serogroups (>25% of the total cases) of *N. meningitidis* reported from various countries between 2010 and 2016.
Source: From the Reference #4.

In India, outbreaks of meningococcal meningitis were reported in 1883–1884.[6] Confirmed outbreaks occurred in 1961–61, 1966–67, 1985–86, 2005–2006 in New Delhi and 2008–2009 in Meghalaya and Tripura.[5] Serogroup A was found in these outbreaks.

Outbreaks have been reported more in temperate northern than tropical southern regions of the country. Large cities of North and coastal areas like Mumbai, Kolkata are being affected sparing the southern and central regions. 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 onward. 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.

The existence of endemic disease is recognized, but much of the epidemiological data that are available are collected during outbreaks. Unlike *Haemophilus influenzae* type b (Hib), *N. meningitidis* affects adults as well as children. 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. High carrier rates are also found among the military recruits.

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.

Hospital based sentinel surveillance of meningitis in 10 hospitals (one each in Shimla and Bhubaneswar and 8 in Southern parts of India) in 2012 found that out of 257 confirmed cases of meningitis 2.7% (7 of 257) were caused by *N. meningitidis*, 14.4% (37 of 257) by *H. influenzae type B* and the remaining 82.9% (213 of 257) were caused by *S. pneumoniae*.[7] A recently published systematic review and meta-analysis of bacterial meningitis among children between 1 month and 59 months of age in South Asia (including studies from India) found that *Meningococcus* contributed for only 1% (95% CI 0–2%) of the all reported cases of meningitis.[8]

VACCINES

Two types of meningococcal vaccines have been developed but all are not available everywhere in the world **(Table 1)**. They include:

- Meningococcal polysaccharide vaccines (MPSV)
- Meningococcal polysaccharide-protein conjugate vaccines (MCV).

TABLE 1: Licensed meningococcal vaccine in India.

Type	*Valency/strains covered*	*Brand/manufacturer*	*Nature and diluent*	*Dose and schedule*
Polysaccharide (MPSV: Meningococcal polysaccharide vaccine)	*Quadrivalent* (Serogroups A, C, W-135 and Y; contains individual capsular polysaccharides 50 µg each) *Bivalent* (Serogroups A and C contains individual capsular polysaccharides 50 µg each)	Mencevax, GSK; Quadri Meningo, BioMed MPV A+C, GSK; Bi Meningo, BioMed	Lyophilized, sterile distilled water	0.5 mL by SC or IM, recommended in children > 2 years#, revaccination after 3–5 years in high-risk children and adolescents
MCV: Meningococcal conjugate vaccine	*Quadrivalent* (Serogroups A, C, W-135 and Y; contains 4 µg each of A, C, Y and W-135 polysaccharide conjugated to 48 µg of diphtheria toxoid) **Monovalent* (Serogroup A: 10 µg of group A polysaccharide conjugated to 10–33 µg tetanus toxoid, with alum as adjuvant and thiomersal as preservative)	Menactra, Sanofi Pasteur Serum Institute of India Ltd.	Menactra®, Meningococcal (Groups A, C, Y and W-135) Conjugate Vaccine Solution for Intramuscular Injection Lyophilized vaccine	0.5 mL by deep IM, revaccination after 3–5 years in high-risk children and adolescents 0.5 mL IM single administration for individuals 1–29 years of age

** Going to be available very soon in Indian market.*
 # In infants aged 3 months to 2 years, MPSV may be given if risk for meningococcal disease is high, e.g. outbreaks/close household contacts: 2 doses 3 months apart.
(SC: subcutaneous; IM: intramuscular; GSK: GlaxoSmithKline)

Meningococcal Polysaccharide Vaccines

These are either bivalent (A+C) or quadrivalent (A, C, Y, W-135) and contain 50 μg of each of the individual polysaccharides, available in lyophilized form, reconstituted with sterile water and stored at 2–8°C. These "T cell independent" vaccines do not induce immunological memory and the response in children younger than 2 years is poor. Hence these are indicated for adults and children older than 2 years (only under special circumstances in children 3 months to 2 years of age).

Immunogenicity and Efficacy

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 3 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% or higher among children 5 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.

Duration of Protection

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 3 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 serogroups 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.

Meningococcal Conjugate Vaccines

Currently, two different types of MCVs are licensed in India. The *first* which is now readily available in private market also, is a quadrivalent vaccine Menactra® from Sanofi Pasteur, and *second is* a monovalent serogroup A vaccine from Serum Institute of India (SII).

Quadrivalent Meningococcal Polysaccharide-protein Conjugate Vaccine (MenACWY-D, Menactra®, Manufactured by Sanofi Pasteur)

This is a quadrivalent (A, C, W-135, Y) meningococcal conjugate vaccine using diphtheria toxin as carrier protein (A, C, W-135, Y-D), and was licensed in the US in 2005. However, it is licensed in India only in 2012 for use among persons aged 2–55 years. In 2011, the Advisory Committee on Immunization Practices (ACIP) recommended a two-dose series of this vaccine for use in children aged 9–23 months. 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 intramuscular (IM) is recommended beyond 24 months of age. This vaccine had comparable immunogenicity to the previously used polysaccharide vaccine.

Recent estimates of the effectiveness of MenACWY-D, the first licensed quadrivalent vaccine suggest that within 3–4 years after vaccination, effectiveness is 80–85%.[9,10] There is higher level of evidence for protection of children against meningococcal disease in children > 12 months to < 5 years of age than in individuals aged ≥ 5 years.[10]

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. 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. Interference with PCV13 immune responses was noted when MenACWY-D and PCV13 were administered simultaneously in patients with asplenia. Hence, CDC ACIP has now recommended that at least 1 month interval should

be kept between PCV13 and MenACWY-D, and PCV13 should be administered first.[11]

A safety and immunogenicity open label non-randomized multicentric phase III trial of the MenACYW-DT vaccine amongst Indian children, adolescents and adults, found a robust and protective immune response 30 days post-vaccination against meningococcal serogroups A, C, Y, and W-135 in nearly all (96.9–100%) of the Indian study participants aged 2–55 years and it was well tolerated.[12]

Monovalent Serogroup A Conjugate Vaccine (PsA–TT, MenAfriVac®, Manufactured by Serum Institute of India)

Meningococcal group A conjugate vaccine (PsA-TT) is a lyophilized vaccine of purified meningococcal A polysaccharide covalently bound to tetanus toxoid (TT) which acts as a carrier protein. It contains 10 μg of group A polysaccharide conjugated to 10–33 μg tetanus toxoid, with alum as adjuvant and thiomersal as preservative.[3] The vaccine is licensed in India since 2009 and prequalified by WHO in 2010, but the company has not launched this inexpensive vaccine (costing around half a cent to African nations) in India so far. It has been used in large campaigns in Burkina Faso, Mali, and Niger and is being progressively introduced in other countries of the African meningitis belt.[3]

It should be administered as a single intramuscular injection of 0.5 mL to individuals 1–29 years of age.[3] The possible need for a booster dose has not yet been established. Persons who have previously received a meningococcal A polysaccharide-containing vaccine can be vaccinated with the conjugate vaccine.

The single intramuscular dose induces functional antibody titers against meningococcal serogroup A which are significantly higher and more persistent than those induced by a corresponding polysaccharide vaccine.[13-15] The immune response seems to persist for a long time. The vaccine has also got a very good safety profile. There is moderate level of evidence for protection of children against group A meningococcal disease in both children >12 months to < 5 years, and in individuals ≥ 5 years old.[11] Furthermore, the vaccine has demonstrated a great effectiveness when used in Africa in campaigns.

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 the 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 16–21 years. This is the reason why ACIP has now recommended revaccination with MCV 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.

RECOMMENDATIONS FOR USE

Individual Use

The current epidemiology and burden of meningococcal diseases in India do not justify routine use of meningococcal vaccines. Meningococcal vaccines are recommended only for certain high-risk conditions and 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). Conjugate vaccines are preferred over polysaccharide vaccines due to their potential for

herd protection and their increased immunogenicity, particularly in children < 2 years of age.

IAP Recommendations on Dosage in Different Categories[12]

Indian Academy of Pediatrics (IAP) now recommends the use of MCVs in different categories as per following description:

A. During disease outbreaks: Due to the limited efficacy of polysaccharide vaccines in children < 2 years of age, conjugate vaccines should be used for protection of those aged 12–24 months, particularly for Men A disease. Since majority of documented outbreaks in India are caused by Men A, monovalent MCV, like PsA-TT should be employed in mass vaccination.

B. Vaccination of persons with high-risk conditions/situations

- *Children with terminal complement component deficiencies:* A two-dose primary series of MCV administered 8–12 weeks apart is recommended for persons aged 24 months through 55 years with persistent deficiencies of the late complement component pathway. A booster dose should be administered every 5 years. Children who receive the primary series before their seventh birthday should receive the first booster dose in 3 years and subsequent doses every 5 years.
- *Children with functional/anatomic asplenia/hyposplenia (including sickle cell disease):* Administer two primary doses of either MCV with at least 8 weeks between doses for individuals aged 24 months through 55 years. Vaccination should ideally be started two weeks prior to splenectomy.
- *Persons with human immunodeficiency virus:* Administer two doses at least 8 weeks interval.
- *Laboratory personnel and healthcare workers:* Who are exposed routinely to *N. meningitidis* in solutions that may be aerosolized should be considered for vaccination. A single dose of MCV is recommended. A booster dose should be administered every 5 years if exposure is ongoing.
- *Adjunct to chemoprophylaxis:* In close contacts of patients with meningococcal disease (healthcare workers in contact with secretions, household contacts, day care contacts) single dose of appropriate group MCV is recommended.

C. *International travelers:*
- *Students going for study abroad:* Some institutions have policies requiring vaccination against meningococcal disease as a condition of enrolment (mandatory in most universities in the USA). Persons aged ≤21 years should have documentation of receipt of a MCV not more than 5 years before enrolment. In the US, ACIP recommends routine vaccination of all adolescents with single dose of MCV4 at age 11–12 years, with a booster dose at age 16 years (available online at http:// www.cdc.gov/vaccines/pubs/acip-list.htm). For further details, follow the catch-up recommendations for meningococcal vaccination of the destination country.
- *Hajj pilgrims:* Vaccination in the 3 years before the date of travel is required for all travelers to Mecca during the annual Hajj. The quadrivalent vaccine is preferred for Hajj pilgrims and international travelers as it provides added protection against emerging W-135 and Y disease in these areas. A single dose 0.5 mL IM is recommended in age group 2–55 years.
- *Travelers to countries in the African meningitis belt:* A single dose of monovalent or quadrivalent vaccine is recommended. Conjugate vaccine is preferred to polysaccharide vaccine. A booster dose of MCV is needed if the last dose was administered 5 or more years previously.

PUBLIC HEALTH PERSPECTIVES

Sporadic outbreaks of meningococcal disease have been recorded for last many decades in India. These outbreaks, particularly the larger epidemics have almost universally been caused by serogroup A meningococci.[5] The committee believes that the new affordable serogroup A containing monovalent conjugate vaccine manufactured by SII should have a critical role in containing future epidemics. The Academy urges the Indian manufacturer to make this vaccine available in the country also. The quadrivalent MenACWY-D should be employed in individuals having certain high-risk conditions and situations and amongst international travelers (mentioned earlier).

Conjugated meningococcal vaccines are more expensive than polysaccharide vaccines. Based on results on the cost-effectiveness of use of MCVs in Australia, Canada, Netherlands, Portugal, Switzerland and United Kingdom, it was found that one dose in the second year of life was more cost-effective than a 3-dose infant schedule. The most cost-effective strategy was routine vaccination of children at 12 months of age combined with a catch-up campaign for all children and adolescents <18 years of age.[16] No studies on the cost-effectiveness of meningococcal vaccination have yet been reported from India.

Decision to Vaccinate

If ≥3 cases of meningococcal disease have occurred in either an organization or a community-based outbreak during <3 months (starting at the time of the first confirmed or probable case), a primary attack rate should be calculated. Attack rate per 100,000 = (number of primary confirmed or probable cases during a 3-months period)/(number of population at risk) × 100,000.

If the attack rate of the meningococcal disease exceeds 10 cases per 100,000 persons, then vaccination of the population at risk should be considered keeping following factors in sight.[2]

Outbreak Identification and Management

A decision to carry out mass vaccination is based on following conditions:

- Completeness of case reporting and number of possible cases of meningococcal disease for which bacteriologic confirmation or serogroup data are not available.
- Occurrence of additional cases of meningococcal disease after recognition of a suspected outbreak (e.g. if the outbreak occurred 2 months before and if no additional cases have occurred, in which case vaccination might be unlikely to prevent additional cases of meningococcal disease).
- Logistic and financial considerations. Because available vaccines are not effective against *N. meningitidis* serogroup B, vaccination should not be given during serogroup B outbreaks.
- Age consideration. Meningococcal disease outbreaks occur predominantly among persons aged < 30 years. If the calculated

attack rate remains >10 cases/100,000 persons, then vaccination should be considered for part or all of the population at risk.

- In infants aged 3 months to 2 years, meningococcal conjugate vaccine is preferred.
- If MCVs are not available, two doses of MPSV given 3 months apart may be administered if the risk for meningococcal disease is high, e.g. outbreaks/close household contacts.
- Close child contacts of a patient with invasive meningococcal disease are at increased risk of secondary disease. Most secondary cases occur within the first 72 hours after presentation of the index case; risk of secondary disease decreases to near baseline by 10–14 days.[9] Meningococcal vaccines may be given to pregnant women during epidemics.

When there is an outbreak, immediate action is taken by the government. However, in remote areas of the country, more time may be needed before remedial action can be expected. A rapid response team typically composed of an epidemiologist, medical professionals and a microbiologist is deployed to identify individuals exposed to meningococcal disease and to assist in the management of those who are ill. If diagnostic facilities are not available locally, as is typical for remote areas of the country, patient samples are sent to the NCDC for diagnostic testing. During the recent outbreaks, microscopy, culture and latex agglutination tests were employed for diagnosis. Polymerase chain reaction (PCR) was also used to investigate the epidemic in New Delhi.

Outbreak Prevention and Control Actions in India

Following actions should be urgently taken after confirmation of an outbreak **(Box 1)**:

- Active case surveillance
- Early diagnosis and prompt treatment
- Chemoprophylaxis of close contacts (household members, healthcare professionals)
- Fostering disease awareness within the community, including the need to seek medical help and to avoid crowded places
- Respiratory isolation of patients for 72 hours
- Reactive vaccination of high-risk groups.

BOX 1: Use of meningococcal vaccine.

- Recommended only for certain high-risk group of children, during outbreaks, and international travelers, including students going for study abroad and travelers to *Hajj* and sub-Sahara Africa.
- Both meningococcal conjugate vaccines (Quadrivalent MenACWY-D, Menactra® by Sanofi Pasteur and monovalent group A, PsA-TT, MenAfriVac® by Serum Institute of India) and polysaccharide vaccines (bi- and quadrivalent) are licensed in India. PsA-TT is not freely available in market.
- Conjugate vaccines are preferred over polysaccharide vaccines due to their potential for herd protection and their increased immunogenicity, particularly in children <2 years of age.
- As of today, quadrivalent conjugate and polysaccharide vaccines are recommended only for children 2 years and above.
- Monovalent group A conjugate vaccine, PsA-TT can be used in children above 1 year of age.

REFERENCES

1. Granoff DM, Gilsdorf JR. *Neisseria meningitidis*. In: Kleigman RM, Stanto BFn, St Geme JW, Schor NF, Behrman RE (Eds). Nelson textbook of Pediatrics, 19th edition. Philadelphia: Elsevier Saunders; 2012. pp. 929-33.
2. Centers for Disease Control and Prevention. Meningococcal disease. [online] Available from http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious- diseases-related-to-travel/meningococcal-disease. [Last Accessed on August, 2019].
3. Meningococcal vaccines: WHO position paper, November 2011. Wkly Epidemiol Rec. 2011;86:521-39.
4. Peterson ME, Li Y, Bita A, et al. Meningococcal serogroups and surveillance: a systematic review and survey. J Glob Health. 2019;9(1):010409.
5. Sinclair D, Preziosi MP, Jacob John T, et al. The epidemiology of meningococcal disease in India. Trop Med Int Health. 2010;15:1421-35.
6. Patel PT. Cerebrospinal fever in Bombay. A study of 170 consecutive cases during the years 1921-24. Lancet. 1926;11:539-41. [*Meningococcal meningitis was known as cerebrospinal fever at that time.*]
7. Jayaraman Y, Veeraraghavan B, Chethrapilly Purushothaman GK, et al. Burden of bacterial meningitis in India: Preliminary data from a hospital based sentinel surveillance network. PLoS One. 2018;13(5):e0197198.
8. Ali M, Chang BA, Johnson KW, et al. Incidence and aetiology of bacterial meningitis among children aged 1-59 months in South Asia: systematic review and meta-analysis. Vaccine. 2018;36(39):5846-57.

9. Macneil JR, Cohn AC, Zell ER, et al. Early estimate of the effectiveness of quadrivalent meningococcal conjugate vaccine. Pediatr Infect Dis J. 2011;30:451-5.
10. WHO. Grading of scientific evidence– Table VI a and b (efficacy of quadrivalent meningococcal conjugate vaccines). [online] Available from http://www.who.int/entity/immunization/meningococcal_grad_efficacy.pdf. [Last Accessed on August, 2019].
11. Kroger A. General Recommendations on Immunization. ACIP Presentation Slides: February 2013 Meeting. Atlanta: CDC; 2013.
12. Yadav S, Manglani MV, Narayan DA, et al. Safety and immunogenicity of a quadrivalent meningococcal conjugate vaccine (MenACYW-DT): a multicenter, open-label, non-randomized, phase III clinical trial. Indian Pediatr. 2014;51(6):451-6.
13. Kshirsagar N, Mur N, Thatte U, et al. Safety, immunogenicity, and antibody persistence of a new meningococcal group A conjugate vaccine in healthy Indian adults. Vaccine. 2007;25(Suppl 1):A101-7.
14. Sow SO, Okoko BJ, Diallo A, et al. Immunogenicity and safety of a meningococcal A conjugate vaccine in Africans. N Engl J Med. 2011;364:2293-304.
15. Hirve S, Bavdekar A, Pandit A, et al. Immunogenicity and safety of a new meningococcal A conjugate vaccine in Indian children aged 2–10 years: a phase II/III double-blind randomized controlled trial. Vaccine. 2012;30(45):6456-60.
16. Welte R, Trotter CL, Edmunds WJ, et al. The role of economic evaluation in vaccine decision making: focus on meningococcal group C conjugate vaccine. Pharmacoeconomics. 2005;23(9):855-74.

3.16 RABIES VACCINES

Vijay Kumar Guduru

BACKGROUND

Rabies is a viral zoonosis and is transmitted by bites, scratches, and licks on mucous membrane or nonintact skin by a rabid animal. Human-to-human transmission occurs almost exclusively as a result of organ or tissue transplantation (including cornea). The incubation period usually averages 4–6 weeks but can range from 5 days to 6 years. The disease is uniformly fatal and only six survivors have been reported in world literature.

In India, the most common transmitting animal is dog, accounting for more than 96% cases. As per the national multicentric rabies survey done in 2003,[1] about 17 million animal bites occur annually out of which 20,000 human rabies deaths occur in India. About 35% of these are in children.[2]

About 59,000 human deaths occur every year due to rabies, over 3.7 million disability-adjusted life years lost every year and about 15 million people receive post-exposure prophylaxis (PEP) annually. Approximately 40% of cases occur in children aged <15 years.[3]

Analysis of Million Death Study by verbal autopsy in 2005, estimated that there were 12,700 [99% confidence interval (CI) 10,000–15,500] symptomatically identifiable furious rabies deaths in India. Most rabies deaths were in males (62%), in rural areas (91%), and in children below the age of 15 years (50%). The overall rabies mortality rate was 1.1 deaths per 100,000 population (99% CI 0.9–1.4). As verbal autopsy is not likely to identify atypical or paralytic forms of rabies, figure of 12,700 deaths due to classic and clinically identifiable furious rabies underestimates the total number of deaths due to this virus. One-third of the national rabies deaths were found in Uttar Pradesh (4,300) and nearly three-quarters (8,900) were in seven central and south-eastern states: Chhattisgarh, Uttar Pradesh, Odisha, Andhra Pradesh, Bihar, Assam, and Madhya Pradesh.[4]

Fig. 1: Global distribution of deaths occurred due to rabies.

GLOBAL BURDEN (FIG. 1)

Globally, 61,000 deaths due to rabies occur annually. In India, estimated 17.4 million animal bites and 20,000 deaths due to rabies occur per year. 15 million people receive PEP annually estimated to prevent hundreds of thousands of deaths possibly due to rabies. 40% of bites are received by children. 98% of human rabies deaths are due to rabid dog. Rabies is not a notifiable disease **(Fig. 2)**.

CATEGORY OF WOUNDS

The following categories describe the risk of a rabies virus (RABV) exposure according to the type of contact with the animal suspected of having rabies. The category of exposure determines the indicated PEP procedure.

Category I	Touching or feeding animals, animal licks on intact skin (no exposure)
Category II	Nibbling of uncovered skin, minor scratches, or abrasions without bleeding (exposure)
Category III	Single or multiple transdermal bites or scratches, contamination of mucous membrane or broken skin with saliva from animal licks, exposures due to direct contact with bats (severe exposure)

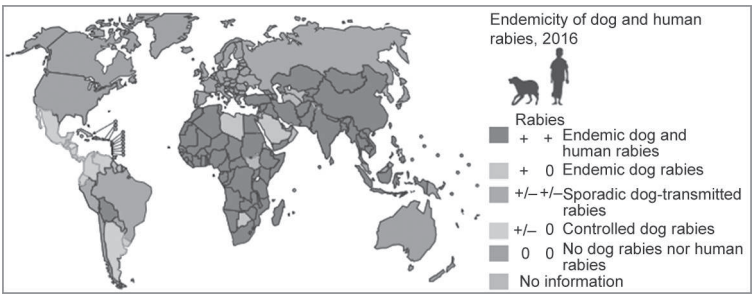

Fig. 2: Zero by 30, the Global Strategic Plan to End Human Deaths from Dog-mediated rabies by 2030, WHO, FAO of UN, Geneva 2018.

World Health Organization (WHO) Expert Consultation on Rabies, third report: WHO Technical Series Report No. 1012, Geneva, 2018 (ISBN 978-92-4-121021-8).[5]

CARE OF ANIMAL-BITE WOUNDS

The first step is thorough cleansing of the wound with soap and flushing under running water for 15 minutes as per WHO recommendation. 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. Rabies immunoglobulin (RIg) should be infiltrated in and around the wound in category III bites (for information on exposure categories, see section "Post-exposure prophylaxis"). 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. Only stay suturing is advocated initially. Delayed suturing may be done after 48 hours if needed.

MANAGEMENT

Category	*Management*
I	Wound care, no prophylaxis is required
II	Appropriate wound care + Immediate PEP
III	Appropriate wound care + Immediate PEP + MAB or HRIg or ERIg

Passive Immunization

Human Monoclonal Antibody

Rabishield (rabies human monoclonal antibody), developed by an Indian firm Serum Institute of India in technical collaboration with Mass Biologics, University of Massachusetts Medical School, Boston, USA, is a safe alternative to RIg. It is a recombinant human immunoglobulin G1 (IgG1), antirabies monoclonal antibody (SII RMab) superior alternate to serum-derived RIG. This human IgG1 monoclonal antibody (Mab) binds to the ectodomain of G glycoprotein **(Fig. 3)**.

Rabies human monoclonal antibody (HuMAb) (Rabishield) neutralizes 25 different wild-type or street RABV isolates. Efficacy is proved in an animal model of PEP in Syrian hamsters challenged with wild virus. HuMAb 17C7 was the most promising antibody identified because it neutralized all RABV isolates tested. HuMAb 17C7 recognizes a conformational epitope on the RABV glycoprotein, which includes antigenic site III. HuMAb 17C7 protected hamsters from a lethal dose of RABV in a well-established *in vivo* model of PEP.[6]

Advantages of RMab include easier to produce in bulk. All adverse reactions of blood born products are avoided. Dose: 3.33 IU/kg, hence less quantity and less pain. Nearly more than 2 lakhs vials used and postmarketing have not reported any serious adverse events. RMab can be started till 7th day of first dose of vaccine.

Presentation: Vial of 2.5 mL, 1 mL containing 40 IU, 100 IU per vial.

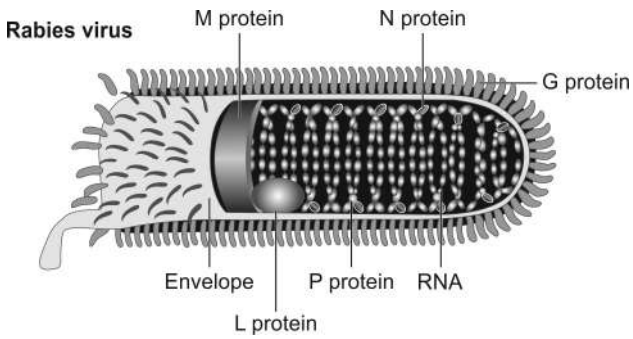

Fig. 3: Various rabies viral proteins.

Rabies Immunoglobulin

Dosage: It contains specific antirabies antibodies that neutralize the RABV and provide passive protection till active immunity is generated. There are two types of RIg:

- Human rabies immunoglobulin (HRIg—dose is 20 U/kg body weight, maximum dose 1,500 IU)
- Equine rabies immunoglobulin (ERIg—dose is 40 U/kg, maximum dose 3,000 IU).

Human rabies immunoglobulin 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.[7]

Administration: RIg is indicated in all cases of category III wounds where it should be infiltrated thoroughly into and around the wound. Entire dose of immunoglobulin is to be infiltrated in and around the wound. Intramuscular (IM) administration is no longer recommended. In case RIg dose (quantity) is insufficient for adequate infiltration of extensive or multiple wound, it may be diluted with normal saline so that all the wounds can be thoroughly infiltrated. If RIg could not be given when antirabies vaccination was began, it should be administered as early as possible but no later than the 7th day after the first dose of vaccine was given. From the 8th day onward, 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/PEP in the past.[8]

Adverse reactions: Include tenderness/stiffness at the injection site, low-grade fever; sensitization may occur after repeated injections.

Active Immunization

Rabies Vaccines

Vaccines are the mainstay for prevention of development of rabies. The nerve tissue vaccines, used earlier, are no longer available due to poor efficacy and life-threatening adverse effect of neuroparalytic reactions.

The currently available vaccines are:

- The cell culture vaccines (CCVs) and include purified chick embryo cell vaccine (PCECV), purified Vero cell rabies vaccine (PVRV); and purified duck embryo vaccine (PDEV).

It is to be noted that all CCVs and PDEV should have potency (antigen content) greater than 2.5 IU per intramuscular dose irrespective of whether it is 0.5 mL or 1.0 mL vaccine by volume.

Efficacy and effectiveness: The vaccines are available in lyophilized form with sterile water as diluent, are stable for 3 years at 2–8°C and should be used within 6 hours of reconstitution. All CCVs 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-exposure prophylaxis/PEP. Studies from many countries in South-East Asia have established the effectiveness of CCVs for both pre-exposure prophylaxis and PEP. In both pre-exposure and post-exposure use, these vaccines induce an adequate antibody response in almost all individuals. Prompt post-exposure use of CCVs combined with proper wound management and simultaneous administration of RIG is almost invariably effective in preventing rabies, even following high-risk exposure. However, delays in starting or failure to complete correct prophylaxis may result in death, particularly following bites in highly innervated regions, such as the head, neck, or hands, or following multiple wounds.[3]

Duration of immunity: The current CCVs possess immunological memory after vaccination, and individuals who had received their primary series 5–21 years previously showed good anamnestic responses after booster vaccination even when antibodies are no longer detectable.[2]

Adverse effects: The main adverse effects are local pain, swelling, and redness and less commonly fever, headache, dizziness, and gastrointestinal side effects. Systemic hypersensitivity reactions in vaccines 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.[2]

Post-exposure Prophylaxis

Post-exposure prophylaxis is a medical urgency and is indicated following a significant contact (discussed in detail below) with any warm-blooded animal. These include dogs, cats, cows, buffaloes, sheep, goats, pigs, donkeys, horses, camels, foxes, jackals, monkeys, mongoose, bears, and others. In case of bites by pet animals, PEP should be started immediately. The vaccination status of the suspect animal should not be the deciding factor when considering to initiate PEP or not when the vaccination status of the animal is questionable. A history of rabies vaccination in an animal is not always a guarantee that the biting animal is not rabid. Animal vaccine failures may occur because of improper administration or poor quality of the vaccine, poor health status of the animal, and the fact that vaccine does not always provide long-lasting protection against rabies infection. Rabies due to rodent bites has not been reported in India till date and PEP is not normally recommended for these bites. PEP should be initiated as soon as possible and should not be delayed till results of lab tests or animal observation is available.

Because rabies is a lethal disease, there are no contraindications for PEP including infants, and pregnant and lactating women. 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 1)**.[2]

TABLE 1: Categories of rabies exposure and recommended postexposure prophylaxis.

Category	*Type of contact*	*Type of exposure*	*Recommended post-exposure prophylaxis*
I	• Touching or feeding of animals • Licks on intact skin	None	None, if reliable case history is available
II	• Nibbling of uncovered skin • Minor scratches or abrasions without bleeding	Minor	Wound management + Antirabies vaccine

Contd...

Contd...

Category	*Type of contact*	*Type of exposure*	*Recommended post-exposure prophylaxis*
III	• Single or multiple trans-dermal bites or scratches, licks on broken skin • Contamination of mucous membrane with saliva (i.e. licks)	Severe	Wound management + Rabies immunoglobulin + Antirabies vaccine

NB: Bites from unidentified animal is classified as category III.

Schedule of Vaccination

The standard schedule is a 4-dose schedule on days 0-3-7-14 to 28 days. A regimen of 4 doses of available anti-rabies vaccine should be administered IM to previously unvaccinated persons. The first dose of the four-dose course should be administered as soon as possible after exposure. This date is then considered day 0 of the PEP series. Additional doses should then be administered on 3, 7 and 14 to 28 days after the first vaccination.

A reduced, four-dose vaccine schedule (1-1-1-1-0) for healthy people is supported by the peer-reviewed literature, unpublished data, epidemiological reviews, and expert opinion. This shortened Essen regimen, consisting of one dose on each of days 0, 3, 7, and 14, may be used as an alternative for healthy, fully immune competent, exposed people provided that they receive wound care plus rabies immunoglobulin in category III as well as in category II exposures and a WHO-prequalified rabies vaccine.[9]

Most interruptions in the vaccine schedule do not require reinitiation of the entire series. For most minor deviations from the schedule, vaccination can be resumed as though the patient were on schedule. For example, if a patient misses the dose scheduled for day 7 and presents for vaccination on day 10, the day 7 dose should be administered that day and the schedule resumed, maintaining the same interval between doses. In this scenario, the remaining doses would be administered on days 17 and 31. The dose is same at all ages and is 1 mL IM for HDCV, PCEV, PDEV, and 0.5 mL for PVRV.

Alternative 4-day Schedule, if an Accelerated Response is Considered Necessary

As an alternative, the 2-1-1 regimen (Zagreb schedule) may be used. Two doses are given on day 0 in the deltoid muscle, right and left arm. In addition, one dose in the deltoid muscle on day 7 and one on day 21 are administered. This schedule is, however, not approved for use in India.

Any of the CCVs may be used intramuscularly in anterolateral thigh or the deltoid. Rabies vaccine should never be injected in the gluteal region. 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 days 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.

Intradermal Vaccination

Intradermal vaccination is a cost-effective alternative to intramuscular vaccination as the dose required is only 0.1 mL irrespective of reconstituted volume (0.5 mL or 1 mL for IM route). Only two of the three WHO-prequalified vaccines—purified Vero cell rabies vaccine and purified chick embryo cell vaccine—have been shown to be safe and effective when administered intradermally at a dose of 0.1 mL in a WHO-recommended pre-exposure prophylaxis or PEP regimen.[10] The intradermal schedules have been used successfully in Thailand, Philippines, and Sri Lanka.[8-10] The unit dose of 0.1 mL for intradermal should have at least 0.25 units.[11]

Based on WHO recommendation and results of various safety, efficacy studies and feasibility trial conducted by ICMR, Drug Controller General of India (DCGI) approved the use of intra-dermal vaccination regimen for rabies post-exposure prophylaxis. In India too, it is being used for more than 10 years in Govt sector but not in private sector. The recommended ID schedule for PEP is 2-sites ID on days 0, 3 and 7. Another schedule not currently approved by DCGI is the 8-site regimen (8-0-4-0-1-1; eight intradermal doses on

each upper arm, each lateral lower abdominal quadrant, each thigh, and each suprascapular region on day 0; four doses on day 7 on each thigh and upper arm; and one dose on days 30 and 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. Latest WHO guidelines recommend 2-sites ID on days 0, 3 and 7 as PEP.

The criteria for selection of antirabies center for ID use are:

- Attendance of minimum 50 patients per day for PEP
- Has adequately trained staff to give ID inoculation
- 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.

Postexposure Prophylaxis of Immunocompromised Patients

Several studies of patients with human immunodeficiency virus/acquired immunodeficiency syndrome have reported that those with low CD4 (<200 counts) will mount a significantly lower or no detectable neutralizing antibody response to rabies. In such patients and those in whom the presence of immunological memory is no longer assured as a result of other causes, proper and thorough wound management and antisepsis accompanied by local infiltration of RIG followed by antirabies vaccination are of utmost importance. Even immune-compromised patients with category II exposures should receive RIG in addition to a full postexposure vaccination. Preferably, if the facilities are available, antirabies antibody estimation should be done 10 days after the completion of course of vaccination.

Postexposure prophylaxis in previously vaccinated children: Children who have received previously full rabies PEP or pre-exposure vaccination (either IM or ID route) with CCV/PDEV should be given only two booster doses, either intramuscularly (0.5 mL/1 mL) or

intradermally (0.1 mL at a single site only, using ID compliant vaccine) on days 0 and 3. This is given irrespective of the duration of previous vaccination except if complete PEP or PrEP already received within 3 months previously. In these situations, treatment with RIg is not necessary. As always, proper wound toilet should be done. In case of travelers who cannot come for the second visit, a single-visit four-site (0.1 mL × 4 ID sites, two deltoids and two suprascapular or thighs) ID booster may be given as per WHO recommendation.[2]

Pre-exposure Prophylaxis

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

- *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, and forest staff.
- *Infrequent exposure*:
  - Postmen, policemen, and courier boys
  - Travelers to rabies endemic countries particularly those who intend to backpack/trek.

Most Indian children are at risk for rabies. Therefore, Advisory Committee on Vaccines and Immunization Practices (ACVIP) 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. For immunologically naive individuals of all age groups WHO currently recommends the following PrEP schedules: a 2 sites ID or a 1-site IM vaccine administration on days 0 and 7. A routine PrEP booster or serology for neutralizing antibody titres is recommended only if a continued, high risk of rabies exposure remains.

Routine assessment of antirabies 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-exposure prophylaxis or PEP, 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.

Public Health Perspective

Rabies is not a notifiable disease and the deaths reported by national authorities represent mainly the deaths reported from hospitals. Further atypical paralytic cases are likely to remain undiagnosed. As such, number of deaths due to rabies may be many times more than the reported numbers. Rabies is endemic in all states of India except Andaman, Nicobar, and Lakshadweep Islands. Although all age groups are susceptible, rabies is most common in children aged <15 years.[2] Children are also at high risk, as they are likely to have contact with stray or community-owned animals while playing outside and may not be able to ward off aggressive animals as easily as an adult.

There are no estimates of number of dogs and cats in India. In an epidemiological study about 17% of households reported having a pet/domesticated dog and the pet dog:man ratio was 1:36. Pet dog care/management practices were not satisfactory with a low veterinary consultation (35.5%) and vaccination (32.9%). A high proportion of bite victims did not wash their wounds with soap and water (39.5%). The recourse to indigenous treatment (45.3%) and local application to wound (36.8%) was quite prevalent.[12]

Currently, a few activities are underway to prevent rabies occurrence in humans and to control rabies in dogs, even when the number of human deaths, especially involving children is high. Further, most of the patients do not receive the necessary RIg because

Rabies vaccines.

- Only modern tissue culture vaccines (MTCVs) and intramuscular (IM) routes are recommended for both "postexposure" and "pre-exposure" prophylaxis in office practice.
- Postexposure prophylaxis is recommended following a significant contact with dogs, cats, cows, buffaloes, sheep, goats, pigs, donkeys, horses, camels, foxes, jackals, monkeys, mongoose, bears, and others. Rodent bites do not require postexposure prophylaxis in India.
- Postexposure prophylaxis:
  - Modern tissue culture vaccines are recommended for all category II and III bites.
  - *Dose*: 1.0 mL IM in anterolateral thigh or deltoid (never in gluteal region) for purified chick embryo cell (PCEC) vaccine, purified duck embryo vaccine (PDEV); 0.5 mL for purified Vero cell rabies vaccine (PVRV). Intradermal (ID) administration is not recommended in individual practice.
  - *Schedule*: 0, 3, 7 and 14–28 days with "0" being the day of commencement of vaccination. An additional dose on day 90 is optional and may be offered to patients with severe debility or those who are immunosuppressed.
  - Rabies immunoglobulin (RIg) along with rabies vaccines are recommended in all category III bites.
  - Equine rabies immunoglobulin (ERIg) (dose 40 U/kg) can be used if human rabies immunoglobulin is not available.
- Pre-exposure prophylaxis:
  - Two doses as a 1-site IM vaccine administration on days 0 and 7 on deltoid or anterolateral thigh.
  - For re-exposure >3 months after completed (and documented) pre- or post-exposure prophylaxis, two doses are given on days 0 and 3.
  - Rabies immunoglobulin should not be used during reexposure therapy.

of a perennial global shortage and because of its high price, so that it is unaffordable and not easily available at all places.

Canine rabies can be eliminated, as demonstrated in North America, Western Europe, Japan, and many areas of South America and parts of Asia. It is, however, still widespread, occurring in over 80 countries and territories, predominantly in the developing world.[7] In the current scenario, it is unlikely that in India, national dog rabies control would be instituted in foreseeable future.

Mass vaccination campaigns targeting dogs constitute the principal strategy for rabies control by interrupting RABV transmission between dogs and reducing transmission to humans and other mammals. This strategy has been effective in different settings in Africa, Asia, Europe,

and the Americas. However, successful rabies control also depends on measures such as managing the dog population, mainly by promoting responsible dog ownership; compulsory notification of rabies in humans and animals; ensuring the availability of reliable diagnostic procedures; conducting postmortem examinations to confirm the cause of death in people suspected to have been infected with rabies, etc.[2] These prerequisites are not feasible to fulfil by public health department of the country, which is nonexistent in almost all states. Hence, this is not a doable option, and under the circumstance, ACVIP is of the opinion that universal pre-exposure vaccination especially for children could reduce the number of human rabies dramatically. Use of intradermal vaccination would bring down the vaccine cost for the program substantially.[13]

Rabies Vaccine Booster Doses in Exposure of Previously Vaccinated Individuals

Several studies have indicated that persons who have previously received complete pre-exposure prophylaxis or PEP will elicit an anamnestic response (rapid appearance of antibodies) to one or more booster doses of rabies vaccine even if the initial series of vaccination was administered several years previously.

Based on the aforementioned text if reexposed persons who have previously received and documented full pre-exposure prophylaxis or PEP (either by IM or ID route) with a cell-culture vaccine or PDEV should now be given only two booster doses intramuscularly on days 0 and 3. Proper wound toilet should be done. Treatment with RIg/monoclonal antibodies is not required.

REFERENCES

1. Assessing Burden of Rabies in India, WHO sponsored national multi-centric rabies survey. Association for Prevention and Control of Rabies in India. May 2004. [online] Available from: http://rabies.org.in/rabies/wp-content/uploads/2009/11 /whosurvey.pdf. [Last Accessed October 2019].
2. Rabies vaccines. WHO position paper. Wkly Epidemiol Record. 2010;85:309-20.
3. Tarantola A. Four thousand years of concepts relating to rabies in animals and humans, its prevention and its cure. Trop Med Infect Dis. 2017;2(2):5.

4. Suraweera W, Morris SK, Kumar R, et al. Deaths from symptomatically identifiable furious rabies in India: a nationally representative mortality survey. PLoS Negl Trop Dis. 2012;6(10):e1847. [online] Available from: http://www.plosntds.org/article/info%3Adoi%2F10.1371%2Fjournal.pntd.0001847. [Last Accessed October 2019].
5. WHO Expert Consultation on Rabies, third report: WHO Technical Series Report No. 1012, Geneva, 2018 (ISBN 978-92-4-121021-8).
6. Gogtay NJ, Munshi R, Ashwath Narayana DH, et al. Comparison of a novel human rabies monoclonal antibody to human rabies immunoglobulin for postexposure prophylaxis: a phase 2/3, randomized, single-blind, noninferiority, controlled study. Clin Infect Dis. 2018;66(3):387-95.
7. WHO Expert Consultation on Rabies: first report. Geneva, World Health Organization, 2005. WHO Technical Report Series, No. 931. [online] Available from: http://whqlibdoc.who.int/trs/WHO_TRS_931_eng.pdf. [Last Accessed October 2019].
8. Manual on RIG administration. Association for prevention and control of rabies in India. Bangalore, 2009. [online] Available from: http://rabies.org.in/rabies/wp-content/uploads/2009/11/Manual-on-Rabies-Immunoglobulin-Administratio.pdf. [Last Accessed October 2019].
9. Rupprecht CE, Briggs D, Brown CM, et al. Use of a reduced (4-dose) vaccine schedule for postexposure prophylaxis to prevent human rabies: recommendations of the advisory committee on immunization practices. MMWR Recomm Rep. 2010;59(RR-2):1-9.
10. WHO Technical Report Series 982. WHO Expert Consultation on Rabies. Second report 2013. [online] Available from: http://apps.who.int/iris/bitstream/10665/85346/1/9789241209823_eng.pdf. [Last Accessed October 2019].
11. Briggs DJ, Banzhoff A, Nicolay U, et al. Antibody response of patients after postexposure rabies vaccination with small intradermal doses of purified chick embryo cell vaccine or purified Vero cell rabies vaccine. Bull World Health Organ. 2000;78(5):693-8.
12. Quiambao BP, Dimaano EM, Ambas C. Reducing the cost of post-exposure rabies prophylaxis: efficacy of 0.1 ml PCEC rabies vaccine administered intradermally using the Thai Red Cross post-exposure regimen in patients severely exposed to laboratory-confirmed rabid animals. Vaccine. 2005;23(14):1709-14.
13. Madhusudana SN, Sanjay TV, Mahendra BJ, et al. Comparison of safety and immunogenicity of purified chick embryo cell rabies vaccine (PCECV) and purified Vero cell rabies vaccine (PVRV) using the Thai Red Cross intradermal regimen at a dose of 0.1 mL. Hum Vaccin. 2006;2(5):200-4.

3.17 CHOLERA VACCINES

Vijay Kumar Guduru

BACKGROUND

Cholera is an important public health problem in developing countries with poor sanitation and hygiene as well as in displaced populations. It occurs over a wider geographic area in India than was previously recognized.

The predominant strain is *Vibrio cholerae* (*V. cholerae*) O1 (classical and El Tor biotype). *V. cholerae* O139 is an emerging strain. Cholera is an extremely virulent disease that can cause severe acute watery diarrhea. Incubation period after ingestion of cholera organisms by contaminated food or water is 12 hours to 5 days. Cholera affects both children and adults and can kill within hours if untreated.

GLOBAL BURDEN

Cholera remains a global threat to public health and an indicator of inequity and lack of social development. Researchers have estimated that every year, there are roughly 1.3–4.0 million cases, and 21,000–143,000 deaths worldwide due to cholera.[1]

After penetrating the mucus layer, *V. cholerae* colonizes the epithelial lining of the gut. Cholera toxin, which is secreted by toxigenic *V. cholerae* O1 or O139, affects the small intestine. The toxin depends on a specific receptor: the monosialosyl ganglioside GM-1. The binding (B) subunit of the toxin attaches to GM-1 and releases the active (A) subunit, which enters the host cell. This activation results in massive loss of intravascular and extracellular fluids and electrolytes.[2]

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.[3]

In a longitudinal community-based surveillance study in urban slums of Kolkata, the overall incidence was around 1.6/1,000 person

years with the highest incidence seen in children below the age of 2 years (8.6/1,000 per year) followed by 6.2 in the age group 2–5 years and 1.2 in those aged above 5 years.[4]

As the World Health Organization (WHO) collaborating Centre for Diarrhoeal Disease Research and Training, the National Institute of Cholera and Enteric Diseases (NICED) received during 1990–2007, a total of 16,624 strains of *V. cholerae* from 24 states, of which 7,225 strains of *V. cholerae* were included for phage typing study. Of the total strains received, 96.5% strains were serotyped as Ogawa and the remaining 3.5% were Inaba. Periodic shifts in the occurrence of Ogawa and Inaba serotypes in a given area are usual phenomenon and are thought to be a consequence of population-level immunity patterns.[5]

Young children living in endemic areas are most affected by the disease, but any age group may suffer. In a prospective study, cholera surveillance was conducted in selected slums in Kolkata, India, Beira, Mozambique, and North Jakarta, Indonesia.[1] Children aged 2–4 years had annualized incidence rates of 8.8/1,000 in Beira, 6.2/1,000 in Kolkata, and 1.2/1,000 in North Jakarta. Although these rates were 2–4 times higher than those found in the overall population, children aged <2 years had highest incidence rates of 8.6/1,000 in Kolkata and 3.2/1,000 in Jakarta.[2]

Endemic cholera: Exogenous reintroduction of the pathogen is not required. Endemic disease happens in younger age groups, three of last 5 years suffer from cholera.

Epidemic cholera happens due to exogenous introduction of *V. cholerae*, not recurrent, clinically more severe, and all age groups suffer.[6]

VACCINES

The parenteral killed vaccine which had a 3-month efficacy of 45% is no longer recommended. The killed whole cells of *V. cholerae* 01 and recombinant cholera toxin B subunit (WC-rBS) vaccine available internationally as Dukoral oral vaccine and widely used in travelers

is a vaccine comprising of killed *V. cholerae* O1 with recombinant B subunit of cholera toxoid. Because of similarity in the structure and functions of the cholera toxin B, this vaccine provides cross-protection against enterotoxigenic *Escherichia coli* (*E. coli*). However, this vaccine is no longer marketed in India and not produced any more.[7]

The variant WC-rBS vaccine first developed and licensed in Vietnam comprises only killed whole-cell *V. cholerae* O1 (classical and El Tor) and *V. cholerae* O139. There is no recombinant beta-subunit toxoid and will therefore not protect against enterotoxigenic *E. coli*. This inexpensive oral vaccine is administered as two doses 2 weeks apart and protection starts about 1 week after the last scheduled dose. A booster dose is recommended after 2 years. The vaccine has been demonstrated to have 50% efficacy for up to 3 years after vaccination. This vaccine (Shanchol™) is now manufactured and licensed in India for children above the age of 1 year. It is provided in a single dose vials and does not require a buffer or water for administration, although water may be given. The vaccine has a shelf-life of 2 years at 2–8°C. The vaccine has a good safety profile.[8]

This vaccine is available as mORCVAX in Vietnam and Euvichol in Korea.

Shanchol™ as programmatic vaccine to control stable endemic cholera disease in rural India has conferred efficacy of 69% and 53% in Bangladesh.[6]

Efficacy and Effectiveness

A randomized double-blind immunogenicity trial with this vaccine in Kolkata demonstrated fourfold rise in titers in 53% of adults and 80% of children with response to O139 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 up to 2 years after vaccination and 3 years efficacy is 65%. Subsequent study by the same authors has also shown that the cumulative efficacy at 5 years is also 65%.[9] No adverse effects were noted.

Parenteral vaccines are under development.

Recommendations for Use

Public Health Perspectives

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 years old population would be highly cost-effective.

Individual Use

The Indian Academy of Pediatrics-Advisory Committee on Vaccines and Immunization Practices (IAP-ACVIP) has included the cholera vaccine in the category of vaccines to be used under special circumstances only. 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 second dose **(Box 1)**.

BOX 1: Recommendations for use of cholera vaccine.

- *Minimum age*: One year [killed whole cell *Vibrio cholerae* (Shanchol™)]
- Not recommended for routine use in healthy individuals; recommended only for the vaccination of persons residing in highly endemic areas and travelling to areas where risk of transmission is very high like Kumbh Mela, etc.
- Two doses 2 weeks apart for >1 year old.

REFERENCES

1. Ali M, Nelson AR, Lopez AL, et al. Updated global burden of cholera in endemic countries. PLoS Negl Trop Dis. 2015;9:e0003832.
2. Cholera vaccines: WHO position paper. Wkly Epidemiol Rec. 2010;85:117-28.
3. Verma R, Khanna P, Chawla S. Cholera vaccine: new preventive tool for endemic countries. Hum Vaccin Immunother. 2012;8:682-4.

4. Deen JL, von Seidlein L, Sur D, et al. The high burden of cholera in children: comparison of incidence from endemic areas in Asia and Africa. PLoS Negl Trop Dis. 2008;2:e173. .
5. Sarkar BL, Kanungo S, Nair GB. How endemic is cholera in India? Indian J Med Res. 2012;135:246-8.
6. Clemens JD, Desai SN, Quadri F, et. al. Cholera vaccines. In: Plotkin S, Orenstein W, Offit P, Edwards KM (Eds). Plotkin's Vaccines, 7th edition. New York: Elsevier; 2017. pp. 185-6.
7. Lopez AL, Clemens JD, Deen J, et al. Cholera vaccines for the developing world. Hum Vaccine. 2008;4:165-9.
8. Mahalanabis D, Lopez AL, Sur D, et al. A randomized, placebo-controlled trial of the bivalent killed, whole-cell, oral cholera vaccine in adults and children in a cholera endemic area in Kolkata, India. PLoS One. 2008;3:e2323.
9. Bhattacharya SK, Sur D, Ali M, et al. 5 year efficacy of a bivalent killed whole-cell oral cholera vaccine in Kolkata, India: a cluster-randomised, double-blind, placebo-controlled trial. Lancet Infect Dis. 2013;13:1050-6.

3.18 YELLOW FEVER VACCINE

Vijay Kumar Guduru

BACKGROUND

Yellow fever (YF) is caused by yellow fever virus (YFV), a single-stranded ribonucleic acid (RNA) virus that belongs to the genus *Flavivirus*. Vector-borne transmission occurs via the bite of an infected mosquito *Aedes* or *Haemagogus spp*. Humans infected with YFV experience the highest levels of viremia and can transmit the virus to mosquitoes shortly before onset of fever and for the first 3–5 days of illness.

Yellow fever is 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. Though YF 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 YF endemic countries.

EPIDEMIOLOGY AND RISK FOR TRAVELERS

Yellow fever is endemic and intermittently epidemic in sub-Saharan Africa and tropical South America. The growth of air travel has diminished the barriers to the spread of YF, posing a threat to regions that have not previously been reached by the disease but are considered receptive, including the Middle East, coastal East Africa, the Indian subcontinent, Asia, and Australia. The risk for travelers to endemic areas of Africa has been estimated as 23.8/100,000/week, in epidemic areas 357/100,000/week.[1]

Data from the US travelers produced an estimate of 0.4–4.3 cases/million travelers to YF endemic areas.[2] Each year, approximately 9 million tourists travel to countries where YF is endemic.[3] A traveler's risk for acquiring YF is determined by various factors, including immunization status, location of travel, season, duration of exposure,

occupational and recreational activities while traveling, and local rate of virus transmission at the time of travel. For a 2-week stay, the risks for illness and death due to YF for an unvaccinated traveler traveling to an endemic area are as follows:[4]

- West Africa are 50 per 100,000 and 10 per 100,000, respectively
- South America are 5 per 100,000 and 1 per 100,000, respectively.

The Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO), and other YF experts recently completed a comprehensive review of available data and revised the criteria and global maps designating the risk of YFV transmission. The new criteria establish four categories of risk for YFV transmission that apply to all geographic areas:

1. Endemic
2. Transitional
3. Low potential for exposure
4. No risk.

Yellow fever vaccination is recommended for travel to endemic and transitional areas. Although vaccination is generally not recommended for travel to areas with low potential for exposure, it might be considered for a small subset of travelers whose itinerary could place them at increased risk for exposure to YFV (such as prolonged travel, heavy exposure to mosquitoes, or inability to avoid mosquito bites).

Based on the revised criteria for YF risk classification, the current maps and country-specific information (YF and malaria information, by country) designate three levels of YF vaccine recommendations: (1) recommended, (2) generally not recommended, (3) and not recommended.[5]

VACCINE

It is a live-attenuated vaccine derived from 17D strain of the virus grown in chick 140 embryo cells. The 17D live YF vaccine has been widely acknowledged as one of the most effective and safe vaccines in use and is the only commercially available YF vaccine.[6]

The vaccine is available as a freeze-dried preparation in single/multidose vials that should be stored at 2–8°C (must not be frozen)

along with sterile saline as diluent. The reconstituted vaccine is heat labile, must be stored at 2–8°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.

Vaccine Safety and Adverse Reactions

About 10-30% of vaccines report mild systemic adverse events like low-grade fever, headache, and myalgias that begin within days after vaccination and last 5–10 days. Severe adverse reactions are rare and include immediate hypersensitivity reactions, characterized by rash, urticaria, bronchospasm, or a combination of these. Anaphylaxis after YF vaccine is reported to occur at a rate of 1.8 cases per 100,000 doses administered.

Serious adverse events following immunization (AEFI) with YF vaccine fall into three categories:

1. *Immediate severe hypersensitivity or anaphylactic reactions*: Anaphylactic reactions have been estimated to occur in 0.8 per 100,000 vaccinations, most commonly in people with allergies to eggs or gelatin.
2. *Yellow fever vaccine-associated neurologic disease (YEL-AND)*: YEL-AND represents a conglomerate of different clinical syndromes, including meningoencephalitis, Guillain-Barré syndrome, acute disseminated encephalomyelitis, bulbar palsy, and Bell's palsy. The onset of illness for documented cases is 3–28 days after vaccination, and almost all cases were in first-time vaccine recipients. YEL-AND is rarely fatal. The incidence of YEL-AND in the United States is 0.8 per 100,000 doses administered. The rate is higher in people aged ≥60 years, with a rate of 1.6 per 100,000 doses in people aged 60–69 years and 2.3 per 100,000 doses in people aged ≥70 years.
3. *Yellow fever vaccine-associated viscerotropic disease (YEL-AVD)*: YEL-AVD is a severe illness similar to wild-type disease, with vaccine virus proliferating in multiple organs and often leading

to multisystem organ failure and death. Since the initial cases of YEL-AVD were published in 2001, more than 50 confirmed and suspected cases have been reported throughout the world. YEL-AVD appears to occur after the first dose of YF vaccine, rather than with booster doses. The onset of illness for YEL-AVD cases averaged 3 days (range 1–8 days) after vaccination. The case-fatality ratio for reported YEL-AVD cases is 65%. The incidence of YEL-AVD in the United States is 0.4 cases per 100,000 doses of vaccine administered. The rate is higher for people aged ≥60 years, with a rate of 1.0 per 100,000 doses in people aged 60–69 years and 2.3 per 100,000 doses in people aged ≥70 years.[5,7,8]

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 < 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 >65 years, and in pregnant and lactating women. The contraindications and precautions to YF vaccine are given in **Table 1**.

TABLE 1: Contraindications and precautions to yellow fever vaccine administration.

Contraindications	*Precautions*
• Allergy to vaccine component • Age < 6 months • Symptomatic human immunodeficiency virus (HIV) infection or CD4 T-lymphocytes < 200 cells/mm^3 (or <15% of total in children aged <6 years)[1] • Thymus disorder associated with abnormal immune-cell function • Primary immunodeficiencies • Malignant neoplasms • Transplantation • Immunosuppressive and immunomodulatory therapies	• Age 6–8 months • Age ≥ 60 years • Asymptomatic HIV infection and CD4 T-lymphocytes 200–499 cells/mm^3 (or 15–24% of total in children aged <6 years)[1] • Pregnancy • Breastfeeding

Recommendations for Use

The vaccine is mandatory for all travelers to YF endemic zones as per the International Health Regulations (IHR). All vaccinees receive an international certificate for vaccination duly dated, stamped, and signed by the center administering the vaccine.

Dosage and Administration

Yellow fever vaccines are given as a single dose (0.5 mL) and the manufacturers recommend that the vaccine can be injected either subcutaneously or intramuscularly. The vaccination site is usually the lateral aspect of the upper part of the arm or the anterolateral aspect of the thigh in babies and very young children.[9]

Endemic countries: In these countries, YF vaccine is given to children at age of 9–12 months at the same time as the measles vaccine. Vaccination should be provided to everyone aged ≥9 months in any area with reported cases.[9]

Travelers to endemic countries: Vaccine should be offered to all unvaccinated travelers aged >9 months, traveling to and from at-risk areas, unless they belong to the group of individuals for whom YF vaccination is contraindicated.[9]

The vaccine is contraindicated in children aged <6 months and is not recommended for those aged 6–8 months, except during epidemics when the risk of infection with the YF virus may be very high.[9]

International Certificate of Vaccination or Prophylaxis

New yellow fever vaccination requirements for travelers:[10,11] Travelers need to check with the destination country's embassy or consulate before departure. Under the revised IHR (2005), in May 2014, the World Health Assembly adopted an amendment to Annexure 7 of the IHR (2005), which stipulates that the period of protection afforded by YF vaccination, and the term of validity of the certificate will change from 10 years to the duration of the life of the person vaccinated. On 11 July 2016, the amended IHR Annexure 7 entered into force and is legally binding upon all IHR States Parties. The revised third edition of the IHR includes this amended text.

Thus, *from 11 July 2016, the certificate of vaccination against YF is valid for the life of the person vaccinated*. This lifetime validity applies automatically to all existing and new certificates, beginning 10 days after the date of vaccination. Accordingly, as of 11 July 2016, revaccination or a booster dose of YF vaccine will not be required for international travelers as a condition of entry into a State Party, regardless of the date that their international certificate of vaccination was initially issued.

Yellow fever is the only disease specified in the IHR for which countries may require proof of vaccination from travelers as a condition of entry under certain circumstances. Likewise, countries may take certain measures if an arriving traveler is not in possession of such a certificate.

Currently, valid IHR international certificates of vaccination are now automatically valid for life of the traveler indicated. Nothing needs to be modified in the certificate; indeed under the IHR, any changes, deletions, erasures, or additions may cause a certificate to be rendered invalid (https://www.who.int/ith/updates/20160727/en/#.XRlhcJGhBL8.gmail)

The current advice by the WHO secretariat for international travelers going to areas in Brazil deemed to be at risk is the following:

- Vaccination against YF at least 10 days prior to the travel. Note that, as per Annexure 7 of the IHR (2005), a single dose of a YF vaccine approved by WHO is sufficient to confer sustained immunity and life-long protection against YF disease. Travelers with contraindications for YF vaccine (children below 9 months, pregnant or breastfeeding women, people with severe hypersensitivity to egg antigens, and severe immunodeficiency) or over 60 years of age should consult their health professional for advice.
- Adoption of measures to avoid mosquito bites.
- Awareness of symptoms and signs of YF.
- Seeking care in case of symptoms and signs of YF, while traveling and upon return from areas at risk for YF transmission.

For 2017, updates on country requirements for the International Certificate of Vaccination or Prophylaxis (ICVP), with proof of vaccination against YF, and the WHO vaccination recommendations

for international travelers, are available on the WHO International Travel and Health website: Annexure 1 and country list. More specific information about requirements for the ICVP, with proof of vaccination against YF, implemented by member states related to the current situation in Brazil in the Region of the Americas is available on the Pan American Health Organization (PAHO) YF website.

India

Any traveler (except infants <9 months old) arriving by air or sea without a certificate is detained in isolation for up to 6 days if that person:

- Arrives within 6 days of departure from an area with risk of YFV transmission
- Has been in such an area in transit (except those passengers and members of flight crews who, while in transit through an airport in an area with risk of YFV transmission, remained in the airport during their entire stay and the health officer agrees to such an exemption)
- Arrives on a ship that started from or touched at any port in an area with risk of YFV transmission up to 30 days before its arrival in India, unless such a ship has been disinsected in accordance with the procedure recommended by WHO, or
- Arrives on an aircraft that has been in an area with risk of YFV transmission and has not been disinsected in accordance with the Indian Aircraft Public Health Rules, 1954, or as recommended by the WHO **(Box 1)**.

The following countries and areas are regarded as having risk of YFV transmission:

- *Africa*: Angola, Bénin, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea, Ethiopia, Gabon, The Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Liberia, Mali, Niger, Nigeria, Rwanda, Senegal, Sierra Leone, Sudan, Togo, and Uganda.
- *Americas*: Bolivia, Brazil, Colombia, Ecuador, French Guiana, Guyana, Panama, Peru, Suriname, Trinidad and Tobago, and Venezuela.

BOX 1: Yellow Fever Vaccin.

- Not for routine vaccination in India
- Only needed for those individuals traveling to sub-Saharan Africa and few tropical South American countries
- A single dose of yellow fever (YF) vaccine is sufficient to confer sustained lifelong protective immunity against YF disease; a booster dose is not necessary
- It is recommended that YF vaccine be given to children at age 9–12 months at the same time as the measles vaccine
- The vaccine is contraindicated in children aged <6 months and is not recommended for those aged 6–8 months, except during epidemics when the risk of infection with the YF virus is very high. Other contraindications for YF vaccination are severe hypersensitivity to egg antigens and severe immunodeficiency
- Preventive mass vaccination campaigns are recommended for inhabitants of areas at risk of YF where there is low vaccination coverage
- Vaccination should be provided to everyone aged ≥9 months, in any area with reported cases. Noting that YF is a live vaccine, a risk-benefit assessment should be undertaken for all pregnant and lactating women
- Vaccine should be offered to all unvaccinated travelers aged ≥9 months, traveling to and from at-risk areas, unless they belong to the group of individuals for whom YF vaccination is contraindicated
- YF vaccine may be administered simultaneously with other vaccines
- Live-attenuated, single-dose vaccine sufficient to confer sustained lifelong protection
- *Dose*: 0.5 mL subcutaneously or intramuscularly in lateral aspect of the upper arm or the anterolateral thigh
- *Minimum age*: 9 months

REFERENCES

1. Khromava AY, Barwick ER, Weld LH, et al. Yellow fever vaccine: an updated assessment of advanced age as a risk factor for serious adverse events. Vaccine. 2005;23:3256-63.
2. Centers for Disease Control and Prevention. Health information for international travel 2003–2004. Atlanta: U.S. Department of Health and Human Services, Public Health Service; 2003.
3. Barnett ED, Wilder-Smith A, Wilson ME. Yellow fever vaccines and international travelers. Expert Rev Vaccines. 2008;7:579-87.
4. Staples JE, Gershman M, Fischer M, et al. Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2010;59:1-27.
5. Centers for Disease Control and Prevention (CDC). (2014). Infectious disease related to travel. [online] Available from http://wwwnc.cdc.

gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/yellow-fever [Last accessed October, 2019].
6. Kay A, Chen LH, Sisti M, et al. Yellow fever vaccine seroconversion in travelers. Am J Trop Med Hyg. 2011;85:748-9.
7. Thomas RE, Lorenzetti DL, Spragins W, et al. Reporting rates of yellow fever vaccine 17D or 17DD-associated serious adverse events in pharmacovigilance data bases: systematic review. Curr Drug Saf. 2011; 6:145-54.
8. Silva ML, Espírito-Santo LR, Martins MA, et al. Clinical and immunological insights on severe, adverse neurotropic and viscerotropic disease following 17D yellow fever vaccination. Clin Vaccine Immunol. 2010;17:118-26.
9. Vaccines and vaccination against yellow fever. WHO position paper—June 2013. Wkly Epidemiol Rec. 2013;88:269-83.
10. World Health Organization (WHO). (2016). New yellow fever vaccination requirements for travelers. [online] Available from https://www.who.int/ith/updates/20160727/en/ [Last accessed October, 2019].
11. World Health Organization (WHO). (2019). Yellow fever Brazil. [online] Available from https://www.who.int/csr/don/11-february-2019-yellow-fever-brazil/en/ [Last accessed October, 2019].

4

CHAPTER

Vaccination of Special Groups

4.1 IMMUNIZATION OF ADOLESCENTS

Pallab Chatterjee

Immune protection induced by vaccines given during infancy wanes over the years.[1,2] This leads to higher than expected incidence of vaccine-preventable diseases in adolescents and young adults. Now vaccines have been developed suitable for administering at adolescent age giving protection against many diseases. Important adolescent vaccines related to pertussis, human papillomavirus (HPV), and meningococcal vaccines are available in many countries including India.[3] Indian Academy of Pediatrics (IAP)-recommended vaccines for adolescents are given in **Table 1**.

SIGNIFICANCE OF ADOLESCENT IMMUNIZATION

Vaccines are offered to adolescents with following aims:

1. To protect them against the diseases that have higher morbidity (hepatitis A, varicella), or higher incidence (mumps, meningococcal infection) during adolescent period.

TABLE 1: IAP recommended vaccines for adolescents (10–18 years).

Vaccine	*Schedule*
Tdap/Td*	10 years
HPV†	9 years

* Tdap preferred to Td, followed by repeat Td every 10 years (Tdap to be used once only).
† Only females, two doses at 0 and 6 months (ages 9–14 years) or 0, 1, or 2 (depending on the vaccine used) and 6 months (above 14 years).
(IAP: Indian Academy of Pediatrics; HPV: human papillomavirus; Td: tetanus and diphtheria; Tdap: diphtheria toxoid and acellular pertussis)

2. For boosting the waning immune responses of certain vaccines administered during infancy/early childhood (measles, pertussis, tetanus, diphtheria, etc.).
3. To take care of the upward shift of epidemiology to right, e.g. Hepatitis A
4. To provide protection against diseases such as cervical cancer appearing during adulthood.
5. As a part of control or elimination projects of some VPDs such as measles elimination, and rubella and congenital rubella syndrome (CRS) control program.
6. The tendency of the adolescents to indulge in certain risky activities such as substance abuse, intravenous administration of drugs, etc., exposing exposes them to certain diseases which are VPDs, e.g. hepatitis B and human papilloma virus (HPV) infection.
7. For travel and abroad study
8. As a catch up who missed the previous opportunities.

PERTUSSIS VACCINATION

Pertussis vaccination in adolescents is of particular interest, as it is known that the humoral and cellular immunity evoked by vaccines tends to wane after some years, and this has been confirmed by immunological and clinical studies in recent years.[4,5] Many factors determine the speed at which the immunity wanes like vaccination schedule and the type of vaccine. Acellular pertussis vaccines have shown to provide shorter-lasting protection than whole-cell pertussis (wP) vaccines.[6] Waning of protection has led to increase in incidence of pertussis in older children and adolescents worldwide. In fact, adolescents have become the main cause of the spread of pertussis in the community and the persistently high incidence of disease in infants, who are at the greatest risk of severe disease because they are not fully vaccinated.[7] Pertussis vaccination in adolescents has many advantages including significant lowering of new cases among vaccinated subjects. A retrospective analysis of pertussis cases reported in the United States between 1990 and 2009 showed that the introduction of diphtheria toxoid and acellular pertussis (Tdap) for adolescents in 2005 was associated with a considerable decrease

in the number of cases involving subjects aged 11–18 years.[8] It is also expected that unvaccinated or partially vaccinated infants may benefit from herd effect due to reduction of circulation of pertussis organism. In Australia, where Tdap was administered to all high school students during the 2008–2009 epidemic, there was a decrease in pertussis case reports involving adolescents and infants aged <6 months.[9]

Adolescents vaccination is also highly cost effective: vaccination of all in 10–19 years age group in the United States in 2005 may prevent 0.4–1.8 million cases of pertussis and lead to 10-year savings of US $0.3–1.6 billion.[10] A detailed account on pertussis immunization through all ages is available in a recent publication.[11]

HUMAN PAPILLOMAVIRUS VACCINE

Human papillomavirus vaccination (HPV) in adolescents also deserves special attention as HPV infection is the most common sexually transmitted infection in humans. HPV is closely associated with the development of various anogenital and oropharyngeal cancers, of which cervical cancer is the most frequent and most infections are acquired very early during adolescence, at the time of initial sexual activities.[12] HPV-related diseases are mainly due to a few types of HPV and three vaccines have been developed for use in many countries. One contains types 16 and 18 (mainly responsible for cervical cancer) and is known as bivalent HPV vaccine, another one has additionally types 6 and 11 (also responsible for anogenital warts), known as quadrivalent HPV vaccine, and the third, a nonavalent vaccine, that over and above types 6, 11, 16, and 18, have types 31, 33, 45, 52, and 58. Extensive trials have shown that all the vaccines are safe and efficacious against precancerous lesions due to types 16 and 18 of HPV in 90–100% of cases.[13]

Regarding the time of administration, it is generally agreed that HPV vaccines should be administered to adolescents before they start to engage in sexual activity.[14] This is due to the fact that HPV vaccines are inactive against the types of HPV previously acquired by a vaccine recipient and because antibody responses are the highest between the ages of 9 and 15 years. There are national differences in the recommendations of the subjects to whom HPV vaccine should

be administered. The most recent recommendation in the United States considers that adolescents of both sexes should be vaccinated at the age of 9–12 years. Either vaccine may be used for females, but only quadrivalent or nonavalent vaccine for males. American experts strongly support the vaccination of males because they think that it provides a direct benefit for the vaccinated subjects, including the prevention of genital warts and anal cancer, and an indirect benefit for females through herd immunity.[14]

However, in Europe and many countries including India, HPV vaccine is only recommended for girls.

CURRENT STATUS OF ADOLESCENT'S IMMUNIZATION

In India, routine immunization given to young children is dismally low. National Family Health Survey 4 (2015–16) shows that only 62.0% children aged 12–23 months are fully immunized. There is also tremendous heterogeneity in state- and district-level immunization coverage in India with immunization coverage ranging from 91.3% in Puducherry to 35.7% in Nagaland.[15] It is thus likely that many children reach adolescent period with no or partial immunization. A large number of adolescents thus are at greater risk of vaccine-preventable diseases as they are more exposed to infection due to greater mobility.

The only VPD which was targeted, till recent past, for adolescents and adults immunization was tetanus. However, with the substitution of Tetanus-Toxoid (TT) with Tetanus-diphtheria (low adult dose) (Td) vaccine and the recent launch of Measles-Rubella vaccination campaign, three more diseases, i.e. measles, rubella and diphtheria have joined tetanus as the vaccine preventable diseases (VPDs) targeted for prevention and control amongst adolescents. Japanese encephalitis vaccine is also offered to adolescents and adults, but only in endemic districts of few states.

Considering that teenage pregnancy rate is very high in the country, catch-up vaccination program of adolescents, especially girls, not only will protect them but will also have a direct role in protecting young infants from diseases like pertussis. IAP recommendations for catch-up immunization in adolescents are given in **Table 2**. There are

TABLE 2: IAP recommendations for catch-up immunization in adolescents.

Vaccine	*Schedule*
MMR	Two doses at 4–8 weeks interval*
Hepatitis B	Three doses at 0, 1, and 6 months†
Hepatitis A	Two doses at 0 and 6 months (prior check for anti-HAV IgG may be cost effective)†,‡
Typhoid TCV®	Single dose
Varicella	Two doses at 4–8 weeks of interval

*One dose if previously vaccinated with one dose.
† Combination of hepatitis B and hepatitis A may be used in 0, 1, and 6 months of schedule.
‡ TCV can be given 4 weeks after pure polysaccharide vaccine.
(IAP: Indian Academy of Pediatrics; IgG: Immunoglobulin G; HAV: Hepatitis A; MMR: measles, mumps, and rubella; TCV: typhoid conjugate vaccine)

TABLE 3: 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	Two doses 5 years apart†
Rabies vaccine 0, 3, 7, and 14 days	As soon as possible after exposure

*Only in endemic area as catch up.
† Maximum number of doses—two.
(PPSV: pneumococcal polysaccharide vaccine)

also special circumstances for adolescents and vaccination schedule for these situations are given in **Table 3**. For adolescents going abroad, information on travelers vaccination can be obtained in Chapter 4.3 and from the Center for Disease Control and Prevention website at following link: http://wwwnc.cdc.gov/travel/.

WHAT IS NEEDED?

Getting adolescents vaccinated, however, is not an easy job who undergo great emotional and psychological development at this stage. A few adolescents seek medical care and that too from diverse set of medical specialties. Even in countries with well-established

TABLE 4: IAP ACVIP-recommended immunization schedule for adolescents, 2018 (with range).

Age ► Vaccine ▼	*7–10 years*	*11–12 years*	*13–18 years*
Tdap	One dose (if indicated)	One dose	One dose (if indicated)
HPV-1	2 doses 0–6 months after 9 years	2 doses 0–6 months till 14 years	Above 15 years: 3 doses 0–1 or 2–6 months
MMR	Complete two-dose series		
Varicella	Complete two-dose series		
Hepatitis B	Complete three-dose series		
Hepatitis A	Complete two-dose series		
Typhoid TCV®	Single dose		
Influenza vaccine	One dose every year		
Japanese Encephalitis vaccine	Catch-up, up to 15 years		
Pneumococcal vaccine 2	See footnote 2		
Meningococcal vaccine 3	See footnote 3		

Range of recommended ages for all children.
Range of recommended ages for catch-up immunization.
Range of recommended ages for certain high-risk groups.

(ACVIP: Advisory Committee on Vaccines and Immunization Practices; IAP: Indian Academy of Pediatrics; MMR: measles, mumps, and rubella; Tdap: diphtheria toxoid and acellular pertussis; HPV-1: human papillomavirus 1; TCV: typhoid conjugate vaccine)
Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines.

vaccination program, it has been difficult to implement second-dose measles, mumps, and rubella (MMR) vaccine to older children and adolescents leading to outbreak of measles.[16]

For a successful adolescent vaccine program, there is a need to sensitize medical professionals, health workers, parents, and importantly adolescents. Currently, the United States is the only country to issue recommendations for adolescent immunization, which is regularly prepared and annually updated since 2005. These recommendations **(Table 4)** highlight the importance of catch-up strategies for adolescents who did not regularly complete

their childhood immunizations as well as the need of vaccination in adolescents of high-risk groups because of underlying chronic disease.[17]

FOOTNOTES

1. HPV vaccines

Routine vaccination:

- Minimum age: 9 years
- HPV4 (Gardasil) and HPV2 (Cervarix) are licensed and available. HPV9 (Gardasil 9) is yet to be available.
- HPV4 and HPV2 are recommended in a two-dose series (0 and 6–12 months) for females aged 9–14 years of age.
- Either HPV4 (0, 2, and 6 months) or HPV2 (0, 1, and 6 months) is recommended in a three-dose series for females aged 15–45 years.
- HPV4 can also be given in a three-dose series for males aged 11 or 12 years, but not yet licensed for use in males in India.
- The vaccine series can be started beginning at age 9 years.

Catch-up vaccination:

- Administer the vaccine series to females (either HPV2 or HPV4) at age 13 through 45 years if not previously vaccinated.
- Administer the second dose 1–2 months after the first dose and the third dose 6 months after the first dose (at least 24 weeks after the first dose).

2. Pneumococcal vaccines

- Pneumococcal conjugate vaccine (PCV) and pneumococcal polysaccharide vaccine (PPSV) both are used in certain high-risk group of children.
- A single dose of PCV may be administered to children aged 6 through 18 years who have anatomic/functional asplenia, human immunodeficiency syndrome infection, or other immunocompromising condition, cochlear implant, or cerebral spinal fluid leak.
- Administer PPSV at least 8 weeks after the last dose of PCV to children aged 2 years or older with certain underlying medical conditions, including a cochlear implant.

- A single revaccination (with PPSV) should be administered after 5 years to children with anatomic/functional asplenia or an immunocompromising condition.

3. Meningococcal vaccine

- Recommended only for certain high-risk group of children, during outbreaks, children residing in endemic zones, and international travelers, including students going for study abroad and travelers to Hajj and sub-Saharan Africa.
- Both meningococcal conjugate vaccines (Quadrivalent MenACWY-D, Menactra® Sanofi Pasteur and monovalent group A, PsA-TT, MenAfriVac® by Serum Institute of India) and polysaccharide vaccines (bi- and quadrivalent) are licensed in India. PsA-TT is not freely available in market.

REFERENCES

1. Hinman AR, Orenstein WA, Schuchat A. Vaccine-preventable diseases, immunizations, and the Epidemic Intelligence Service. Am J Epidemiol. 2011;174(Suppl 11):S16-22.
2. Pichichero ME. Booster vaccinations: can immunologic memory outpace disease pathogenesis? Pediatrics. 2009;124(6):1633-41.
3. Schiller JT, Castellsagué X, Garland SM. A review of clinical trials of human papillomavirus prophylactic vaccines. Vaccine. 2012;30 (Suppl 5):F123-38.
4. Tartof SY, Lewis M, Kenyon C, et al. Waning immunity to pertussis following 5 doses of DTaP. Pediatrics. 2013;131(4):e1047-52.
5. Esposito S, Agliardi T, Giammanco A, et al. Long-term pertussis-specific immunity after primary vaccination with a combined diphtheria, tetanus, tricomponent acellular pertussis, and hepatitis B vaccine in comparison with that after natural infection. Infect Immun. 2001;69(7):4516-20.
6. Clark TA, Messonnier NE, Hadler SC. Pertussis control: time for something new? Trends Microbiol. 2012;20(5):211-3.
7. Cherry JD. Epidemic pertussis in 2012—the resurgence of a vaccine-preventable disease. N Engl J Med. 2012;367(9):785-7.
8. Skoff TH, Cohn AC, Clark TA, et al. Early Impact of the US Tdap vaccination program on pertussis trends. Arch Pediatr Adolesc Med. 2012;166(4):344-9.
9. Quinn HE, McIntyre PB. The impact of adolescent pertussis immunization, 2004–2009: lessons from Australia. Bull World Health Organ. 2011;89(9):666-74.

10. Hay JW, Ward JI. Economic considerations for pertussis booster vaccination in adolescents. Pediatr Infect Dis J. 2005;24(Suppl 6): S127-33.
11. Vashishtha VM, Bansal CP, Gupta SG. Pertussis vaccines: position paper of Indian Academy of Pediatrics (IAP). Indian Pediatr. 2013;50(11): 1001-9.
12. Forman D, de Martel C, Lacey CJ, et al. Global burden of human papillomavirus and related diseases. Vaccine. 2012;30(Suppl. 5): F12-23.
13. Lehtinen M, Dillner J. Clinical trials of human papillomavirus vaccines and beyond. Nat Rev Clin Oncol. 2013;10(7):400-10.
14. American Academy of Pediatrics. Policy Statement. HPV vaccine recommendations. Pediatrics. 2012;129(3):602-6.
15. National Health Profile (NHP) of India – 2018, Government of India, Central Bureau of Health Intelligence, DGHS. Ministry of Health and Family Welfare. [online] Available from http://cbhidghs.nic.in/WriteReadData/1892s/Chapter%203.pdf. [Last accessed September, 2019].
16. Cottrell S, Roberts RJ. Measles outbreak in Europe. BMJ. 2011;342:d3724.
17. Capua T, Katz JA, Bocchini Jr JA. Update on adolescent immunizations: selected review of US recommendations and literature. Curr Opin Pediatr. 2013;25(3):397-406.

4.2 IMMUNIZATION IN SPECIAL SITUATIONS

Digant D Shastri

IMMUNIZATION IN IMMUNOCOMPROMISED

The immunocompromised are in greater need for vaccines as they are more susceptible to infections. But at the same time the immunogenicity or efficacy is lower and risk of adverse effects with live vaccines is higher. However, vaccination in an immunocompromised is rather safe than often perceived.

GENERAL PRINCIPLES FOR IMMUNOCOMPROMISED CHILD

General principles for vaccination of the immunocompromised are:[1-3]

- All inactivated vaccines can be given but immunogenicity and efficacy may be lower.
- In severe immunodeficiency, all live vaccines are contraindicated. In mild or 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.
- Ideally, antibody titers should be checked postimmunization on regular basis, and regular boosters may be administered if needed.
- Higher doses and/or greater number of doses should be given if indicated (hepatitis B), antibody titers should be checked postimmunization on regular basis and regular boosters administered, if needed. For major or contaminated wounds tetanus immunoglobulin (Ig) is required in addition to tetanus toxoid (TT) even if three or more doses of TT have been received in the past.
- Household contacts of immunocompromised should not receive transmissible vaccines such as oral polio vaccine (OPV) but can safely receive other nontransmissible live vaccines such as measles, mumps and rubella (MMR) and varicella. All household contacts should be fully immunized including varicella and influenza to reduce risk of transmission to the immunocompromised.
- Some vaccines including pneumococcal, varicella (depending on degree of immunocompromise), hepatitis A, and inactivated

influenza vaccines should be given. There is at present insufficient data on the safety and efficacy of the rotavirus vaccine in the immunocompromised.

An international panel of experts prepared an evidence-based guideline for vaccination of immunocompromised adults and children. These guidelines are intended for use by primary care and subspecialty providers who care for immunocompromised patients.[4]

HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Children infected by human immunodeficiency virus (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. Generally, cluster of differentiation 4+ (CD4+) counts less than 200 cells/mm^3 is known to elicit minimal or no host response. Even if there is a better antibody response, such antibody response may wane at a faster rate in HIV infected persons. Antiretroviral therapy can improve immune responses to vaccine but not to the levels of an uninfected subject. Live viral and bacterial vaccines pose an enhanced risk for uncontrolled replication of the vaccine strains.

Vaccination is usually safe and effective early in infancy before HIV infection causes severe immune suppression. The duration of protection may be compromised as there is impairment of memory response with immune attrition. In older HIV-1 infected children and adults, the immune response to primary immunization may be less but protective immunity to vaccines received prior to the infection is usually maintained. However, immunity to measles, tetanus, and hepatitis B wanes faster than other antigens.[5]

Indian Academy of Pediatrics (IAP), World Health Organization (WHO), American Academy of Pediatrics (AAP), Advisory Committee on Immunization Practices (ACIP), and Centers for Disease Control and Prevention (CDC) recommend all the live vaccines in asymptomatic HIV-1 infected children except OPV. However, in a symptomatic child, all live vaccines are forbidden, but at times measles/MMR/varicella vaccines may be considered on individual

merit. Yellow fever vaccine is contraindicated in symptomatic but can be given in asymptomatic and those at risk of exposure. For killed vaccines in an HIV infected child, ideally postvaccination monitoring of seroconversion is desirable. In an HIV-infected child, there is a multifold enhanced risk of diseases like tuberculosis, hepatitis (A and B), measles, influenza, varicella, pneumococcal, and meningococcal disease. Hence in such situations a judicious and intelligent decision of the physician is warranted. **Table 1** summarizes IAP recommendations for vaccination of HIV-infected children.

TABLE 1: IAP recommendations for immunization of HIV-infected children.

Vaccine	*Asymptomatic*	*Symptomatic*
BCG	Yes (at birth)	No
DTwP/DTaP/Td/Tdap	Yes, as per routine schedule at 6, 10, 14 weeks, 18 months, and 5 years	
Polio vaccines	IPV at 6, 10, 14 weeks, 12–18 months, and 5 years	
	If indicated IPV to household contacts	
Measles	Yes, at 9 months	Yes, if CD4+ count >15%
MMR	Yes, at 15 months and 5 years	Yes, if CD4+ count >15%
Hepatitis B	Yes, at 0, 1, and 6 months*	Yes, four doses, double dose, check for seroconversion and give regular boosters
Hib	Yes, as per routine schedule at 6, 10, 14 weeks, and 12–18 months	
Pneumococcal vaccines (PCV and PPSV23)	*PCV*: Yes, as per routine schedule at 6, 10, 14 weeks, and 12–15 months *PPSV23*: One dose 2 months after PCV, 2nd dose 5 years after first dose (not more than two doses)	
Inactivated influenza vaccine	Yes, as per routine schedule beginning at 6 months, revaccination every year	
Rotavirus vaccine	Insufficient data to recommend, to be given as per ACIP/WHO recommendations in asymptomatic	
Hepatitis A vaccine	Yes	Yes, check for seroconversion, boosters if needed

Contd...

Contd...

Vaccine	*Asymptomatic*	*Symptomatic*
Varicella vaccine	Yes, two doses at 4–12 weeks interval. Use single antigen vaccine, MMRV in HIV infected children have not been studied**	Yes, if CD4 count ≥15% <5 years for ≥6 months, CD4 count >200/mm^3 for ≥6 months Two doses at 4–12 weeks apart
Vi-typhoid/Vi-conjugate vaccine	Yes, as per routine schedule	
HPV vaccine	Yes (females only), as per routine schedule of 3 doses at 0, 1–2 and 6 months starting at 10 years of age	

* Administer monovalent HepB to newborns before hospital discharge. Normal-weight infants of mothers who are hepatitis B surface antigen (HBsAg)-negative should receive HepB within 24 hours of birth or at discharge, whichever comes first. If mother is HBsAg-positive, administer HepB and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours after birth. If mother's HBsAg status is unknown, administer HepB within 12 hours after birth. Determine mother's HBsAg status as soon as possible and, if HBsAg-positive, administer HBIG as soon as possible. If the infant weighs <2,000 g at birth, do not wait more than 12 hours after birth to administer HBIG. If the infant weighs ≥2,000 g at birth, do not wait more than 7 days to administer HBIG.

** As per ACIP/Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO). If varicella vaccine was given before initiation of combination antiretroviral therapy (c-ART), repeat the doses of varicella vaccine after start of c-ART.

(ACIP: Advisory Committee on Immunization Practices; BCG: Bacille Calmette-Guérin; CD: cluster of differentiation; DTP: diphtheria, tetanus, and pertussis; Hib: Haemophilus influenzae type b; HIV: human immunodeficiency virus; HPV: human papillomavirus; IAP: Indian Academy of Pediatrics; IPV: inactivated poliovirus vaccine; MMR: measles, mumps, and rubella; OPV: oral polio vaccine; PCV: pneumococcal conjugate vaccine; PPSV: pneumococcal polysaccharide vaccine; TT: tetanus toxoid)

CORTICOSTEROIDS/OTHER IMMUNOSUPPRESSIVE THERAPY

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 1 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. Low or moderate doses of systemic corticosteroids or locally administered corticosteroids in children who have a disease (e.g. systemic lupus erythematosus) that in itself is considered to suppress the immune response. The same holds good for those who are receiving immunosuppressant medications other than corticosteroids. These children should not receive live virus vaccines during therapy except in special circumstances.[6]

CANCER CASES ON CHEMOTHERAPY/RADIOTHERAPY

Influence of cancer per se on immune function is minimal and does not contribute to a major extent in inducing immunocompromised state. Total Ig concentrations, specific antibody concentrations to already given vaccines are normal at the time of diagnosis indicating that the effect of cancer on the adaptive immune system is likely to be small.[7] However, chemotherapy for cancer causes major secondary immunodeficiency. The effects of radiotherapy on immune function are likely to be small in comparison to chemotherapy. Vaccination requirements for cancer cases need special consideration as described below.[8]

Highly immunocompromised cancer patients are those who have received chemotherapy and/or radiation therapy within the preceding 3 months, those who have generalized malignancy or hematologic malignancy, and those who have received the equivalent of ≥20 mg prednisone daily for ≥2 weeks, as well as stem cell transplant recipients within 2 years of transplant (or beyond 2 years, if there is ongoing evidence of graft-vs-host disease).

Specific recommendations for children with cancer and their family members:

- Annual inactivated influenza vaccine is the only vaccine recommended for all children during chemotherapy[8,10] whereas hepatitis B vaccine is recommended only for previously unimmunized children with risk of transfusion associated transmission,[11,12]
- Post-treatment reimmunization or catch-up schedule largely depends on the prechemotherapy immunization status.
- Sibling immunization should continue uninterrupted except for oral polio vaccine which needs to be substituted by the injectable vaccine. Inactivated influenza vaccine is recommended and varicella vaccine is encouraged for all contacts including siblings or parents. OPV is contraindicated including pulse polio doses. Sibling should receive inactivated poliovirus vaccine (IPV) and if OPV is either given by mistake or given because there is no other option, then the sibling should remain away from index child for at least 2 weeks.[13,14] Newly diagnosed children with cancer are to receive pneumococcal vaccines as per age (PCV13 and PCV23), if not administered earlier.

The vaccine recommendations in child who has received chemotherapy are shown in **Table 2**.

TABLE 2: Recommendations in children post-chemotherapy.

Vaccines	*Catch-up**	*Those with completed primary schedule**
DPT[15,16]	• *In previously unimmunized children*: If <7 years of age three doses at 0, 1, and 6 months (DwPT or DaPT; if >7 years of age) Tdap first dose followed by Td 2nd and 3rd dose	*In children with previously completed immunization*: Single booster dose (DwPT or DaPT if <7 years of age; Tdap if >7 years of age)
IPV[17,18]	• *In previously unimmunized children*: Two doses of IPV 2 months apart, and the 3rd dose 6 months after the 2nd dose • *But if it is not accessible*: OPV to be given. Upper age limit 5 years.	• *In children with previously completed immunization with IPV*: Single booster dose of IPV • *In children with previously completed immunization with OPV*: Two doses of IPV 1 month apart (*Note*: IPV is the preferred vaccine in these)
HBV[14,18]	• *In previously unimmunized children*: Three doses at 0, 1 and 6 months** • No upper age limit	*In children with previously completed immunization*: Single booster dose
Haemophilus influenzae[11,12]	IAP recommended upper age limit for vaccination is 5 years. *In previously unimmunized children*: • *Age 6–12 months*: Two doses 8 weeks apart, followed by booster at 12 months • *Age 12–15 months*: One dose and booster at 18 months • *Age 15–60 months*: One dose	In children with previously completed immunization: Single booster dose

Contd...

Contd...

Vaccines	*Catch-up**	*Those with completed primary schedule**
Pneumococcal vaccine[18]	Indian Academy of Pediatrics (IAP) recommended upper age limit for vaccination is 5 years. *In previously unimmunized children*: • *Age <1 year*: Two doses of PCV at 4–8 weeks interval followed by a booster dose between 12 months and 15 months age • *Age 1–2 years*: Two doses of PCV 8 weeks apart • *Age 2–5 years*: Single dose of PCV PPSV not recommended	*In children with previously completed immunization*: Single booster dose of PCV. PPSV not recommended
HAV[11,12,15]	• There is no IAP recommended upper age limit for vaccination. *In previously unimmunized children*: Two doses 6 months apart	*In children with previously completed immunization*: Single booster dose
Typhoid[11,13]	*In previously unimmunized children*: • *Age >2 years*: Single dose of Vi polysaccharide vaccine and then every 3 years thereafter • *Alternatively, age >9 months*: Two doses of typhoid conjugate vaccine 2 years apart	• *Age >2 years*: *Single booster dose Vi* polysaccharide *vaccine and then every 3 years thereafter* • Alternatively, single booster of typhoid conjugate vaccine
HPV[9,19]	*In previously unimmunized children*: • *Age 9–14 years*: Two doses 6 months apart in females • *Age >14 years*: Three doses at 0, 1 and 6 months (HPV2) or 0, 2 and 6 months (HPV4) in females Not licensed for use in male children in India	• No data to make any recommendation but single dose may be considered in females
BCG[11,20]	• Indian Academy of Pediatrics recommended upper age limit for vaccination is 5 years • *In previously unimmunized children*: Single dose BCG	• *In children with previously completed immunization*: No dose required

Contd...

Contd...

Vaccines	*Catch-up**	*Those with completed primary schedule**
MMR[11,21]	• No IAP recommended upper age limit for vaccination • *In previously unimmunized children*: Two doses 1–3 months apart	• *In children with previously completed immunization*: Single dose
Varicella[6,19]	• *In children with previous history of chickenpox prior to treatment*: No vaccine needed • *In previously unimmunized children*: – *<13 years age*: Two doses of vaccine >3 months apart – *>13 years age*: Two doses of vaccine >1 months apart	• *In children with previously completed immunization*: Single booster dose
Rotavirus[23]	• IAP recommended upper age limit for vaccination is 8 month of age • *In previously unimmunized children*: Generally child outgrows the maximum permissible age, therefore not indicated	• *In children with previously completed immunization*: Generally child outgrows the maximum permissible age, therefore not indicated
Influenza***	• Read text below****	• Read text below****

BCG VACCINE:
IAP recommended upper age limit for vaccination is 5 years. It is contraindicated during ongoing chemotherapy and can only be given after 6 months of completion of chemotherapy as a single dose in previously unimmunized children. In children with previously completed immunization with visible scar no further doses are recommended.

*Catch-up vaccination for children with cancer should be given 6 months after stoppage of chemotherapy. Exception is HBV and influenza vaccine. No vaccine is recommended while ongoing chemotherapy.

**For HBV vaccine in those previously unimmunized and started on chemotherapy—Unimmunized and who is hepatitis B surface antigen negative, then it is recommended to administer four doses of vaccine at 0, 1, 2 and 12 months at double dosage as well as age appropriate dose of hepatitis B immunoglobulin every 3 months till there is no risk of exposure to blood products.

***No IAP recommended upper age limit for vaccination.
Recommended during ongoing chemotherapy and up to 1 year after completion of treatment: Age 6 months to 9 years—two doses 1 month apart and then single dose every year till indicated. Age >9 years—single dose every year till indicated.[4,5] Recommended time to vaccinate—as soon as the new vaccine is released and available in market. Just before the onset of the rainy season (before June for most of India and before October for some of the southern states).

****Recommendation 1 year after stoppage of chemotherapy—not recommended routinely unless the child continues to have high-risk conditions necessitating influenza vaccination, e.g. chronic cardiac, pulmonary, liver and renal disease, diabetes, human immunodeficiency virus (HIV), etc.

(BCG: Bacille Calmette-Guérin; DPT: diphtheria, pertussis, and tetanus; HAV: hepatitis A virus; HBV: hepatitis B virus; HPV: human papillomavirus; IAP: Indian Academy of Pediatrics; IPV: inactivated poliovirus vaccine; MMR: measles, mumps, and rubella; OPV: oral polio vaccine; PCV: pneumococcal conjugate vaccine; PPSV: pneumococcal polysaccharide vaccine)

Special Situations in Cancer Patients

- *Postexposure prophylaxis for rabies*:[11] Children with cancer undergoing treatment may mount a significantly lower or no detectable neutralizing antibody response to rabies. In such patients in whom the presence of immunological memory is no longer assured as a result of other causes, proper and thorough wound management and antisepsis accompanied by local infiltration of rabies Ig or monoclonal antibody followed by antirabies vaccination are of utmost importance. Even immunocompromised patients with category II exposures should receive passive prophylaxis for rabies in addition to a full postexposure vaccination including the 6th dose on day 90 which is also mandatory.
- *Tetanus prophylaxis in wound management*:[11] All patients presenting with skin wounds or 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. In a child with cancer who is on treatment and who then gets a wound, it can be assumed that the antibody levels are inadequate. So tetanus wound management is as follows:
  - *In a clean, minor wound*: TT booster regardless of immunization status.
  - *All other wounds*: TT + tetanus Ig.
- *Varicella post-exposure prophylaxis*: Children exposed to varicella infection during ongoing chemotherapy should be given prophylaxis with VZIg/IVIg and/or oral acyclovir. Under ideal circumstances VZV IgG levels should be assessed at the time of exposure and children with less than protective levels, varicella zoster immunoglobulin (VZIg) should be offered (Dose 0–5 years 250 mg, 6–10 years 500 mg, 11–14 years 750 mg, ≥15 years 1000 mg given by slow intramuscular injection). Alternatively, human normal immunoglobulin at 0.2 g/kg can be given intravenously, in case both the above are unaffordable high dose oral acyclovir prophylaxis (age <2 years 200 mg QID, 2–6 years 400 mg QID, >6 years 800 mg QID) has to be started from day 7 and continued till day 21 from the time of exposure.[35]

- *Other vaccines*: Other nonlive vaccines like meningococcal vaccine, Japanese encephalitis vaccine, cholera vaccine, and yellow fever vaccine are not recommended by IAP for routine use in healthy children. They also have no specific role in children with cancer during or after treatment. It is recommended to consider special conditions for these vaccines as mentioned in respective vaccination recommendation.

Table 3 indicates quality of evidence and grades of recommendation of vaccines in cancer patients.

TRANSPLANT RECIPIENTS

Hematopoietic Stem Cell Transplants (HSCT)

Recipients of HSCT are like the unimmunized as they have lost all memory responses during marrow ablation. Vaccination requirements for recipients of HSCT cases need special consideration as described below:[4]

- Three doses of tetanus or diphtheria-containing vaccine should be administered 6 months after HSCT. For patients aged ≥7 years, a dose of Tdap vaccine may be administered followed by two doses of Td vaccine.
- Three doses of IPV, *Haemophilus influenzae* type b (Hib), hepatitis B vaccine should be administered 6–12 months after HSCT. If a postvaccination hepatitis B surface antibody (antiHBs) concentration of ≥10 mIU/mL is not attained, hepatitis B vaccine course can be repeated.
- Three doses of pneumococcal conjugate vaccine (PCV) should be administered to adults and children starting at age 3–6 months after HSCT. At 12 months after HSCT, one dose of pneumococcal polysaccharide vaccine 23 (PPSV23) should be given provided the patient does not have chronic graft-versus-host disease (GVHD). For patients with chronic GVHD, a fourth dose of PCV can be given at 12 months after HSCT.
- One dose of influenza (IIV) should be administered annually to persons aged ≥6 months starting 6 months after HSCT and starting 4 months after if there is a community outbreak of influenza. For children aged 6 months to 8 years, who are receiving influenza

TABLE 3: Immunization of patients with cancer in children.

Vaccine	*Prior to or during chemotherapy*		*Starting >3 months postchemotherapy and >6 months post anti-B cell antibodies*	
	Recommendation	*Strength, evidence of quality*	*Recommendation*	*Strength, evidence of quality*
DT, TT, aP, Td, Tdap	U	Weak, low	U	Strong, moderate
Hepatitis B	U	Weak, low	U	Strong, moderate
Hepatitis A	U	Weak, low	U	Strong, very low
Hib	U	Weak, low	U	Strong, moderate
PCV 13	R	Strong, low, very low	U	Strong, low
PPSV23	R >2 years	Strong, low	U	Strong, low
IIV	U	Strong, low to moderate	U	Strong, moderate
IPV	U	Weak, low	U	Strong, low
Meningococcal conjugate	U	Weak, low	U	Strong, low
MMR— live*	X	Strong, moderate	Starting 3 months: U	Strong, low
Varicella— live*	X	Strong, moderate	Starting 3 months: U	Weak, very low
Rotavirus— live*	X	Strong, very low	Not applicable	

Note:
R: Recommended—administer if not previously administered or not current; such patients may be at increased risk for this vaccine-preventable infection.
U: Usual—administer if patient not current with recommendations for dose(s) of vaccine for immunocompetent persons in risk and age categories.
X: Contraindicated
*These live vaccines should not be administered unless the vaccine is otherwise indicated as per updated recommendations and the patient is not immunosuppressed and there will be an interval of >4 weeks prior to initiation of chemotherapy.
Quality of evidence and the grade of recommendation are based on Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.

(DTP: diphtheria, tetanus, and pertussis; Hib: *Haemophilus influenzae* type b; IIV: inactivated influenza virus; IPV: inactivated poliovirus; MMR: measles, mumps, and rubella; PCV: pneumococcal conjugate vaccine; PPSV: pneumococcal polysaccharide vaccine; Td: tetanus and diphtheria toxoids; Tdap: tetanus, diphtheria, acellular pertussis)

Source: Adapted from Reference 4; for details see Reference 4.

vaccine for the first time, two doses should be administered. Influenza vaccine is recommended annually lifelong in post-transplant recipient **(Tables 4 and 5)**.

TABLE 4: Immunization of patients with hematopoietic stem cell transplant (HSCT) in children.

Vaccine	*Pre-HSCT*		*Post-HSCT*	
	Recommendation	*Strength, evidence of quality*	*Recommendation*	*Strength, evidence of quality*
DT, TT, aP, Td, Tdap	U	Strong, low	R; <7 years DTaP; 6 months; 3 doses	Strong, low
DTaP, DT, Td, Tdap	U	U	R; >7 years; 1 dose Tdap, then 2 doses Td; 6 months	Weak, low
Hepatitis B	U	Strong, very low	R; 6 mo; 3 doses	Strong, moderate
Hepatitis A	U	Weak, low	R; 6 months; 2 doses	Weak, low
Hib	U	Strong, moderate	R; 3 months; 3 doses	Strong, moderate
PCV 13	R	Strong, low	R; 3 months; 3 doses	Strong, low
PPSV23	R	Strong, very low	R; >12 months post if no GVHD	Strong, low
IIV**	U	Strong, low	R; 4 months	Strong, moderate
IPV	U	Strong, very low	R; 3 mo; 3 doses	Strong, moderate
Meningococcal conjugate	U	Strong, very low	R; 6 months; 2 doses	Strong, low
MMR— live*	U	Strong, very low	X	Strong, low
Varicella— live*	U	Strong, low	X	Strong, low

Contd...

Contd...

Vaccine	*Pre-HSCT*		*Post-HSCT*	
	Recommendation	*Strength, evidence of quality*	*Recommendation*	*Strength, evidence of quality*
Rotavirus—Live	X	Weak, very low	X	Weak, very low

Note:
R: Recommended—administer if not previously administered or not current; such patients may be at increased risk for this vaccine-preventable infection.
U: Usual—administer if patient not current with recommendations for dose(s) of vaccine for immunocompetent persons in risk and age categories.
X: Contraindicated.
**These live vaccines should not be administered unless the vaccine is otherwise indicated as per updated recommendations and the patient is not immunosuppressed and there will be an interval of >4 weeks prior to initiation of chemotherapy*
***Live attenuated influenza vaccine (LAIV) can be given if HSCT >2 weeks back, if GVHD and household contacts is given LAIV avoid contact between the patients and individual who received LAIV for at least 7 days (CDC ACIP)*
Quality of evidence and the grade of recommendation are based on Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system

(ACIP: Advisory Committee on Immunization Practices; CDC: Centers for Disease Control and Prevention; DTP: diphtheria, tetanus, and pertussis; GVHD: graft versus host disease; Hib: *Haemophilus influenzae* type b; IIV: inactivated influenza virus; IPV: inactivated poliovirus; MMR: measles, mumps, and rubella; PCV: pneumococcal conjugate vaccine; PPSV: pneumococcal polysaccharide vaccine; Td: tetanus and diphtheria toxoids; Tdap: tetanus, diphtheria, acellular pertussis)

Source: Adapted from Reference 4; for details see Reference 4.

- Two doses of meningococcal conjugate vaccine (MCV4) should be administered 6–12 months after HSCT, if the risk of meningococcal disease is high.
- Three doses of human papillomavirus (HPV) vaccine 6–12 months after HSCT for female patients aged 11–26 years may be considered.
- Live vaccines should not be administered to HSCT patients with active GVHD or ongoing immunosuppression. MMR and varicella vaccines should be administered 24 months after transplantation if the HCT recipient is presumed to be immunocompetent.[11,22]

Quality of evidence and the grade of recommendation of vaccines for use in HSCT cases based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) system are given in **Table 4**.

Solid Organ Transplants

The need for immunization in solid organ transplant (SOT) recipients can arise from three factors, each causing a suppression of the immune system: The immunosuppressive activity of the underlying disease (e.g. chronic renal failure), rejection of the organ graft, and the immunosuppressive therapy given after transplantation. Immunizations can be given to candidates awaiting transplantation because the immune response then is more likely to be less suppressed and the patient more likely to respond, after transplantation, or both.[24] Many of the conditions for which patients undergo organ transplantation are at least to some extent immunosuppressive, and vaccinations should be considered early during the disease. In general, standard vaccine series should be given to children awaiting SOT. Recipients of SOTs should complete all immunizations prior to transplant in accelerated schedules if needed. Vaccination with live

TABLE 5: Vaccinations prior to or after solid organ transplant.

Vaccine	*Pre-transplant*		*Post-SOT*	
	Recommendation	*Strength, evidence of quality*	*Recommendation*	*Strength, evidence of quality*
DTaP, Tdap	U	Strong, moderate	U, if not completed pretransplant	Strong, moderate
Hepatitis B	U: Age 1–18 years R: ≥18 years	Strong, moderate Strong, moderate	R, if not completed pretransplant*	Strong, moderate
Hepatitis A	U: Age 12–23 months R: ≥2 years	Strong, moderate Strong, moderate	R, if not completed pretransplant	Strong, moderate
Hib	U	Strong, moderate	U	Strong, moderate
PCV	U: Age ≤5 years R: Age ≥6 years**	Strong, moderate Strong, very low	U: Age 2–5 years R: Age ≥6 years if not administered pretransplant**	Strong, moderate Strong, very low

Contd...

Contd...

Vaccine	*Pre-transplant*		*Post-SOT*	
	Recommendation	*Strength, evidence of quality*	*Recommendation*	*Strength, evidence of quality*
PPSV23	R: Age ≥2 years	Strong, moderate	R: Age ≥2 years, if not administered pretransplant	Strong, moderate
Influenza (IIV)	U	Strong, moderate	U***	Strong, moderate
Polio (IPV)	U	Strong, moderate	U	Strong, moderate
HPV	U: Females 11–26 years	Strong, moderate	U: Females 11–26 years	Strong, moderate
MMR—live	R^: 6–11 months U^^: Age ≥12 months	Weak, very low Strong, moderate	X	Strong, low
Varicella—Live	R#: 6–11 months U^^	Weak, very low Strong, low	X##	Strong, low
Rotavirus—live	U#	Strong, moderate	X	Strong, low

Note:
R: Recommended—administer if not previously administered or not current; such patients may be at increased risk for this vaccine-preventable infection.
U: Usual—administer if patient not current with recommendations for dose(s) of vaccine for immunocompetent persons in risk and age categories.
X: Contraindicated.
*Consider hepatitis B vaccine for hepatitis B-infected liver transplant patients (weak, low)
**For patients aged ≥19 years who have received PPSV23, PCV13 should be administered after an interval of ≥1 year after the last PPSV23 dose (weak, low)
***Inactivated influenza vaccine may be administered to solid organ transplant recipients despite intensive immunosuppression (e.g. during the immediate post-transplant period) (weak, low)
^Administer only if patient is not immunosuppressed and the timing is ≥4 weeks prior to transplant
^^Administer only if patient is nonimmune, not severely immunosuppressed, and the timing is ≥4 weeks prior to transplant
#Administer only if patient is not immunosuppressed and the timing is ≥4 weeks prior to transplant
##Selected seronegative patients with renal or liver transplant have been safely vaccinated

(DTP: diphtheria, tetanus, and pertussis; Hib: Haemophilus influenzae type b; HSCT: hematopoietic stem cell transplant; IIV: inactivated influenza virus; IPV: inactivated poliovirus; MMR: measles, mumps, and rubella; PCV: pneumococcal conjugate vaccine; PPSV: pneumococcal polysaccharide vaccine; Td: tetanus and diphtheria toxoids; Tdap: tetanus, diphtheria, acellular pertussis)

Source: Adapted from Reference 4; for details see Reference 4.

vaccines should be completed at least 4 weeks prior to transplant.[25] It is desirable that seroconversion be documented.

The optimal time to begin vaccine administration after transplantation is not defined. Immunosuppressive therapy is often most intense during the first couple of months and might influence the effect of vaccination. 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 or when antibody levels wane (hepatitis A and B) starting 6 months post-transplant. Annual influenza vaccination is recommended. All household and health care workers (HCW) contacts should be immunized against influenza, measles, rotavirus, and varicella. For details on strength of recommendation and quality of vaccines used in SOT cases **(See Table 5)**.

ASPLENIA OR HYPOSPLENIA

Asplenia or hyposplenia may result from sickle cell disease or radiation therapy involving spleen. Children with asplenia or hyposplenia are at high risk of serious infections with encapsulated organisms. Vaccination with pneumococcal (both conjugate and polysaccharide), Hib, meningococcal, and typhoid vaccines is indicated in addition to all routine vaccines. In patients with planned splenectomy, vaccination should be initiated at least 2 weeks prior to splenectomy for achieving a superior immunologic response. In those who have undergone emergency splenectomy, studies indicate that vaccination done 2 weeks after splenectomy is associated with a superior functional antibody response as compared to vaccination immediately following surgery. All live vaccines may be safely given.[26,27]

CONGENITAL IMMUNODEFICIENCY

In patients with severe B cell immunodeficiency (X-linked agammaglobulinemia) live vaccines including all live bacterial [Bacille Calmette-Guérin (BCG), oral typhoid] and live viral (OPV, MMR, measles, varicella, and live attenuated influenza) are contraindicated.

Measles and varicella vaccines may be given but may be ineffective due to concomitant Ig therapy. Inactivated vaccines may be given but are ineffective. Pneumococcal and Hib are risk specific recommended in such children. 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 inactivated vaccines are ineffective. Risk specific recommended vaccine is pneumococcal and Hib but response is variable. 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 and other vaccines may be safely and effectively given.[28] In phagocyte defects that are undefined or associated with T cell and natural killer (NK) cell dysfunction (such as Chediak-Higashi syndrome, leukocyte adhesion deficiency, and myeloperoxidase deficiency) all live bacterial and viral vaccines are contraindicated but all inactivated vaccines are safe and likely to be effective. Pneumococcal vaccine is specifically recommended.[28]

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 are lower than healthy children and hence if needed higher antigen content/more doses (Hepatitis B) assessment of antibody response and frequent boosters (Hepatitis A and B) are recommended.

It is important to stress the role of hepatitis A vaccine in patients with liver disease and pertussis booster in those with stable neurologic disease. Children with severe cardiac and pulmonary diseases should receive pneumococcal and annual influenza vaccines.[28]

IMMUNIZATION IN CHILDREN WITH HISTORY OF ALLERGY

First time immunization with any vaccine is contraindicated in children with history of serious hypersensitivity or anaphylaxis to any of vaccine components. The package label should always be checked for vaccine constituents which in addition to antigen include stabilizers or buffers, preservatives, antibiotics, and residue from the manufacturing process. Yellow fever vaccine is contraindicated for people who have a history of a severe (anaphylactic) allergy to eggs. People with a history of egg allergy who have experienced only hives after exposure to egg should receive any influenza vaccine (inactivated, recombinant or live attenuated) without specific precautions (except a 15-minute observation period for syncope). People who report having had an anaphylactic reaction to egg (more severe than hives) may also receive any age- and condition-appropriate influenza vaccine (inactivated, recombinant or live- attenuated) in a medical setting and should be supervised by a healthcare provider who is able to recognize and manage severe allergic condition.

Measles and MMR vaccines can also be safely given.

Children with history of any hypersensitivity are at increased risk for allergic reactions with inactivated mouse brain Japanese encephalitis vaccines and thus should be monitored carefully. People with a history of anaphylactic reactions to latex should generally not be given vaccines that have been in contact with natural rubber or latex, either in the vial or in the syringe, unless the benefit of vaccination outweighs the risk of a potential allergic reaction. People with latex allergies that are not anaphylactic in nature may be vaccinated as usual. Children who have had a serious hypersensitivity reaction or 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.[28]

IMMUNIZATION IN RELATION TO ANTIBODY-CONTAINING PRODUCTS (WHOLE BLOOD, PACKED RED CELLS, PLASMA, IMMUNOGLOBULIN)

Live Vaccines

Blood (e.g. whole blood, packed red blood cells, and plasma) and other antibody-containing blood products [e.g. Ig, hyperimmunoglobulin, and intravenous immunoglobulin (IGIV)] can inhibit the immune response to live vaccines such as measles and rubella vaccines for 3 months. The effect of blood and Ig preparations on the response to mumps and varicella vaccines is unknown; however commercial Ig preparations contain antibodies to these viruses. Other live vaccines like Ty21a typhoid, rotavirus, yellow fever, live attenuated influenza vaccine (LAIV), and zoster vaccines may be administered at any time before, concurrent with, or after administration of any Ig, hyperimmunoglobulin, or IGIV.[28] The length of time that interference with injectable live-virus vaccine can persist after the antibody-containing product depends upon the amount of antigen-specific antibody contained in the product. Therefore, after an antibody-containing product is received, live vaccines (other than oral Ty21a typhoid, LAIV, rotavirus zoster, and yellow fever) should be delayed until the passive antibody has degraded **(Table 6)**.

If a dose of injectable live virus vaccine (other than yellow fever and zoster) is administered after an antibody-containing product but at an interval shorter than recommended **(Table 6)**, the vaccine dose should be repeated unless serologic testing is feasible and indicates a response to the vaccine. The repeat dose or serologic testing should be performed after the interval indicated for the antibody-containing product **(Table 7)**. Although passively acquired antibodies can interfere with the response to rubella vaccine, the low dose of antiRho(D) globulin administered to postpartum women has not been demonstrated to reduce the response to the rubella vaccine.[11] Because of the importance of rubella and varicella immunity among women of child-bearing age, the postpartum vaccination of women without evidence of immunity to rubella or varicella with MMR or varicella vaccines should not be delayed because of receipt of antiRho(D) globulin or any other blood product during the last trimester of

TABLE 6: Guidelines for administering antibody-containing products* and vaccines.[28]

Type of administration	*Products administered*	*Recommended minimum interval between doses*	
Simultaneous (during the same office visit)	Antibody-containing products and inactivated antigen	Can be administered simultaneously at different anatomic sites or at any time interval between doses	
	Antibody-containing products and live antigen	Should not be administered simultaneously.† If simultaneous administration of measles-containing vaccine or varicella vaccine is unavoidable, administer at different sites and revaccinate or test for seroconversion after the recommended interval (Table 7)	
Non-simultaneous	Administered first	Administered second	
	Antibody-containing products	Inactivated antigen	No interval necessary
	Inactivated antigen	Antibody-containing products	No interval necessary
	Antibody-containing products	Live antigen	Dose-related†,§
	Live antigen	Antibody-containing products	2 weeks†

*Blood products containing substantial amounts of immunoglobulin include intramuscular and intravenous immunoglobulin, specific hyperimmunoglobulin (e.g. hepatitis B immunoglobulin, tetanus immunoglobulin, varicella zoster immunoglobulin, and rabies immunoglobulin), whole blood, packed red blood cells, plasma, and platelet products.

†Yellow fever vaccine; rotavirus vaccine; oral Ty21a typhoid vaccine; live attenuated influenza vaccine; and zoster vaccine are exceptions to these recommendations. These live, attenuated vaccines can be administered at any time before or after or simultaneously with an antibody-containing product.

§The duration of interference of antibody-containing products with the immune response to the measles component of measles-containing vaccine, and possibly varicella vaccine is dose-related (Table 7).

TABLE 7: Recommended intervals between administration of antibody-containing products and measles or varicella-containing vaccine, by product and indication for vaccination.[28]

Product/indication	*Dose (mg IgG/kg)*	*Route**	*Recommended interval before measles containing vaccine† or varicella vaccine administration (months)*
Tetanus Ig	250 units (10 mg IgG/kg)	IM	3
Hepatitis A Ig	0.02–0.06 mL/kg (3.3–10 mg IgG/kg)	IM	3
Hepatitis B Ig	0.06 mL/kg (10 mg IgG/kg)	IM	3
Rabies Ig	20 IU/kg (22 mg IgG/kg)	IM	4
Varicella Ig	125 units/10 kg (60–200 mg	IM	5
	IgG/kg) maximum 625 units		
Measles prophylaxis Ig			
Standard	0.25 mL/kg (40 mg IgG/kg)	IM	5
Immunocompromised	0.50 mL/kg (80 mg IgG/kg)		6
Blood transfusion			
RBCs, washed	10 mL/kg, negligible IgG/kg		None
RBCs, adenine-saline added	10 mL/kg (10 mg IgG/kg)	IV	3
Packed RBCs (hematocrit 65%)§	10 mL/kg (60 mg IgG/kg)		6
Whole blood (hematocrit 35–50%)§	10 mL/kg (80–100 mg IgG/kg)		6
Plasma/platelet products	10 mL/kg (160 mg IgG/kg)		7

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Product/indication	*Dose (mg IgG/kg)*	*Route**	*Recommended interval before measles containing vaccine† or varicella vaccine administration (months)*
IVIG			
Replacement therapy for immune deficiencies¶	300–400 mg/kg	IV	8
Immune thrombocytopenic purpura treatment	400 mg/kg		8
Postexposure varicella prophylaxis**	400 mg/kg		8
Immune thrombocytopenic purpura treatment	1,000 mg/kg		10
Kawasaki disease	2 g/kg		11
Monoclonal antibody to respiratory syncytial virus (MedImmune)††	15 mg/kg	IM	None
Cytomegalovirus IGIV	150 mg/kg maximum	IV	6

*This table is not intended for determining the correct indications and dosages for using antibody-containing products. Unvaccinated persons might not be protected fully against measles during the entire recommended interval, and additional doses of Ig or measles vaccine might be indicated after measles exposure. Concentrations of measles antibody in an Ig preparation can vary by manufacturer's lot. Rates of antibody clearance after receipt of an Ig preparation also might vary. Recommended intervals are extrapolated from an estimated half-life of 30 days for passively acquired antibody and an observed interference with the immune response to measles vaccine for 5 months after a dose of 80 mg IgG/kg.
†Does not include zoster vaccine. Zoster vaccine may be given with antibody-containing blood products.
§ Assumes a serum IgG concentration of 16 mg/mL.
¶ Measles and varicella vaccinations are recommended for children with asymptomatic or mildly symptomatic HIV infection but are contraindicated for persons with severe immunosuppression from HIV or any other immunosuppressive disorder.
** The investigational VariZIG, similar to licensed varicella-zoster Ig (VZIG), is a purified human Ig preparation made from plasma containing high levels of antivaricella antibodies (IgG). The interval between VariZIG and varicella vaccine is 5 months.
††Contains antibody only to respiratory syncytial virus.
(HIV: human immunodeficiency virus; Ig: immunoglobulin; IM: intramuscular; IV: intravenous; IVIG; intravenous immunoglobulin; RBC: red blood cells)

pregnancy or at delivery. These women should be vaccinated immediately after giving birth and, if possible, tested ≥3 months later to ensure immunity to rubella and measles.[28]

Interference might occur if administration of an antibody-containing product becomes necessary after administration of MMR or varicella vaccines. Usually, vaccine virus replication and stimulation of immunity occurs 1–2 weeks after vaccination. If the interval between administration of any of these vaccines and subsequent administration of an antibody-containing product is <14 days, vaccination should be repeated after the recommended interval **(Tables 6 and 7)** unless serologic testing indicates a protective antibody response.[28]

Inactivated Vaccines

Antibody-containing products interact less with inactivated vaccines, toxoids, recombinant subunit, and polysaccharide vaccines than with live vaccines. Therefore, administering inactivated vaccines and toxoids either simultaneously with or at any interval before or after receipt of an antibody-containing product should not substantially impair development of a protective antibody response [exception is administration of rabies immunoglobulin (RIg) 7 days after rabies vaccine]. The vaccine or toxoid and antibody preparation should be administered at different sites using the standard recommended dose. Increasing the vaccine dose volume or number of vaccinations is not indicated or recommended.[28]

IMMUNIZATION DURING ILLNESS

Immunization during acute illness may lead to lower immunogenicity or vaccine failure. Hence, vaccination should be postponed in a moderate or severe acute illness and parents instructed to return for vaccination when the illness resolves. Vaccination is also postponed to avoid superimposing vaccine reaction on the underlying illness and to mistakenly attribute a manifestation of underlying illness to vaccination. However, vaccination opportunity should not be missed during minor illnesses like upper respiratory tract infections, mild diarrhea, and otitis media.[28]

IMMUNIZATION OF CHILDREN WITH BLEEDING DISORDERS OR THOSE RECEIVING ANTICOAGULANTS

Persons with bleeding disorders such as hemophilia and persons receiving anticoagulant therapy are at increased risk for bleeding after intramuscular (IM) injection. When vaccines recommended to be given only by the IM route are to be given, vaccination can be scheduled shortly after administration of clotting factor replacement.

A 23 gauge or smaller needle should be used for the vaccination and firm pressure without rubbing should be applied to the site for at least 5–10 minutes. Alternately, vaccines recommended for IM injection could be administered subcutaneously to persons with a bleeding disorder if the immune response and clinical reaction to these vaccines are expected to be comparable by either route of injection, such as Hib conjugate vaccine, IPV, pneumococcal polysaccharide vaccine, etc.[28]

IMMUNIZATION IN PREGNANCY

Live vaccines are generally contraindicated in pregnant women. The yellow fever vaccine should be avoided in pregnant women as far as possible. However, if travel is unavoidable, the vaccine should be given as the risks of infection outweigh the risks of vaccination (preferably in the 1st trimester).[29] Measles, MMR, and varicella vaccines are contraindicated in pregnancy and pregnancy should be avoided for 4 weeks after vaccination. However, routine testing for pregnancy prior to immunizing with these vaccines is not recommended. If the vaccine is inadvertently given during pregnancy or pregnancy occurs within 4 weeks of vaccination, termination of pregnancy is not warranted. Small cohort studies show no increased rates of congenital abnormalities in infants born to mothers inadvertently vaccinated in pregnancy. Measles, MMR, and varicella vaccines can be safely given to contacts of pregnant women as these vaccines do not spread from vaccine to contacts. Smallpox vaccine is the only vaccine known to be harmful to the fetus.

All inactivated vaccines may be safely given during pregnancy and readers are referred to the chapters on individual vaccines for recommendations. Important are Td/TT/Tdap vaccines. The IAP ACVIP and CDC ACIP have recommended immunization with Tdap in every pregnancy preferably in the third trimester to reduce the burden of pertussis in young infants.[30,31] Inactivated influenza vaccine and hepatitis B are other vaccines of importance in pregnant women. Pregnant women should not be given LAIV.[6] Rabies vaccine should be administered to pregnant women if indicated and is safe.

Passive immunization with Ig containing preparations is safe in pregnancy. All pregnant women should be evaluated for immunity to rubella, varicella, and hepatitis B and those found susceptible should be vaccinated immediately after delivery. All pregnant women should be tested for hepatitis B virus surface antigen (HbsAg) and if found HBsAg positive should be followed carefully to ensure that the infant receives hepatitis B immunoglobulin (HBIg) and begins the hepatitis B vaccine series no later than 12 hours after birth and completes the recommended hepatitis B vaccine series on schedule.

IMMUNIZATION IN LACTATION

All inactivated vaccines whether conjugated, toxoid, or subunit vaccines are safe in breastfeeding women and pose no harm to the babies. Although live vaccines multiply in the body of the mother, most pose no harm to the babies as they are generally not excreted in breast milk. Rubella vaccine may be excreted in milk but does not infect the baby or if it all causes mild asymptomatic infection. The only exception to live vaccine use is yellow fever vaccine. Transmission of the yellow fever vaccine virus through breast milk and resulting in infantile meningoencephalitis has been described. Hence, yellow fever vaccine should be avoided in breastfeeding mothers. If mandatory, then breastfeeding should be interrupted for the 10 day postvaccination viremic period.[29]

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 and preterm babies after stabilization and preferably at the time of discharge.[32,33] Studies have shown that the take of BCG as assessed by induration following Mantoux test and lymphocyte migration inhibition test (LMIT) is similar in preterm or low birth weight babies whether given at discharge or later.[34] The birth dose of hepatitis B vaccine can be administered at any time after birth in babies weighing 2 kg. However, in babies less than 2 kg that immunogenicity of the birth dose of the vaccine has been shown to be suboptimal in some studies.[32] Hence, the birth dose of hepatitis B vaccine in these babies should be delayed till the age of 1 month. Alternatively, these babies may also be given the first dose of the vaccine at the time of discharge if consistent weight gain is achieved. 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 three more doses at 1, 2, and 6 months are recommended. All other childhood vaccines may be given as per chronologic age if medically stable infant while in hospital except rotavirus vaccine, which should be deferred until discharge from hospital to prevent the potential health care-associated spread of this live vaccine virus and have acceptable safety, immunogenicity, and efficacy. Full dose of the vaccines should be used. Since preterm and low birth weight babies may have low muscle mass, the use of needles with lengths of 5/8 inch or less is appropriate to ensure effective, safe, and deep anterolateral thigh intramuscular administration. As preterm, low birth weight babies have increased susceptibility to infections, vaccines such as PCV, rotavirus, and influenza should be offered if resources permit. Preterm babies are at increased risk of chronic complication from influenza, immunization of babies age appropriate (6 months) as well as immunization of health care personnel handling babies and all household contacts should be considered.[6]

LAPSED IMMUNIZATION/PREPONED 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 PPSV 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.[28]

INTERCHANGIBILITY OF BRANDS

It is preferable and ideal that doses of vaccine in a series should be from the same manufacturer; however, if this is not possible or if the manufacturer of doses given previously is unknown, healthcare personnel should administer the vaccine that they are readily available.

The exception to this is HPV vaccine. Further it is to be kept in mind that there are no robust data for interchangeability of different brands of DTaP vaccines.

CATCH-UP IMMUNIZATION

Vaccination catch up regimens should preferably be individualized. The basic principles are discussed. Any number of vaccines live or inactivated may be given on the same day either singly or as combination vaccines maintaining a gap of 5 cm between different vaccines. Inactivated vaccines can be given at any time in relation to any other live or inactivated vaccines. If not given on the same day, a gap of 4 weeks should be maintained between two live injectable vaccines, especially MMR and varicella and also yellow fever and LAIV. However OPV, rotavirus and oral typhoid vaccines may be given at any time in relation to any live or inactivated vaccine. For catch-up immunization, doses should preferably be given at the minimum possible interval to entail early protection.[28]

REFERENCES

1. Casswall TH, Fischler B. Vaccination of the immunocompromised child. Expert Rev Vaccines. 2005;4:725-38.
2. McFarland E. Immunizations for the immunocompromised child. Pediatr Ann. 1999;28:487-96.
3. Canadian Immunization Guide. (2013). General recommendations and principles. [online] Available from http://www.phac-aspc.gc.ca/publicat/cig-gci/p03-07-eng.php#a7. [Accessed December 2013].
4. Rubin GL, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guidelines for vaccination of the immunocompromised host. Clin Infect Dis. 2014;58:e44-100.
5. Moss W, Halsey N. Vaccination of human immunodeficiency virus-infected persons. In: PlotkinS, Orenstein W, Offit P (Eds). Vaccines, 5th edition. US: Saunders Elsevier Publishers & Distributors; 2008. pp. 1417-30.
6. American Academy of Pediatrics. Immunization in special clinical circumstances. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS (Eds). Red Book: 2018 Report of the Committee on Infectious Diseases, 28th edition. Elk Grove Village, IL: American Academy of Pediatrics; 2009.
7. Martín Ibáñez I, Arce Casas A, Cruz Martínez O, et al. Humoral immunity in pediatric patients with acute lymphoblastic leukaemia. Allergol Immunopathol (Madr). 2003;31:303-10.
8. Mavinkurve-Groothuis AM, van der Flier M, Stelma F, et al. Absolute lymphocyte count predicts the response to new influenza virus H1N1 vaccination in pediatric cancer patients. Clin Vaccine Immunol. 2013;20:118-21.
9. Patel SR, Ortín M, Cohen BJ, et al. Revaccination of children after completion of standard chemotherapy for acute leukemia. Clin Infect Dis. 2007;44:635-42.
10. Shahmahmoodi S, Mamishi S, Aghamohammadi A, et al. Vaccine-associated paralytic poliomyelitis in immunodeficient children, Iran, 1995-2008. Emerg Infect Dis. 2010;16:1133-6.
11. Indian Academy of Pediatrics Committee on Immunization (IAPCOI). Consensus recommendations on immunization and IAP immunization timetable 2012. Indian Pediatr. 2012;49:549-64.
12. Verma R, Khanna P. Hepatitis A vaccine should receive priority in National Immunization Schedule in India. Hum Vaccin Immunother. 2012;8(8):1132-4.
13. Naqvi A, Fadoo Z, Alvi S. Vaccination guidelines for children with cancer and hematopoietic stem cell transplantation living in resource-poor countries. Pediatr Blood Cancer. 2010;54(1):3-7.

14. Katewa S, Sachdeva A. Vaccination in immunocompromised children. IAP Textbook of Vaccines, 1st edition. New Delhi: Jaypee Brothers, 2014.
15. Chowdhury P, Vashishtha VM. Immunisation in special situations. IAP Guidebook on Immunisation (2013-14)—By Advisory Committee on Vaccines and Immunisation Practices (ACVIP), Indian Academy of Pediatrics. Gwalior: National Publishing House.
16. Stenvik M, Hovi L, Siimes MA, et al. Antipolio prophylaxis of immunocompromised children during a nationwide oral poliovaccine campaign. Pediatr Infect Dis J. 1987;6:1106-10.
17. Zignol M, Peracchi M, Tridello G, et al. Assessment of humoral immunity to poliomyelitis, tetanus, hepatitis B, measles, rubella, and mumps in children after chemotherapy. Cancer. 2004;101:635-41.
18. Ghosh N, Mannan MA, Monjur F, et al. Escalated regimen of hepatitis B vaccine in childhood hematological malignancies while on chemotherapy. Southeast Asian J Trop Med Public Health. 2010;41:555-61.
19. Palefsky JM, Gillison ML, Strickler HD. Chapter 16: HPV vaccines in immunocompromised women and men. Vaccine. 2006;24 Suppl 3:S3/140-6.
20. Succi RC, Farhat CK. Vaccination in special situations. J Pediatr (Rio J). 2006;82:S91-S100.
21. Zengin E, Sarper N. Humoral immunity to diphtheria, tetanus, measles, and haemophilus influenzae type b in children with acute lymphoblastic leukemia and response to re-vaccination. Pediatr Blood Cancer. 2009;53:967-72.
22. Cesaro S, Giacchino M, Fioredda F, et al. Guidelines on vaccinations in paediatric haematology and oncology patients. Biomed Res Int. 2014;2014:707691.
23. Lee PI, Chen PY, Huang YC, et al. Recommendations for rotavirus vaccine. Pediatr Neonatol. 2013;54:355-9.
24. Danzinger-Isakov L, Kumar D. Guidelines for vaccination of solid organ transplant candidates and recipients. Am J Transplant. 2009;9(suppl 4):S258-62.
25. L'Hullier AG, Kumar D. Immunizations in solid organ and hematopoeitic stem cell transplant patients: A comprehensive review. Hum Vaccin Immunother. 2015;11:2852-63.
26. Shatz DV, Schinsky MF, Pais LB, et al. Immune responses of splenectomized trauma patients to the 23-valent pneumococcal polysaccharide vaccine at 1 versus 7 versus 14 days after splenectomy. J Trauma. 1998;44:760-5.
27. Price VE, Blanchette VS, Ford-Jones EL. The prevention and management of infections in children with asplenia or hyposplenia. Infect Dis Clin North Am. 2007;21:697-710.

28. Centers for Disease Control and Prevention (CDC). General Recommendations on Immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2019;60:1-61.
29. Imbert P, Moulin F, Mornand P, et al. Should yellow fever vaccination be recommended during pregnancy or breastfeeding? Med Trop (Mars). 2010;70:321-4.
30. Centers for Disease Control and Prevention (CDC). Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women—Advisory Committee on Immunization Practices (ACIP), 2012. MMWR Morb Mortal Wkly Rep. 2013;62:131-5.
31. Vashishtha VM, Kalra A, Bose A, et al. Indian Academy of Pediatrics (IAP) Recommended Immunization Schedule for Children Aged 0 through 18 years—India, 2013 and Updates on Immunization. Indian Pediatr. 2013;50:1095-108.
32. Saari TN, American Academy of Pediatrics Committee on Infectious Diseases. Immunization of preterm and low birth weight infants. Pediatrics. 2003;112:193-8.
33. Thayyil-Sudhan S, Singh M, Broor S, et al. Is zero dose oral polio vaccine effective in preterm babies? Ann Trop Paediatr. 1998;18:321-4.
34. Thayyil-Sudhan S, Kumar A, Singh M, et al. Safety and effectiveness of BCG vaccination in preterm babies. Arch Dis Child Fetal Neonatal Ed. 1999;81:F64-6.
35. Bate J, Chisholm J, Heath PT, Breuer J, Skinner R, Manley S, et al. PEPtalk: postexposure prophylaxis against varicella in children with cancer. Arch Dis Child. 2011;96:841-5.

4.3 VACCINATION STRATEGIES FOR TRAVELERS

Digant D Shastri

For travelers, vaccination offers the possibility of avoiding a number of diseases that may be encountered while international travel. While evaluating the need for vaccination in travelers, it is important to consider not only the incidence rate but also the impact of the respective infection.[1] Immunized travelers will also be less likely to contaminate other travelers or the local population with a number of potentially serious diseases.

Travelers in most countries rarely seek health advice before travel. From a cross-sectional survey in Europe, it is noticed that only 52.1% of responders had sought travel health advice.[2]

The travelers need to know about prevalence of diseases in destination country, magnitude and risk of acquiring the diseases, and means to prevent illness. The risk to a traveler of acquiring a disease also depends on age, immunization status and current health state of traveler, travel itinerary, duration, and style of travel. Based on these factors, healthcare professional has to decide about need for immunizations and/or preventive medication (prophylaxis) and provide advice. Regardless of administration of vaccine/medications, traveler should always follow all possible precautions against infection for avoiding disease.

VACCINATION SCHEDULE

There cannot be a single schedule for the administration of immunizing agents, which may be applicable to all travelers. With considering individual traveler's immunization history, the countries to be visited, the type and duration of travel, and the availability of time for vaccination before departure, a tailored-made schedule should be suggested to travelers.

TIMING OF VACCINATION

Traveler should consult healthcare provider sufficiently in advance before departure about the need of immunization. The time period may vary depending on type of vaccine and number of doses required for immunity to develop. At times, usual vaccination schedule may

have to vary marginally to meet the requirement of the travelers. If full vaccination is not possible, partial vaccination may be done with advice to complete the schedule after reaching the destination country. If multiple live vaccines are to be given, they should be simultaneously at multiple sites, as otherwise inoculation of two live virus vaccines should be separated by at least 4 weeks.

Combination vaccines offer important advantages of compliance because of reduced number of injection and visits.

CHOICE OF VACCINES

Vaccines for travelers include: (1) basic vaccines used in routine immunization programs in all age groups and (2) vaccines that may be advised before travel to countries or areas at risk of these diseases. As per International Health Regulations, vaccination to prevent yellow fever and meningococcal diseases is required for visiting certain countries.[3]

The vaccines that may be recommended or considered for travelers are summarized in **Table 1**.

ROUTINE VACCINATION

Travelers need to have undergone routine immunizations or have a change in the routine immunization schedule as it applies to travelers.[3,4]

Bacillus Calmette–Guérin Vaccine

Bacillus Calmette–Guérin immunization may be considered for travelers planning extended stays in areas of high tuberculosis prevalence and where tuberculin skin testing and appropriate chemoprophylaxis may not be feasible or where primary isoniazid resistance of *Mycobacterium tuberculosis* is high.

Diphtheria, Tetanus, and Whole-cell Pertussis/Diphtheria, Tetanus, and Acellular Pertussis/Diphtheria Toxoid and Acellular Pertussis and its Combination Vaccine

For infants embarking on travel, the primary vaccination series with diphtheria, tetanus, whole cell/acellular pertussis, polio, and *Haemophilus influenzae* type b can be accelerated and can started at

TABLE 1: Vaccines for travelers.

Routine vaccination	• Diphtheria • Hepatitis B • *Haemophilus influenzae* type b • Seasonal influenza • Measles • Mumps • Pertussis • Rubella • Pneumococcal disease • Poliomyelitis (Polio) • *Rotavirus* • Tuberculosis (TB) • Tetanus • Varicella
Selective use for travelers	• Hepatitis A • Typhoid fever • Rabies • Cholera • Japanese encephalitis • Tick-borne encephalitis
Country-specific mandatory vaccines for travelers	• Yellow fever • Meningococcal conjugate • Oral poliovirus vaccines (OPV)

6 weeks of age. For adults who have not previously received a dose of pertussis vaccine, it is recommended that they are offered diphtheria toxoid and acellular pertussis (Tdap) vaccine rather than the tetanus and diphtheria booster dose (Td).

Measles and Measles, Mumps, and Rubella Vaccine

Pan-American Health Organization (PAHO)/World Health Organization (WHO) recommends vaccination against measles and rubella for all travelers visiting countries in the Americas. PAHO also recommends that any resident of the Americas planning to travel to other regions of the world should be protected against measles and rubella prior to departing on their trip. Two doses of measles-containing vaccine measles, mumps, and rubella vaccine (MMR) are recommended for all unimmunized adult travelers who were born in or after 1957 and who are en route to a measles-endemic area, unless

there is serologic proof of immunity or physician documentation of prior measles. Infants aged 6–11 months should have at least one measles-containing vaccine (MCV) dose. Infants vaccinated before age 12 months must be revaccinated on or after the first birthday with two doses of MCV separated by ≥28 days. Preschool children aged ≥12 months should have two MCV doses separated by ≥28 days and school-age children should have two MCV doses separated by ≥28 days.[3,5]

Hepatitis B Vaccine

Travelers including children who will be visiting areas with high levels of endemic hepatitis B infection and are likely to have contact with blood or blood products are recommended pretravel hepatitis B vaccination.

SELECTIVE USE FOR TRAVELERS

Meningococcal Disease

Invasive meningococcal disease, in both endemic and epidemic forms, is the cause of significant morbidity and mortality worldwide. Among the different serogroups of *Neisseria meningitidis*, serogroups A, B, and C account for up to 90% of the disease.[6] In the last few years, there has been a shift in the epidemic pattern of meningococcal disease during the Hajj (pilgrimage) season, with predominance of *N. meningitidis* serogroup W135.

The recommendation for meningococcal vaccine for travelers mainly relates to: (i) travelers to areas with current outbreaks; (ii) travelers particularly <30 years of age who is traveling to the sub-Saharan meningitis belt during the dry season (December–June); (iii) all pilgrims arriving to Saudi Arabia for purposes of Umrah and Hajj;[7] (iv) refugee settings with overcrowding, and persons who travel to work in these settings; (v) individuals with underlying health problems recognized to increase the risk of acquiring meningococcal disease, e.g. functional or anatomic asplenia, terminal complement deficiency, or any other immune-suppressing conditions.

The quadrivalent meningococcal vaccine is already mandatory for Hajj pilgrims. For travelers or pilgrims who have received prior

bivalent meningococcal vaccine, crossover vaccination with the quadrivalent meningococcal vaccine may be justified in view of the seriousness of the W135 problem. Travelers who have already received the conjugate C vaccine need to additionally receive the quadrivalent meningococcal vaccine, if traveling to countries where serogroups other than serogroup C are prevalent.

Yellow Fever

Yellow fever occurs in sub-Saharan Africa and tropical South America, where it is endemic and intermittently epidemic. In rural West Africa, yellow fever virus transmission is seasonal (usually July–October) while that in South America is highest during the rainy season (January–May).[8]

Yellow fever is currently the only disease for which proof of vaccination may be required for travelers as a condition of entry to a State Party under Annex 7 of the International Health Regulations (2005). The 17D live attenuated yellow fever vaccine is the only commercially available vaccine and has been widely acknowledged as one of the most effective vaccine in use.[9] Yellow fever vaccine is contraindicated for infants aged <9 months, those with history of hypersensitivity and for people with acquired immunodeficiency syndrome. A single subcutaneous (or intramuscular) injection of live, attenuated vaccine should be administered 10 days before the travel date. An important change was made in May 2014, when the World Health Assembly adopted an updated annex (Annex 7), which extends the validity of a certificate of vaccination against yellow fever from 10 years to life.

This change came into force on July 11, 2016. The period of validity of the International Vaccination Certificate for yellow fever is life time beginning 10 days after vaccination and immediately after revaccination.[10]

Hepatitis A

Protection against hepatitis A is highly recommended for all nonimmune travelers to areas or with inadequate sanitary facilities in countries where the disease is endemic. As the hepatitis A virus has

long incubation period even if the inactivated vaccine is administered on the day of departure will be protective. One dose of monovalent hepatitis A vaccine administered at any time before departure can provide adequate protection for most healthy people aged ≤40 years. For adults aged >40 years, immunocompromised people, and people with chronic liver disease or other chronic medical conditions planning to depart to an area in <2 weeks should receive the initial dose of vaccine along with immunoglobulin in dose of 0.02 mL/kg.[11] For infants <1 year of age protection may be provided by immune globulin. Since immune globulin provides protection for only 3–5 months, it should be given immediately before departure and would provide protection for only 3–5 months.

Rabies

Countries are categorized as 1 (no risk) to 4 (high risk). In countries or areas belonging to categories 2–4, pre-exposure immunization against rabies is recommended for travelers. Modern rabies vaccines-cell-culture or embryonated egg origin are safer and more effective. Pre-exposure immunization should be considered for: (i) travelers intending to live or work in areas where rabies is enzootic and rabies control programs for domestic animals are inadequate; (ii) travel to area where adequate and safe postexposure management is not available; (iii) travelers with extensive outdoor exposure in rural areas—such as might occur while running, bicycling, hiking, camping, etc. irrespective of the travel duration; (iv) individuals travelling to countries or areas where modern rabies vaccines are in short supply.

A course of two intramuscular injections of modern vaccines of cell-culture vaccine should be administered in schedule of one on each of days 0 and 14, and 7 and 14 Days.

Japanese Encephalitis

Japanese encephalitis (JE) occurs in many Asian countries. The risk varies according to season, destination, duration of travel, and activities. The recommendations for JE vaccine for travelers is for: (i) travelers who plan to spend ≥1 month in endemic areas during the

JE virus (JEV) transmission season; (ii) expatriates who will be based in urban areas but are likely to visit endemic rural or agricultural areas during a high-risk period of JEV transmission; (iii) short-term (<1 month) travelers to endemic areas during the JEV transmission season for travelers with extensive outdoor exposure (camping, hiking, working, etc.); (iv) travelers to an area with an ongoing JE outbreak.[12]

The live attenuated SA 14-14-2 vaccine is widely used in China and in an increasing number of countries within the Asian region, including India, the Republic of Korea, Sri Lanka, and Thailand. A Vero cell-derived, inactivated JE vaccine was approved in 2009 in North America, Australia, and various European countries. The vaccine is based on the attenuated SA 14-14-2 JE viral strain, inactivated and alum-adjuvanted. The immunization series should be completed at least 1 week before potential exposure to JEV. For the pretravel prophylaxis, two doses are administered 4 weeks apart.

Typhoid Fever

Vaccine should be recommended to those traveling to destinations where the risk of typhoid fever is high, especially individuals staying in endemic areas for >1 month and/or in locations where antibiotic resistant strains of *Salmonella typhi* are prevalent. The vaccination should be given 1 week before departure. Travelers should be informed that typhoid immunization is not 100% effective and other hygienic measure should be undertaken.

Cholera

Cholera vaccination is not required as a condition of entry to any country. The vaccine should be considered for travelers visiting endemic areas and who are at high risk, e.g. emergency or relief workers. In India, killed bivalent oral O1 and O139 is available. Two doses are given 14 days apart for individuals aged ≥1 year. One booster dose is recommended after 2 years. Whenever to be used the first dose should be administered at least 2 weeks before the departure and for the effective protection, ideally the full course of two doses should be completed before departure.

Polio

As per the Government of India regulation, people traveling from India to polio-endemic countries (Afghanistan, Nigeria, and Pakistan) and those traveling to countries where polio virus is in circulation following importation (Ethiopia, Kenya, Somalia, and Syria) will require to take a dose of oral polio at least 4 weeks before the travel date irrespective of the age. The oral poliovirus vaccines (OPV) vaccination certificate will be issued after additional dose and it will remain valid for 1 year.

Any person of any age residing in any of aforementioned countries traveling to India will be supposed to take a single dose of OPV 4 weeks before the travel date.

VACCINATION FOR IMMUNOCOMPROMISED TRAVELERS

Immunocompromised hosts traveling overseas are at risk for exposure to endemic pathogens. In general, the vaccine response rate in these patients is diminished and they may be more likely to have adverse effects from vaccines containing live attenuated virus. In addition, vaccines are immunomodulatory and may impact immunologic conditions. Immunocompromised hosts planning to travel overseas should be evaluated by a travel medicine specialist familiar with the patient's immunocompromised state and medications.[13,14]

The traveler's immune status is particularly relevant to immunizations. Overall considerations for vaccine recommendations, such as destination and the likely risk of exposure to disease, are the same for immunocompromised travelers as for other travelers. The risk of a severe outcome from a vaccine-preventable disease must be weighed against potential adverse events from administering a live vaccine to an immunocompromised patient. In some complex cases when travelers cannot tolerate recommended immunizations or prophylaxis, the traveler should consider changing the itinerary, altering the activities planned during travel, or deferring the trip.[15]

The travelers who has been on corticosteroid therapy for >2 weeks at a dose equivalent to >20 mg per day of prednisone, should be considered analogous to patients with human immunodeficiency virus (HIV) infection with a CD4 cell count <200 cells/mm^3 and decision of

administration of live vaccines should be taken accordingly. Patients receiving other immunosuppressive drugs should be advised on a case-by-case basis depending on the degree of immune suppression as judged by the prescribing physician.

Asplenic patients and persons with terminal complement deficiencies are susceptible to overwhelming sepsis with encapsulated bacterial pathogens. These groups of people should be immunized with the meningococcal A/C/Y/W-135 conjugate vaccine.[16]

Patients with limited immune deficits or asymptomatic HIV going to yellow fever endemic areas may be offered yellow fever vaccine and monitored closely for possible adverse effects. As vaccine response may be suboptimal, such vaccinees are candidates for serologic testing 1 month after vaccination. Travelers with severe immune compromise should not be vaccinated with yellow fever vaccine and should be strongly discouraged from travel to destinations that put them at risk for yellow fever.

VACCINATION FOR PREGNANT TRAVELERS

No evidence exists of risk from vaccinating pregnant women with inactivated virus, bacterial vaccines, or toxoids. The benefits of vaccinating pregnant women usually outweigh potential risks when the likelihood of disease exposure is high, infection would pose a risk to the mother or fetus, and the vaccine is unlikely to cause harm. Pregnant travelers may visit areas of the world where diseases eliminated by routine vaccination in their native country are still endemic, and therefore may require immunizations before travel. If the pregnant traveler is at risk for influenza on this trip (high season), she should be advised to be vaccinated with inactivated whole virus or subunit influenza vaccine.

VACCINATION DOCUMENT

Travelers should be provided with a written record of all vaccines administered preferably using the international vaccination certificate. This certificate must be signed by the clinician or authorized health worker. The certificate must also bear the official stamp of the

administering center. The certificate should be either in English or in French. However, in addition to these two languages the certificate may also be completed in another language on the same document. The traveler should be advised to carry copy of the certificate. As a proof of yellow fever vaccination, traveler must carry the original International Certificate of Vaccination.

REFERENCES

1. Steffen R, Connor BA. Vaccines in travel health: from risk assessment to priorities. J Travel Med. 2005;12(1):26-35.
2. Van Herck K, Van Damme P, Castelli F, et al. Knowledge, attitudes and practices in travel-related infectious diseases: the European airport survey. J Travel Med. 2004;11(1):3-8.
3. Vaccine preventable diseases and vaccines. International travel and health. [online] Available from: International travel and health, Annex 1—As of 1 July 2019.
4. CDC. Traveller's Health. [online] Available from: http://wwwnc.cdc.gov/travel/destinations/list. [Last Accessed October 2019].
5. Epidemiological Alert: PAHO recommendations to travellers to preserve America without measles or rubella (28/04/2011). [online] Available from: http://www.who.int/immunization/GIN_June_2011.pdf. [Last Accessed October 2019].
6. World Health Organization (WHO). Control of Epidemic Meningococcal Disease: WHO Practical Guidelines, 2nd edition. Geneva: WHO; 1998. p. 1, WHO/EMC/BAC/98.3.
7. Ministry of Hajj. Kingdom of Saudi Arabia. Important notices. Visas. 2010. [online] Available from: http://www.hajinformation.com/main/t1510.htm. [Last accessed on October 2019].
8. Monath TP, Cetron MS. Prevention of yellow fever in persons traveling to the tropics. Clin Infect Dis. 2002;34(10):1369-78.
9. Monath TP, Nichols R, Archambault WT, et al. Comparative safety and immunogenicity of two yellow fever 17D vaccines (ARILVAX and YF-VAX) in a phase III multicenter, double-blind clinical trial. Am J Trop Med Hyg. 2002;66(5):533-41.
10. World Health Organization. Yellow fever vaccine. WHO Position Paper. Wkly Epidemiol Rec. 2003;78(40):349-59.
11. CDC. Update: Prevention of hepatitis A after exposure to hepatitis A virus and in international travellers. Updated recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 2007;56(41):1080-4.

12. Fischer M, Lindsey N, Staples JE, et al. Japanese encephalitis vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2010;59(RR-1):1-27.
13. Boggild AK, Sano M, Humar A. Travel patterns and risk behavior in solid organ transplant recipients. J Travel Med. 2004;11:37-43.
14. Roukens AH, van Dissel JT, de Fijter JW, et al. Health preparations and travel-related morbidity of kidney transplant recipients traveling to developing countries. Clin Transplant. 2007;21:567-70.
15. CDC. Immunocompromised Travellers. [online] Available from http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-8-advising-travelers-with-specific-needs/immunocompromised-travelers. [Last accessed on October 2019].
16. Available from https://mohfw.gov.in/sites/default/files/08285260748Requirement.pdf. [Last accessed October 2019].

5

CHAPTER

Future Vaccines and Vaccine Hesitancy

5.1 FUTURE VACCINES

Balasubramanian S, Sanjay Deshpande

INTRODUCTION

Since the introduction of the first vaccine by Edward Jenner in 1798, vaccination has helped control 14 major diseases—smallpox, diphtheria, tetanus, yellow fever, pertussis, *Haemophilus influenzae* type b disease, poliomyelitis, measles, mumps, rubella, typhoid, rabies, rotavirus, and hepatitis B. In the case of smallpox, complete worldwide eradication was achieved in 1980. Cases of poliomyelitis have been reduced by 99% and it is targeted for eradication in the near future. While rubella and congenital rubella syndrome have been declared as eliminated from the Americas in 2015[1], they still persist in other parts of the world. Eradication of more infectious diseases is imminent as newer vaccines are expected to be introduced in the near future.

NEWER VIRAL VACCINES

Dengue Virus Vaccine

Although there are several dengue vaccine prototypes in clinical development, two live attenuated (recombinant) tetravalent vaccines are currently under evaluation in phase III trials. The first licensed

dengue vaccine, chimeric yellow fever dengue-tetravalent dengue vaccine (CYD-TDV) (Dengvaxia®), is a live attenuated, recombinant tetravalent vaccine, which employs the attenuated yellow fever virus 17D strain as the replicative platform. It is licensed for use in individuals aged 9–45 years in dengue-endemic countries (Mexico, Philippines, and Brazil in December 2015, and in El Salvador, Costa Rica, Paraguay, Guatemala, Peru, Indonesia, Thailand, and Singapore in 2016). The vaccination schedule consists of 3 injections of 0.5 mL, administered subcutaneously at 6-month intervals. Pooled efficacies in trial population aged 2–16 years demonstrated a vaccine efficacy against symptomatic virologically confirmed dengue of any of 60.3% [95% confidence interval (CI): 55.7–64.5]. Vaccine efficacy was higher in the older age groups, with 65.6% (95% CI: 60.7–69.9) for those aged 9–16 years versus 44.6% (95% CI: 31.6–55.0) for those younger than 2–8 years.[2]

Current Recommendations by World Health Organization

Clinical trials have established that the live attenuated dengue vaccine CYD-TDV is efficacious and safe in dengue seropositive individuals. Past infection carries an increased risk of severe dengue in (dengue) seronegative individuals and countries should consider introduction of the vaccine only if the minimization of risk among seronegative population can be assured. It has been recommended that countries considering CYD-TDV as a part of their dengue control program, mandate a pre-vaccination screening tool for evidence of a past dengue infection (based on an antibody test, or on a documented laboratory confirmed dengue infection in the past). If a pre-vaccination screening is not possible, vaccination without individual screening can be considered in areas with recent documentation of seroprevalence rates of at least 80% by age 9 years.[2]

Human Immunodeficiency Virus Vaccine

As there is no complete cure for human immunodeficiency virus-acquired immunodeficiency syndrome (HIV-AIDS), a futuristic vaccine remains one of the major landmarks in battling this worldwide pandemic. There have been short-lived achievements in the development of a safe and efficacious vaccine. Firstly, in

relation to envelope protein-based vaccines not being able to create antibodies capable of neutralizing recently isolated HIV viruses and more recently the fact that clinical trials using the "prime-boost" approach failed to live up to the promise of preclinical research. The failure of the large Merck STEP trial was particularly troublesome. The extraordinary genetic diversity and high mutability rate of the virus and its capacity to "evade and escape" inside lymphoid and macrophage cells represent the herculean task. Nevertheless, the possibility of T cell-based or an antibody-based vaccine holds promise and is the cornerstone of future research.[3]

Recently, a surprising result was reported from phase III trials of the Sanofi-Pasteur vaccine™, which tested a heterologous prime-boost regimen consisting of priming with a canary-pox HIV vector ALVAC-HIV and a booster with a full-length recombinant gp120 envelope protein AIDSVAX B/E.

This RV144 trial in 16,000 Thai subjects showed a 31.2% efficacy (74 seroconversions versus 51). There was, however, no effect on viral load at the set point. This can do no more than give modest encouragement. It will be important to evaluate the immune responses induced and to attempt to estimate correlates of protection.

There are many ongoing phase I and II trials utilizing prime-boost strategies. Another approach aims to identify those conserved regions of the envelope protein to which broadly neutralizing anti-HIV monoclonal antibodies bind. Recently isolated monoclonals have outstanding potency. It is important to realize that the native functional envelope protein is a heterotrimer (gp120) (gp41). It is difficult to reproduce this in a recombinant protein, although recent cryo-electron tomographic analysis of native HIV-1 trimer structure will aid the design of recombinant trimers better mimicking the native HIV-1 spike. Two new broad and potent antibodies, PG 9 and PG 16, bind to conserve residues in the V1/V2 and V3 loops of gp120, and their epitopes are preferentially expressed on trimeric HIV-1 env. Another antibody, VRC 01, targets the CD4-binding site of env, a highly conserved area. The challenge then is to build artificial antigens that resemble, as closely as possible, these targets of powerful, broadly neutralizing antibodies. The rational design of peptides mimicking the correct native conformations is a major challenge for protein chemists.

Another strategy employs to seek to capture the transition state of gp120 instantly after CD4 binding. The molecule undergoes an allosteric change exposing the co-receptor binding site. Mimotopes of this transition stage could prove to be powerful vaccine candidates.

The finding that only one or at most a few virions initiate HIV infection adds to the hope that an AIDS vaccine might be possible. Clearly, prevention does not need to neutralize a massive viral load.[3]

Respiratory Syncytial Virus Vaccine

There has been a tremendous surge in respiratory syncytial virus (RSV) vaccine research in the past 5 years, with more than 60 vaccine candidates in clinical development and more than 20 vaccines in clinical trials as of December 2016.

Table 1 lists the recent efforts to develop safe and effective RSV vaccines for populations at risk, with a primary focus on vaccine candidates currently being evaluated in clinical trials.[1]

Epstein-Barr Virus Vaccine

Epstein-Barr virus (EBV) is a ubiquitous human pathogen that infects at least 90% of the world's population and a large proportion of children. EBV causes infectious mononucleosis, which results in significant school or work absenteeism.

Despite the disease burden attributed to EBV, progress on EBV vaccines has been slow partly due to lack of a suitable animal model other than nonhuman primates, selection of the appropriate antigen and adjuvant, and debate over what such a vaccine could actually achieve protective immunity. An ideal prophylactic vaccine is one which provides neutralizing immunity, meaning that after vaccination, the host can never be infected by the same pathogen. In reality, both live attenuated and subunit viral vaccines do not elicit sterilizing immunity in fact they reduce the severity of disease caused by subsequent natural infection. This is likely true for all vaccines including EBV. There actually could be an advantage to this in that subclinical or mild "reinfection" would likely boost the host's vaccine- induced immunity and potentially extend its duration of protection.

TABLE 1: RSV vaccine candidates.

Type	*Pre-clinical*	*Phase 1*	*Phase 2*	*Phase 3*	*Market approved*
Live attenuated/ Chimeric vaccines	• Sendai virus • RSV • Delta-G RSV • PIV1-3/ RSV • BCG-RSV • SeV/RSV	• RSV LID delta • M2-2 • RSV D46 cp delta M2-2 • RSV cps2 • RSV delta NS2 • Delta 1313 • RSV Medi delta • M2-2			
Inactivated	RSV	–	–	–	–
Particle based	• VLP • Peptide Micro-particle • Nano-rings	• RSV BLP • RSV-F • Nano particle	• RSV-F • Nano particle		
Sub-unit vaccine	• RSV-F Protein • RSV-G • Protein • RSV peptide	• RSV-F protein • DPS-RSV-SH protein	RSV-F protein		
Nucleic acid	• RNA • DNA	–	–	–	–
Gene based vectors	• Adenovirus • Alpha-virus • MVA	Adenovirus	MVA		
Combination/ Immuno-prophylaxis	• DNA prime particle boost • DNA+ protein combo • Anti-F Mab	–	• Anti-F • Mab	• Anti-F • Mab	Synagis

(RSV: respiratory syncytial virus; LID: laboratory of infectious diseases; VLP: virus-like particles; BLP: bacterium-like particle; MVA: modified vaccinia ankara; BCG: Bacillus Calmette-Guérin; SH: small hydrophobic; DNA: deoxyribonucleic acid; RNA: ribonucleic acid)

STATUS OF EPSTEIN-BARR VIRUS VACCINES (TABLE 2)

Prophylactic Epstein-Barr Virus Vaccines Tested in Clinical Trials

- Subunit gp350 vaccines
- CD8+ T-cell peptide epitope vaccine.

TABLE 2: Showing EBV vaccines.

Disease reported	*Clinical trials*	*Comments*
Infectious mononucleosis	*Prophylactic vaccines:* Adjuvanted gp350 vaccine 4 phase; 1 phase I CD8+ T-cell epitope vaccine 1 Phase I	The logical target for further development of a prophylactic vaccine
Nasopharyngeal carcinoma	• Adoptive immunotherapy • *Therapeutic vaccines*: Dendritic cells • Incubated with LMP2 peptides 1; phase I MVA with EBNA-1 and LMP2 (MVA-EL) 2 Phase I	Best data are for MVA-EL vaccine
Post-transplant lympho-proliferative	Adoptive immunotherapy	The second choice as target for further development of a disorder prophylactic vaccine
EBV-positive lymphomas	Adoptive immunotherapy	Clinical trial possible but would be lengthy and require a large number of subjects
Endemic Burkitt's lymphoma	–	Clinical trial feasible in focal areas of East Africa where disease is endemic
Miscellaneous • Chronic active • EBV X-linked lympho-proliferative syndrome • Multiple sclerosis	–	Severity of these entities makes them worthy of gastric carcinoma prophylactic and/or therapeutic vaccine trials

(EBV: Epstein-Barr virus; MVA-EL: modified vaccinia Ankara;)

Epstein-Barr virus is a common human pathogen that causes acute and chronic infections, cancers, and autoimmune disease. Prophylactic and therapeutic vaccines could either reduce the disease burden or prevent them from acquiring the disease itself, but they are not yet available for general use. Partnerships between the public and private sector is essential to find the resources from government, industry, and/or philanthropy to conduct the studies necessary to make effective EBV vaccines available to all those who will benefit from them.

Cytomegalovirus Vaccine

From a public health perspective, the most important medical impact of *Cytomegalovirus* (CMV) is the intrauterine infection of the fetus and its catastrophic, life-long sequelae. Lack of a clearly defined correlate of protective immunity is the major hurdle encumbering CMV vaccine development. As human CMV is a large and complex virus encoding at least 200 proteins, the immune control involves more than one arm of the immune system. Antibodies to virally encoded envelope glycoproteins have also been shown to be protective against congenital guinea pig CMV infection.[1]

Recent years have seen a notable increase in the number of candidate CMV vaccines that are undergoing testing in human trials. They can be broadly grouped into three categories—(1) live attenuated vaccines; (2) subunit vaccines based on recombinant proteins and peptides; and (3) vectored vaccines comprising combinations of key CMV immunogens in various expression systems. These categories are individually reviewed in the following section.

The history of efforts to develop a CMV vaccine has been reviewed. The various gene products and the vaccine candidates are listed in **Tables 3 and 4,** respectively.

HEPATITIS C VIRUS VACCINE

Hepatitis C virus (HCV) is a positive-strand ribonucleic acid (RNA) virus, infecting approximately 185 million people worldwide. HCV infection can potentially progress into liver cirrhosis and hepatocellular carcinoma. Till date no effective vaccine is licensed. Recent approvals of direct-acting antiviral agents (DAAs) that can

TABLE 3: *Cytomegalovirus*-encoded proteins that might be included in a subunit vaccine.

CMV gene product	*Host immune response*
Envelope glycoproteins	
gB	Major target of neutralizing antibodies; target of CTLs
gH/gL	Important target of neutralizing antibodies; target of CTLs
gH, gL, UL128–131	PC of gH/gL/UL128/UL130/UL131 on viral (PC) envelope. Target of neutralizing antibodies; antibodies neutralize CMV infection at epithelial and endothelial cell surfaces
gM/gN	Targets of neutralizing antibody responses
Structural proteins	
pp65	Major target of CTLs; target of non-neutralizing antibody responses
pp150, pp28	Targets of CTLs and non-neutralizing antibody responses
pp50	Target of CTLs
pp71, pp52	Targets of non-neutralizing antibody responses
Nonstructural proteins	
IE1	Major target of CTLs; target of non-neutralizing antibody responses

(CMV: *cytomegalovirus*; CTL: cytotoxic T lymphocyte; IE1: immediate-early antigen 1; PC: pentameric complex)

cure HCV infection are quite promising but concerns loom over therapy accessibility and potential drug resistance. Evolution of viral infections have proven that is it has been difficult to eliminate them by therapeutics alone. Therefore, it is essential to develop an effective prophylactic HCV vaccine.

Though a number of potential HCV vaccines have been developed, none of them have proceeded to the late clinical phases. A major hurdle of HCV vaccine development is induction of protective immunity against this virus, which has a high genomic diversity. It has been reported that recombinant soluble E2 (sE2) of a GT1b strain produced from insect cells could induce neutralizing antibodies in mice and macaques and also protect humanized mice from HCV infection. The E2 antigen production is simple and has a high yield (up

TABLE 4: Status of *Cytomegalovirus* vaccines evaluated in clinical trials.

Live attenuated and disabled virus vaccines	
D169 vaccine	• Elicited CMV-specific antibodies in seronegative vaccine recipients • Significant injection-site and systemic reactogenicity
Towne vaccine (± rhIL12)	• Elicits humoral and cellular immune responses • Favorable safety profile; no evidence for latency or viral shedding in recipients • Reduced CMV disease but not infection in renal transplant recipients • Augmented immunogenicity when administered with recombinant IL-12 in Phase I studies
Towne/Toledo chimera vaccines	• Favorable safety profile; no evidence for latency or viral shedding in CMV seropositive subjects • Attenuated compared to Toledo strain of HCMV No efficacy data available; studies in sero-negatives in progress
V160–001 replication-defective vaccine	AD169 backbone with restoration of UL128/130/131 PC components vaccine • Rendered replication-incompetent by inclusion of ddFKBP/Shld1 • Administered with alum-based adjuvant • Phase I studies ongoing
Subunit vaccine	
Glycoprotein B (CHO cell expression) MF59 (Sanofi)/ AS01 (GSK) adjuvants	• Favorable safety profile • High-titer neutralizing antibody and strong cell-mediated immune responses; augments humoral immunity in seropositives (gB/ MF59) • Demonstrated efficacy in young women against primary infection and against CMV disease in solid-organ transplant patients (gB/MF59) • Safety and immunogenicity demonstrated with gB/AS01 in phase 1 (no efficacy data)
PADRE-pp65-CMV and Tet-pp65- CMV fusion peptide vaccines ± CpG DNA adjuvant	• Lipidated fusion peptides constructed from pp65 CTL epitopes • Linked to either a synthetically derived pan-DR or Tet epitope • Phase I studies ongoing

Contd…

Contd…

eVLP vaccine	
eVLP gB vaccine (HEK cells) ± alum adjuvant	• eVLPs formed by cotransfection of MMLV gag and gB constructs • Extracellular domain fused with transmembrane and cytoplasmic domains of VSV G protein • Phase I studies currently in progress
Vectored vaccines	
Glycoprotein B/canarypox vector	Favorable safety profile • Suboptimal immunogenicity • "Prime-boost" effect upon combined administration with Towne
pp65 (UL83)/canarypox vector	Favorable safety profile • Strong antibody and cell-mediated immune responses
gB/pp65/IE1 trivalent DNA vaccine; adjuvant and benzalkonium chloride gB/pp65 bivalent DNA vaccine	• DNA adjuvanted with poloxamer phase II study with bivalent gB/pp65 vaccine in HSC transplant recipients demonstrates impact on CMV disease • Phase III study of bivalent vaccine ongoing in transplant patients • Trivalent vaccine (gB/pp65/IE1) was evaluated with Towne in prime-boost vaccination study
gB/pp65/IE1 alphavirus replicon • Engineered using replication-deficient alphavirus technology trivalent vaccine	• Generation of virus-like replicon particles • Phase I clinical trial recently reported • Virus-neutralizing antibody and cell-mediated immune responses
gB/pp65 LCMV bivalent vectored vaccine	• Vectored using LCMV backbone vaccine • LCMV GP gene replaced by gB, pp65 • Disabled, single round of replication • No antivector immunity (allows for boosting) • Virus-neutralizing antibody, cellular (CD4+, CD8+) responses

(CMV: cytomegalovirus; CpG: cytosine phosphate guanine; CTL: cytotoxic T lymphocyte cell; HCMV: human cytomegalovirus; IE1: immediate-early antigen 1; IL: interleukin; LCMV: lymphocytic choriomeningitis virus; PC: pentameric complex; rhIL: recombinant human interleukin; DNA: deoxyribonucleic acid).

to 100 mg/L culture supernatants), making it technically possible to explore a multivalent vaccine that consists of E2 of multiple genotypes to increase the antigenic coverage.[4]

A new trivalent vaccine, which contains sE2 from genotype 1a, 1, and 3a elicited stronger pan-genotypic neutralizing antibodies than the monovalent vaccine in mice. Each sE2 component of this trivalent vaccine elicited unique spectrum of neutralizing antibodies, which acted synergistically to inhibit HCV infection.[4] The trivalent vaccine triggered stronger and more uniform multi-genotypic neutralizing antibody responses than the monovalent vaccine in rhesus macaques.

Impact on Clinical Practice in the Foreseeable Future

The trivalent sE2 vaccine is a promising prophylactic HCV vaccine candidate for several following reasons. It induces broad and synergistic-acting neutralizing antibodies in mice and non-human primates. It also induces more uniform neutralizing activity in rhesus macaques, which have varying genetic background. No immunogenic interference between individual sE2 components within the trivalent cocktail was observed. Finally, antigen production can be easily scaled up to the manufacture level.[4]

So far, the most promising approaches to Hepatitis C immunization involves the use of recombinant envelope proteins to elicit neutralizing antibodies and CD4+ T cells and defective or attenuated viral vectors to enhance priming of humoral and cellular (CD4+ and CD8+) immune responses to multiple HCV nonstructural gene products expressed by the vector. Ideally, any future HCV vaccine should elicit broad humoral (anti–E1/E2) and cellular immune responses. Several prophylactic or therapeutic vaccine candidates have reached human clinical trials (and more approaches are in preclinical development, including, e.g. a heterologous prime-boost immunization with Ad vectors expressing E1–E2 glycoprotein followed by recombinant E1/E1 heterodimer. With the availability of a system to propagate HCV in vitro, the possibility of using an inactivated HCV vaccine has also started to be explored. In the future, it will be important to better determine correlates of protection, duration of memory of vaccine-induced protection, and the ability to cross-protect against diverse genotypes and to identify optimal vaccine formulations.[1]

Ebola Virus Vaccine

No approved vaccines are available to prevent the spread of Ebola virus however,[5,6] during the epidemic in West Africa accelerated paths were developed for vaccine testing and introduction into field use. The recombinant vesicular stomatitis virus-Zaire Ebola (VSV-Ebola) virus vaccine has been most widely used.[7] A 6-month safety study found that the VSV-Ebola vaccine was generally well tolerated, supporting its use for persons at risk of Ebola virus disease. The recombinant VSV-Ebola vaccine may also have a role in preventing disease and death when administered promptly after an exposure.[8]

Malaria Vaccine

Vaccine development efforts have focused on preventing illness from *P. falciparum* and to a lesser extent, on *P. vivax*. Significant roles for both humoral and cell-mediated effectors have been demonstrated in animal models, and both humoral and cell-mediated immune responses are induced in humans after natural malaria infection and following inoculation of many candidate malaria vaccines including the vaccine described below.[9]

Malarial Vaccines

More than 30 *P. falciparum* malaria vaccine candidates are at advanced preclinical and clinical stages of evaluation. Approaches that use recombinant protein antigens and target different stages of the parasite life-cycle are being developed. The RTS,S/AS01 vaccine has completed phase 3 evaluation and received a positive regulatory assessment.

The phase 3 trial of the RTS,S/AS01 vaccine enrolled two age categories of children—(1) aged 6–12 weeks and (2) 5–17 months at the time of first vaccination. There were 11 trial sites across sub-Saharan Africa.

RTS,S/AS01 is a pre-erythrocytic stage hybrid recombinant protein vaccine, based on the RTS,S recombinant antigen. It comprises the hybrid polypeptide RTS in which regions of the *P. falciparum* circumsporozoite protein known to induce humoral (R region) and cellular immune (T region) responses are covalently bound to the

hepatitis B surface antigen (S). This recombinant fusion protein (RTS) is expressed in *Saccharomyces cerevisiae* together with free hepatitis B surface antigen (S), to form RTS,S virus-like particles. The vaccine is currently produced as a 2-dose glass vial of RTS,S powder to be reconstituted with a 2-dose glass vial of AS01 adjuvant system suspension. After reconstitution, the total volume is 1 mL, of which 0.5 mL represents 1 vaccine dose to be administered intramuscularly. No preservative is included in either RTS,S formulation or AS01E adjuvant system. The vials should therefore be discarded at the end of the vaccination session, or within 6 hours after opening, whichever comes first.[9]

Current Recommendations by WHO

The World Health Organization (WHO) recommends that the pilot implementations use the 4-dose schedule of the RTS,S/AS01 vaccine in 3–5 distinct epidemiological settings in sub-Saharan Africa, at subnational level, covering moderate-to-high transmission settings. Published data from the phase III trial concluded that the vaccine has lower efficacy in younger infants (6–12 weeks) of age.[9]

BACTERIAL VACCINES

Tuberculosis Vaccine

There are in fact 15 candidate vaccines in clinical trial, and over 20 others at an earlier stage. Broadly speaking, these fall into three groups. First, there are live attenuated *Mycobacteria*, modified versions of Bacillus Calmette-Guerin (BCG), new attempts to attenuate *M. tuberculosis* or cross-reactive mycobacterial species. Second, there are subunit vaccine proteins that are intended as boosters to primary BCG vaccination, given to most infants in developing countries at birth. Lastly, there is immunization with viral vectors engineered to encode for a variety of important tuberculosis antigens, again usually used as post-BCG boosting.[3]

During its long period of attenuation in the laboratory of Calmette and Guérin (BCG), has not only lost a large portion of its virulence genes (though not all) but has also lost genes for a variety of soluble proteins, which have been shown to be protective in

animal immunization studies. The newly engineered recombinant BCGs have had further virulence genes deleted but one or more putatively protective genes inserted and overexpressed. The same principles apply to newly engineered *M. tuberculosis* variants. The atypical *Mycobacteria* such as *M. vaccae*, *M. indicus pranii,* and *M. smegmatis* are given as inactivated whole cell vaccines in multiple doses. The relatively old *M. vaccae* vaccine deserves special mention. It is intended as a vaccine for patients carrying latent TB but also HIV. It is given as five intradermal doses over 1 year to HIV seropositive subjects with a BCG scar. In a trial in Dar es Salaam sponsored by the National Institutes of Health, 2013, patients were followed for a median of 3.3 years. The vaccine was well tolerated and proved 39% effective in preventing definite tuberculosis.

The subunit vaccine includes many proteins that are secreted into the medium by cultured *M. tuberculosis*, which includes ESAT-6, antigens 85A and 85B, TB10.4, Mtb72f, and several others.

Among the viral vectors being used to carry tuberculosis antigen genes are poxviruses such as modified vaccinia Ankara (MVA) or fowlpox; adenoviruses such as Ad 5 and Ad 35; and vesicular stomatitis virus (VSV). They are mainly used as boosters to BCG and induce strong CD8+ and Th1-type CD4+ T cell responses. They are being progressed both for prophylaxis and as potential therapeutic vaccines.[3]

STAPHYLOCOCCUS AUREUS VACCINE

Staphylococcus aureus is an important pathogen with protean clinical manifestations; substantial debates exist about whether these infections can be prevented by vaccination. Various vaccine approaches have been used with varying levels of promise and success. Published data regarding vaccine development in *S. aureus* are reviewed.[1]

Live Whole-cell Vaccines

A vaccine isolate from bovine mastitis mutated with nitrosoguanidine. The mutant was selected for its ability to grow well at low temperatures, such as those found in breast tissue, and to replicate poorly at 37°C.

The vaccine was injected into the mammary gland of pregnant or lactating mice and produced IgA and IgG antibody responses in milk and serum as measured by an enzyme-linked immune-sorbent assay using killed *S. aureus* as the coating antigen. This vaccine also primed CD4 and CD8 lymphocyte populations capable of responding to staphylococcal antigens in vitro and in vivo challenge. Immunized mice had a 2-log10 decrease in the quantity of *S. aureus* recovered from milk after challenge. A similar decrease was not observed when the vaccine was given parenterally. Thus, this whole-cell vaccine, injected locally, provided some protection against an infection with pathogenesis that involves access by the microorganism to the breast from the exterior. It is unlikely that a live bacterial vaccine, even if efficacious, would receive serious consideration today.[1]

Killed Vaccines

A similar vaccine, called Staphypan, consisting of a killed suspension of *S. aureus* cells combined with a "toxoided" α-hemolysin (α-toxin) was developed. After a complex immunization schedule consisting of 10 injections, the effectiveness was assessed in patients undergoing continuous ambulatory peritoneal dialysis. Among vaccine recipients, Staphypan was immunogenic stimulating a robust serum antibody response to α-hemolysin and to *S. aureus* cells in the dialysate of vaccine recipients. However, vaccine recipients had rates of peritonitis, catheter-associated infection, and *S. aureus* asymptomatic carriage that did not differ significantly from the unimmunized control group.

Component Protein Vaccine Antigens

The choice of a relevant *S. aureus* protein in a component vaccine has obvious advantages over a whole-cell vaccine, particularly in an era of enhanced concern about vaccine safety. Investigators have attempted to identify one or more protective antigens among the many toxins or "virulence factors" elaborated by *S. aureus* as targets for vaccine development. The virulent factors implicated in the pathogenesis are listed in **Table 5** and various vaccine candidates in clinical trials in **Table 6**. *Staphylococcus aureus* vaccines receiving clinical evaluation as of December 2015 are listed in **Table 6**.

TABLE 5: Virulence mechanism of *Staphylococcus aureus.*

Factor	*Gene*
Virulence-factors involved in attachment	
Clumping factors	*clfA, clfB*
Fibrinogen-binding protein	*fbpA*
Fibronectin-binding protein A	*f fnbB*
Fibronectin-binding protein B	*nbA*
Collagen-binding protein	*can*
Coagulase	*Coa*
Polysaccharide/adhesin	*ica locus*
Virulence factors involved in evasion of host defenses	
Enterotoxins A, B, C1–C3, D, E, H, etc.	*sea-set or entA-T*
Toxic shock syndrome toxin-1	*tst*
Exfoliative toxins A, B	*eta, etb*
Protein A	*Spa*
Lipase	*Geh*
V8 protease	*sasP*
Fatty acid-modifying enzyme	*(FAME)*
Panton-Valentine leukocidin	*lukF-PV, lukS-PV*
Leukocidin	*R luk-F-R, lukS-R*
Capsular polysaccharide type 5	*cap5 locus*
Capsular polysaccharide type 8	*cap8 locus*
Staphylokinase	*Sak*
Virulence-factors involved-in invasion/tissue penetration	
α-Toxin	*Hla*
β-Hemolysin	*Hlb*
γ-Hemolysin	*hlgA, hlgB, hlgC*
δ-Hemolysin	*Hld*
Phospholipase C	*Plc*
Metalloprotease (elastase)	*sepA*
Hyaluronidase, hyaluronate lyase	*hysA*

GROUP A *STREPTOCOCCUS* VACCINE

Streptococcus pyogenes [Group A Beta-hemolytic *Streptococcus* (GAS)] has challenged scientists and clinicians throughout modern medical history. Pharyngitis and impetigo are the most common uncomplicated manifestations of GAS infection. Serious infections result when the organism spreads to contiguous sites or disseminates to normally sterile spaces or deep tissues, which may be accompanied by necrotizing fasciitis or Streptococcal Toxic Shock Syndrome

TABLE 6: Vaccines in clinical trials.

Manufacturer	*Vaccine*	*Type of vaccine*	*Study*
Novartis	4 Components	Safety and immunogenicity–complete	Not publicly disclosed; components are all proteins
Pfizer	4 Components	• Safety and immunogenicity–complete • Efficacy after spinal surgery trial ongoing	Conjugated capsular polysaccharides, types 5 and 8; clumping factor A; manganese transporter C
Novadigm	Recombinant protein	Safety and immunogenicity–complete	rAls3p-N
GlaxoSmithKline	4 Components	Safety and immunogenicity–complete	Capsular polysaccharides conjugated to tetanus toxin, α-toxoid, clumping factor A

(STSS) or both. Major non-suppurative complications of GAS infections are Acute Rheumatic Fever (ARF) and Post-Streptococcal Glomerulonephritis (PSGN), both considered immune-mediated. Epidemic waves that characterize the epidemiology of severe GAS infection have been attributed both to the host and the organism.

Circulating strains produce herd immunity, resulting in decreased transmission and disease severity. GAS acquires virulence factors via transmissible agents, such as bacteriophages or via genetic mutations. Knowledge of the precise immune responses that mediate clinical protection could be exploited in vaccine development, but these remain incompletely elucidated. Even if a safe and effective vaccine were developed, the feasibility of introduction and uptake will be driven by factors such as cost-to-benefit analysis, cost-effectiveness analysis, public perception, and market forces in a given country.[1]

Table 7 lists the various group-A streptococcal candidate vaccine antigens that evoke immune responses in humans after natural infection and demonstrate efficacy in animal models.

TABLE 7: Virulence factors of *S. pyogenes* candidates, only Type M specific peptides have been tested as vaccine candidates.

Antigen	*Function in GAS virulence*
M protein-based vaccines	
Type-specific M peptides	Adhesion; inhibits opsonization by the alternate complement pathway
Conserved M protein epitopes Mucosal synthetic peptide vaccine. *Streptococcus gordonii* vector J8-DT B-cell epitopes, with SpyCEP139, StreptInCor	Inhibits opsonization SpyCEP inhibits neutrophil chemotaxis
Non-M protein antigens Fibronectin-binding proteins	
SfbI, FBP54	Adhesion to pharyngeal epithelium
R28	Adhesion to cervical epithelium
Spy 1536 (and 8 other common antigens identified via antigenomics)	Binding to extracellular matrix proteins
C5a peptidase (SCPA) of the complement system	Adhesion; inactivates a chemokine
Serine protease (SpyCEP or ScpC)	Cleaves interleukin-8
Serine carboxylic esterase	Tissue invasion
Streptococcal pyrogenic exotoxins (SPE)	Super-antigens, tissue damage, shock
Group A carbohydrate synthetic oligosaccharide conjugates	Impedes phagocytosis
Pilus (T serotype antigens)	Adhesion and biofilm formation
Spy 1536 (and 8 other common antigens identified via anti-genomics)	Binding to extracellular matrix proteins
Multi high-throughput approach identified 6 antigens: Spy0167, Spy2010, Spy0146 (SpyCEP), Spy0269 (mediates cell division, among the 9 strains identified by antigenome analysis and reported to be protective), Spy0019, and Spy1361	• Spy0167: streptolysin O precursor (kills eukaryotic cells by forming membrane pores) • Spy2010 (C5a peptidase precursor) Spy0416 (SpyCEP) (above) Spy0269 (mediates cell division) Spy0019 (unknown) • Spy1361 (internalin A precursor)

Shigella Vaccine

Shigellosis is an important cause of morbidity and mortality, particularly in children <5 years old in developing countries. In double-blind trials in Bangladesh, 88 adults and 79 children (8–10 years) were randomized to receive either a single oral dose of 1×10^4, 1×10^5 or 1×10^6 CFU of SC602 (a live, attenuated *Shigella flexneri* 2a strain vaccine).

None of the volunteers developed diarrhea. Overall, SC602 was found to be associated with minimal vaccine shedding, minimal reactogenicity, no transmission risk, and low immune stimulation.[10]

E. coli Vaccine

Enterotoxigenic *Escherichia coli* (ETEC) is a major cause of travelers' diarrhea. A phase 3, randomized, double-blind, placebo-controlled field trial, evaluating the efficacy safety of a skin-patch vaccine containing the pathogen's heat-labile toxin (LT) was carried out in healthy adults (aged 18–64 years) traveling from Germany or the UK to Mexico or Guatemala and were assigned in a 1:1 ratio to receive transcutaneous immunization with a patch containing 37·5 μg of ETEC LT or a placebo patch. Although the LT antigen was delivered effectively by the skin patch, the vaccine did not protect travelers against diarrhea caused by ETEC or other organisms. Future vaccines against travelers' diarrhea might need to include several antigens against various diarrheal pathogens, and might need to be able to generate mucosal and higher systemic immunity.[11]

Group B *Streptococcus* Vaccine

Maternal immunization against group B *Streptococcus* (GBS) during pregnancy might protect infants across the period of susceptibility to invasive disease, but no licensed vaccine exists. A phase 1b/2, randomized, observer-blind single-center study of an investigational trivalent GBS vaccine in healthy nonpregnant women (cohort 1), and a dose-ranging study in healthy pregnant women (cohort 2) assessed the safety and immunogenicity of a CRM197-conjugated trivalent GBS vaccine in nonpregnant and pregnant women, and antibody transfer to their infants. The vaccine was well tolerated and induced

capsular- specific antibody responses, in nonpregnant and pregnant women. Maternal vaccination led to higher GBS serotype-specific antibody concentrations in infants than did placebo, with both interventions resulting in similar safety profiles.[12]

Cancer Vaccines

The only currently approved vaccine-based therapy for advanced cancer is Sipuleucel-T, which is an autologous dendritic-cell preparation engineered to target prostatic acid phosphatase (PAP). It demonstrated an overall survival benefit in men with castrate-resistant prostate adenocarcinoma.[13]

Single-peptide vaccines continue to be tested extensively, especially in "immunogenic" cancers such as melanoma.[14]

A patient-specific anti-idiotypic vaccine in B cell lymphoma, which offers a modest prolongation of remission, is an exception, which has not failed phase III. Therefore, there is currently some interest in different approaches to cancer vaccines, namely seeking to inhibit regulatory pathways which down-modulate the body's own immune response to tumor-associated antigens. In the long run, a better target for cancer vaccines may be minimal residual disease rather than eliminating extensive metastatic deposits.[15]

REFERENCES

1. Stanley A, Walter A, Paul A, et al. Plotkin's Vaccines, 7th edition, Philadelphia, Elsevier, 2018.
2. Dengue Vaccine: WHO Position Paper, September 2018.
3. Nossal G. Vaccines of the future. Vaccine. 2011;29:D111-5.
4. Wang X, Yan Y, Gan T, et al. A trivalent HCV vaccine elicits broad and synergistic polyclonal antibody response in mice and rhesus monkey. Gut. 2017;68(1):140-9.
5. Galvani A, Ndeffo-Mbah M, Wenzel N, et al. Ebola vaccination: if not now, when? Ann Intern Med. 2014;161(10):749.
6. Hampton T. Largest-ever outbreak of Ebola virus disease thrusts experimental therapies, vaccines into spotlight. JAMA. 2014;312(10):987.
7. Henao-Restrepo A, Camacho A, Longini I, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomized trial (Ebola Ça Suffit!). The Lancet. 2017;389(10068):505-18.

8. Feldmann H, Jones S, Daddario-DiCaprio K, et al. Effective post-exposure treatment of Ebola infection. PLoS Pathog. 2007;3(1):e2.
9. Malaria Vaccine: WHO Position Paper, January 2016.
10. Rahman K, Arifeen S, Zaman K, et al. Safety, dose, immunogenicity, and transmissibility of an oral live attenuated Shigella flexneri 2a vaccine candidate (SC602) among healthy adults and school children in Matlab, Bangladesh. Vaccine. 2011;29(6):1347-54.
11. Behrens R, Cramer J, Jelinek T, et al. Efficacy and safety of a patch vaccine containing heat-labile toxin from Escherichia coli against travellers' diarrhea: a phase 3, randomized, double-blind, placebo-controlled field trial in travellers from Europe to Mexico and Guatemala. Lancet Infect Dis. 2014;14(3):197-204.
12. Madhi S, Cutland C, Jose L, et al. Safety and immunogenicity of an investigational maternal trivalent group B streptococcus vaccine in healthy women and their infants: a randomised phase 1b/2 trial. Lancet Infect Dis. 2016;16(8):923-34.
13. Trump D. Commentary on 'Sipuleucel-T immunotherapy for castration-resistant prostate cancer'. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, Redfern CH, Ferrari AC, Dreicer R, Sims RB, Xu Y, Frohlich MW, Schellhammer PF; IMPACT Study Investigators, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA. Urologic Oncology: Seminars and Original Investigations. 2011;29(2):230-1.
14. Ozao-Choy J, Lee D, Faries M. Melanoma vaccines. Surg Clin North Am. 2014;94(5):1017-30.
15. Park HJ, Neelapu SS. Developing idiotype vaccines for lymphoma: from preclinical studies to phase III clinical trials. Br J Haematol. 2008;142(2):179-91.

5.2 VACCINE HESITANCY

Zulkifli Ismail

INTRODUCTION

Vaccine hesitancy, the reluctance or refusal to vaccinate despite the availability of vaccines, threatens to reverse the progress made in tackling vaccine preventable diseases. WHO has declared that vaccine hesitancy is one of the 10 threats to global health in 2019.[1] Vaccine hesitancy and refusal is not a new phenomenon, being present from the first smallpox inoculation by Edward Jenner in 1796. The first documented antivaccine lobby came from John Birch, a physician in the court of King George III who wrote about his apprehension about vaccines being dangerous, could cause the disease that it was intended to prevent, related to other diseases like syphilis (at that time; autism in the current era) and that vaccines did not work. All of these are the same reasons present day antivaxxers or prochoice proponents still use.

Worldwide, despite the success of the vaccination programs and the safety of vaccines, there exist a number of vaccine-hesitant parents and vaccine refusers. These should not be confused with antivaccinationists, otherwise colloquially dubbed as antivaxxers. The WHOs Strategic Advisory Group of Experts (SAGE) on immunization defines vaccine hesitancy as an individual's behavior that is influenced by the 3Cs, i.e. issues of Confidence (no trust in the vaccine or provider), Complacency (does not perceive a need for the vaccine, does not value the vaccine), and Convenience (ease or difficulty of access) (SAGE Vaccine Hesitancy Working Group 2013).[2] Vaccine-hesitant individuals hold varying degrees of indecision regarding certain vaccines or vaccination in general. It is incumbent on us as healthcare professionals to listen to their reasons and try to understand their perspective.

In trying to understand vaccine hesitancy, it is important to conduct a local communication analysis of knowledge, attitudes, and practices (KAP). This analysis should include social norms, cultural beliefs, and traditions associated with health and immunization among primary

stakeholder groups (parents, guardians, and healthcare providers). The analysis should also look into channel availability and audience preferences, including existing community engagement mechanisms that can guide communication interventions.

COMMUNICATION STRATEGIES

The goal is to maintain public trust in vaccines and immunization safety and achieve a high level of immunization coverage. This entails the ability of healthcare workers to understand and be able to communicate the importance and benefits of vaccination, as well as restore confidence in the National Immunization Programme (NIP) should an adverse event following immunization (AEFI) occur. The involvement of community leaders/stakeholders in organizing community dialogs with parents and other target groups for immunization in strengthening the capacity of their healthcare workers to provide inclusive services should be tapped.

Other than concerns about vaccine safety, it is also possible that vaccine hesitancy is increasing now because of the "crowded" vaccination schedule along with "greater access to, and more rapid dissemination of, vaccine-critical messages via digital networks".[3] Lack of awareness of the need to vaccinate is one key factor in people not getting vaccinations.[4]

Concerns that drive vaccine hesitancy have also been found to be highly context specific. This is demonstrated globally, differing within high-, middle-, or low-income countries as well as within countries based on factors such as socioeconomic and educational status. Furthermore, the reasons for rejecting vaccines differ according to the vaccine. For example, concerns related to measles, mumps and rubella (MMR) and thimerosal-containing vaccines are often associated with fear of autism, concerns about the human papillomavirus (HPV) vaccine stem from religious beliefs, and opposition to the influenza vaccine may be related to attitudes about its effectiveness and the need for yearly vaccinations.

Within local regions, there may be reasons related to religious beliefs about the contents of vaccines, belief in naturopathy and alternative medicine, conspiracy theories related to "big pharma", etc.

These have to be determined and answered by the healthcare worker, sometimes with the help of religious leaders, influential individuals, leaders from among the alternative medicine practitioners, etc. who will be able to send a clear message to certain communities to get their buy-in.

SELECTING PROPER MEDIA

We are now in the digital age where new digital technologies have "disrupted" traditional vaccine information communication. This has largely favored antivaccinationists who have leveraged the internet and social media to bypass traditional sources of information and obtain widespread communication and access to the public. The modern communication environment allows any individual with a negative opinion about vaccine safety issues to voice their views online without professional input. In that context, the challenge for NIPs in the region is to proactively apply innovative and participatory communication approaches with evidence-based messages.[5]

Mobile applications have surpassed traditional internet, and will work with social media presence to provide a potential direct channel to communicate with individuals about vaccination. Apps that are helpful in reminding parents of their children's next vaccination appointments while providing information on child development, growth, nutrition, and vaccines would prove to be popular.

There is expected to be a rapid evolution of mobile technologies over the next 5 years with the possible development and widespread use of wearable technologies. Any strategy developed must be highly amendable to change to accommodate new platforms of communication.[6] As technology is highly dynamic, mobile apps should be rapidly produced, introduced, evaluated, and then reiterated to incorporate new findings.

In the short-and long-term, building partnerships with the media and social media influencers is key to keeping the public regularly informed about and engaged with the benefits of immunization and to timely information sharing on vaccine safety issues.[7] The media can reinforce messages shared through interpersonal communication to motivate families and communities to maintain trust in, and sustain their demand for, immunization services.

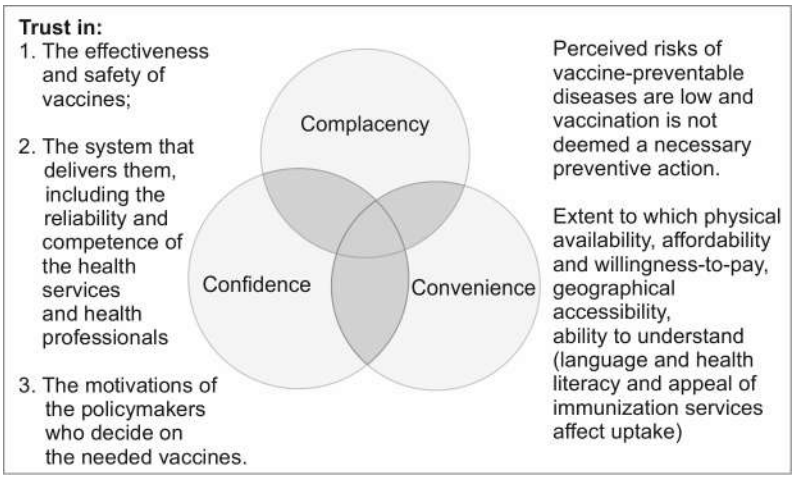

Fig. 1: Vaccine hesitancy determinants.

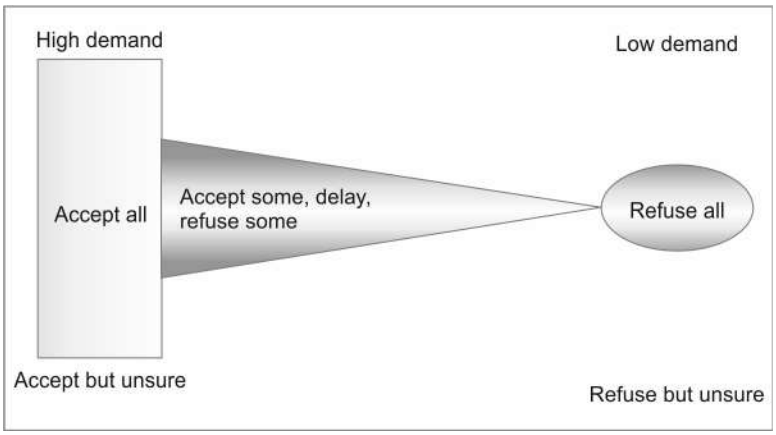

Fig. 2: Vaccine hesitancy continuum.

While vaccine hesitancy should be overcome through face-to-face contact by sufficiently trained and knowledgeable healthcare workers with parents and the public, our presence in social media using more and more advanced technology has to go concurrently to counter the influence of the antivaccination lobbies.

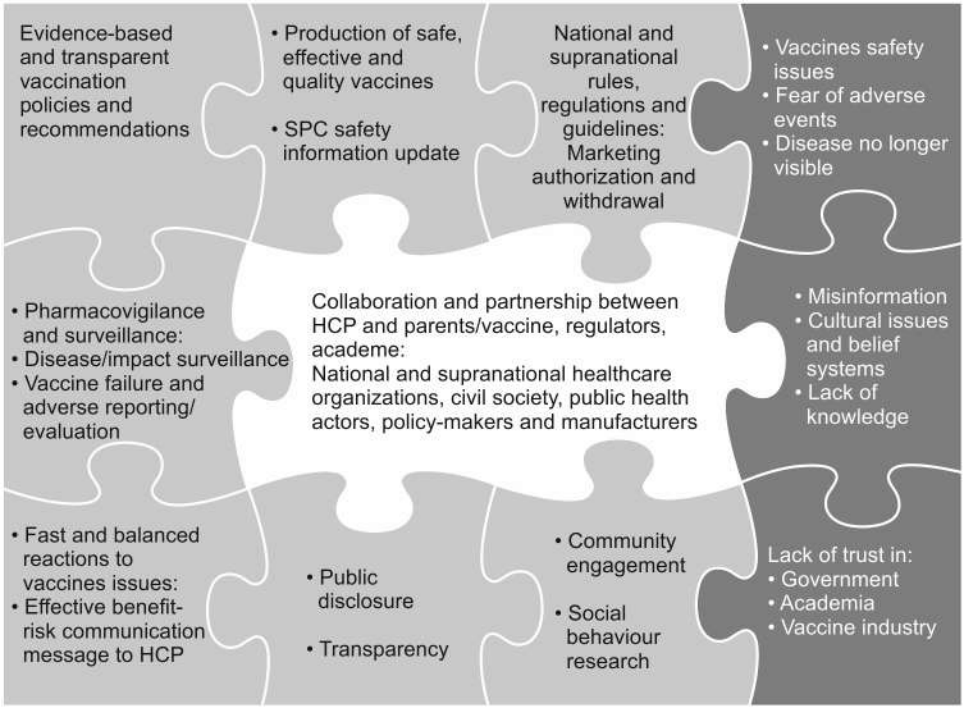

Fig. 3: Factors that promote or undermine vaccine confidence and collaboration with improved public confidence in vaccines.
(HCP: healthcare provider; SPC: Summary of Product Characteristics)
Source: World Health Organization (WHO). Vaccine Safety Communication: Guide for Immunization Programme Managers and National Regulatory Authorities. Manila: WHO Regional Office for the Western Pacific; 2016. p. 76; MDPI. (2019). Vaccines—Open Access Journal. [online] Available from https://www.mdpi.com/journal/vaccines. [Last accessed September, 2019].

REFERENCES

1. World Health Organization (WHO). (2019). Ten threats to global health in 2019. [online] Available from https://www.who.int/emergencies/ten-threats-to-global-health-in-2019. [Last accessed September, 2019].
2. World Health Organization (WHO). Vaccine Safety Communication: Guide for Immunization Programme Managers and National Regulatory Authorities (1. Immunization Programs—Organization and Administration, 2. Safety Management, and 3. Vaccines—Standards. I). Manila: WHO Regional Office for the Western Pacific; 2016. p. 76.
3. Leask J, Willaby HW, Kaufman J. The big picture in addressing vaccine hesitancy. Hum Vaccin Immunother. 2014;10(9):2600-2.
4. Collins J, Alona I, Tooher R, et al. Increased awareness and health care provider endorsement is required to encourage pregnant women to be vaccinated. Hum Vaccin Immunother. 2014;10(10):2922-9.
5. Penţa MA, Băban A. Message Framing in Vaccine Communication: A Systematic Review of Published Literature. Health Commun. 2018;33(3):299-314.
6. Wilson K, Atkinson K, Deeks S. Opportunities for utilizing new technologies to increase vaccine confidence. Expert Rev Vaccines. 2014;13(8):969-77.
7. Stockwell MS, Fiks AG. Utilizing health information technology to improve vaccine communication and coverage. Hum Vaccin Immunother. 2013;9(8):1802-11.

Annexures

Annexure I: IAP Recommended Immunization Schedule 2018
Annexure II: Internet Resources on Immunization Information
Annexure III: Ready Reckoner for Vaccines Currently Available in India
Annexure IV: AEFI Reporting Form

I

ANNEXURE

IAP Recommended Immunization Schedule 2018

IAP RECOMMENDED VACCINES FOR ROUTINE USE

IAP Recommended Vaccines for Routine Use		
Age (completed weeks/months/ years)	*Vaccines*	*Comments*
Birth	BCG OPV0 Hep-B1	• Administer these vaccines to all newborns within 7 days, preferably within 24 hours
6 weeks	DTwP1/DTaP1 IPV1 (or bOPV1 and ID-fIPV1) Hep-B2 Hib1 Rotavirus 1 PCV1	*DTP*: • Both DTwP and DTaP or their combinations can be used in primary series • Immunogenicity and longevity of immune response is better with DTwP • DTaP combinations may be offered as an alternative in view of nonavailability of standalone IPV preparations in the private sector and parental anxiety of increased reactogenicity with DTwP. *Polio*: • No child should leave the facility without polio immunization (IPV or OPV). • Continue birth dose OPV, and OPV on SIAs. • IPV should replace OPV completely as early as possible.

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Age (completed weeks/months/ years)	*Vaccines*	*Comments*
		• Three doses of IM IPV in primary series is the best option. • Two doses of IM IPV instead of three for primary series if started at 8 weeks, with an interval of at least 8 weeks between two doses is the second option. • In case IPV (standalone or in combination) is not available or feasible, the child should be offered bOPV (three doses). In such cases, two fractional doses of IPV at a government facility at 6 and 14 weeks or at least one dose of a IM IPV (either standalone or as a combination) at 14 weeks should be recommended. *Rotavirus*: • Two doses of RV1 or three doses of RV5 and RV116E and BRV-PV • RV1 can be given at 6 and 10 weeks. *PCVs*: • Minimum age: 6 weeks • Both PCV10 and PCV13 are licensed for children from 6 weeks to 5 years of age. • Additionally, PCV13 is also licensed for the prevention of pneumococcal diseases in adults >50 years of age. • Primary schedule (for both PCV10 and PCV13): three primary doses at 6, 10, and 14 weeks with a booster at age 12 through 15 months.
10 weeks	DTwP2 Hepatitis B3 IPV2 (or bOPV2) Hib2 Rotavirus 2 PCV2	• Only two doses of RV1 are recommended. • If RV1 is chosen, the second dose should be given at 10 weeks.

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Age (completed weeks/months/ years)	*Vaccines*	*Comments*
14 weeks	DTwP3 Hepatitis B4 IPV3 (or bOPV3 and ID-fIPV2) Hib3 Rotavirus 3 PCV3	• If any dose in series was RV5 or RV116E or BRV-PV, a total of three doses of RV vaccine should be administered.
6 months	Influenza vaccine	*Influenza vaccine*: • IIV is recommended for routine immunization of children 6–59 months of age. • Children 6–59 months are grouped as "high risk" and should be offered as routine influenza vaccine. • Both IIV3 and IIV4 are licensed in India and can be used. *Minimum age*: 6 months for trivalent (IIV3)/quadrivalent (IIV4). • *First time vaccination*: – 6 months to below 9 years: Two doses 1 month apart – 9 years and above: Single dose • Vaccination can be started after 6 months of age as early as the vaccine for that season is made available, preferably 2 weeks before the season begins. • Annual revaccination with single dose.
6 months onward	TCV	• Single dose of any of the licensed TCV can be administered. • Can be administered with MMR vaccine if started at 9 months.
9 months	MMR1/MR	*MMR/MR*: • Standalone measles will no more be available. • Measles-containing vaccine (MMR/MR) ideally should not be administered before completing 9 months of age. • The second dose must follow in the second year of life.

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Age (completed weeks/months/ years)	*Vaccines*	*Comments*
		• MR is not available in private sector as on date. If available, it should be offered instead of MMR • Additional dose during MR campaign for children of 9 months to 15 years, irrespective of previous vaccination status
12 months	Hep A1	*Hepatitis A*: • Single dose for live attenuated H2-strain Hep A vaccine • Two doses for all inactivated Hep A vaccines are recommended
15 months	MMR2 Varicella 1 PCV booster	*MMR*: • The second dose must follow in the second year of life • However, it can be given at any time 4–8 weeks after the first dose *Varicella*: • The risk of breakthrough varicella is lower if given 15 months onward • MMRV as a combination vaccine is more reactogenic at this age
16–18 months	DTwP B1/DTaP B1 IPVB1 (or bOPV B1) Hib B1	• The first booster (fourth dose) may be administered as early as age 12 months, provided at least 6 months after the third dose • Both DTwP and DTaP as combination vaccine can be offered • No child should leave the facility without booster dose of IPV (standalone or combination) or bOPV vaccination
18 months	Hep A2	*Hepatitis A*: • Second dose for inactivated vaccines only
2 years or more	Typhoid polysaccharide vaccine	• A dose of typhoid vi-polysaccharide (Vi-PS) vaccine can be given only if conjugate vaccine is not available or feasible • Revaccination every 3 years with Vi-PS vaccine. • TCV is preferred even at 2 years of age or more.

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Age (completed weeks/months/ years)	*Vaccines*	*Comments*
4–6 years	DTwP B2/DTaP B2	• Tdap is not recommended here.
	MMRV or MMR3 + Varicella 2	*Varicella*: • A total of two doses of varicella vaccine should be administered. • The second dose of varicella vaccine should be given at 4–6 years of age or at 3 months after the first dose. • MMRV can be used without increased risk of adverse reactions at this age. • MMR third dose is recommended at 4–6 years of age
9–12 years	Tdap/Td	*Tdap*: • Recommended age is 10 years. • Tdap is preferred to Td followed by Td every 10 years.
	HPV	*HPV*: • Only two doses of either of the two HPV vaccines for girls aged 9–14 years • For girls of 15 years and older as well as for immunocompromized individuals, three doses are recommended. • For two-dose schedule, the minimum interval between doses should be 6 months. • For three-dose schedule, the doses can be administered at 0, 1, 2 (depending on brand), and 6 months.

(BCG: Bacillus Calmette–Guérin; OPV: oral poliovirus vaccine; Hep B: Hepatitis B; DTwP: diphtheria, tetanus and whole-cell pertussis; DTaP: diphtheria, tetanus and acellular pertussis; DTP: diphtheria, tetanus toxoids and pertussis; IPV: inactivated polio vaccine; bOPV: bivalent oral poliovirus vaccine; ID-fIPV: intradermal fractional oral poliovirus vaccine; PCV: pneumococcal conjugate vaccine; SIA: supplemental immunization activity; IM: intramuscularly; RV: rotavirus vaccine; BRV-PV: bovine-human reassortant pentavalent rotavirus vaccine; IIV: inactivated influenza vaccine; TCV: typhoid conjugate vaccine; MMR: measles, mumps, and rubella; MR: Measles-rubella; MMRV: measles, mumps, rubella, and varicella; Tdap: diphtheria toxoid and acellular pertussis; Td: tetanus and diphtheria; HPV: human papillomavirus; IAP: Indian Academy of Pediatrics)

IAP RECOMMENDED VACCINES UNDER SPECIAL CIRCUMSTANCES

- Influenza vaccine (above 5 years age)
- Meningococcal vaccine
- Japanese encephalitis (JE) vaccine
- Cholera vaccine
- Rabies vaccine
- Yellow fever vaccine
- *Pneumococcal polysaccharide vaccine 23 (PPSV23)*:
  - *Rabies vaccine*:
    - Four-dose schedule of antirabies vaccine is recommended for postexposure prophylaxis.
    - Rabies monoclonal antibody is as effective as rabies immunoglobulin, and is a cost-effective option.
  - *Japanese encephalitis vaccine*:
    - Only for individuals living in endemic areas
    - For travelers to JE endemic areas provided their expected stay is for a minimum period of 4 weeks
    - Any of the licensed JE vaccine can be administered.
    - Live attenuated SA-14-14-2 is not available in private market.
  - *Meningococcal vaccines*:
    - Any of the licensed vaccine can be administered.
    - *9 months through 23 months*: Two doses at least 3 months apart
    - *2 years through 55 years*: Single dose.
  - *Cholera vaccine*:
    - *Minimum age*: 1 year (killed whole cell Vibrio cholera)
    - Not recommended for routine use in healthy individuals; recommended only for the vaccination of persons residing in high endemic areas and travelling to areas where risk of transmission is very high
    - Two doses 2 weeks apart for >1 year old.
  - Yellow-fever vaccine.

Refer to Topic on Travelers' Vaccination.

High-risk category of children:

- Congenital or acquired immunodeficiency (including HIV infection)
- Chronic cardiac, pulmonary (including asthma if treated with prolonged high-dose oral corticosteroids), hematologic, renal (including nephrotic syndrome), liver disease, and diabetes mellitus
- Children on long-term steroids, salicylates, immunosuppressive or radiation therapy
- Diabetes mellitus, cerebrospinal fluid leak, cochlear implant, and malignancies
- Children with functional/anatomic asplenia/hyposplenia
- During disease outbreaks
- Laboratory personnel and healthcare workers
- Travelers
- Children having pets in home
- Children perceived with higher threat of being bitten by dogs such as hostellers, risk of stray dog menace while going outdoor.
- Influenza vaccination annually is recommended yearly for high risk children from 5 years of age onwards.

II

ANNEXURE

Internet Resources on Immunization Information

No.	*Organization/ Sponsor*	*Web address*	*Salient contents*
1.	National Centre for Biotechnology Information	www.pubmed.com	Abstracts and full texts of vaccine-related articles published in indexed journals
2.	Indian Academy of Pediatrics (IAP) Advisory Committee On Vaccines and Immunization Practices	www.acvip.org	Electronic copy of guidebook, Q&A facility
3.	World Health Organization (WHO)	https://www.who.int/immunization/en/	WHO position papers, WHO policy recommendations, national programs and systems, monitoring and surveillance, prequalification status of vaccines

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No.	*Organization/ Sponsor*	*Web address*	*Salient contents*
4.	Centers for Disease Control and Prevention (CDC)	www.cdc.gov/vaccines/	Advisory Committee on Immunization Practices vaccine recommendations, travel immunization, general best practice guidelines for immunization, Pink Book [epidemiology and prevention of vaccine preventable diseases (VPDs)], vaccine storages
5.	Immunization Action Coalition	www.immunize.org/	Educational material for parents
6.	National Network for Immunization Information	http://www.nnii.org/	Information on VPD, background on vaccine development and vaccine safety, resource kit to help health care providers discuss immunization with their patients
7.	Children's Hospital Philadelphia	www.vaccine.chop.edu/	Information for parents, vaccine safety, vaccine ingredients
8.	Global Alliance for Vaccines and Immunization	www.gavialliance.org	Information on GAVI programmatic policies and funding
9.	PATH	www.path.org/ vaccineresources/index.php	Vaccine resource library
10.	Vaccine manufacturers (in alphabetical order)	www.abbott.in www.bharatbiotech.comwww.biomed.co.in www.biologicale.com www.cadilapharma.com www.cipla.com www.emcure.co.in www.gskvaccines.com	Prescribing information for various vaccines

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No.	*Organization/ Sponsor*	*Web address*	*Salient contents*
		www. indiabullspharmaceuticals.com www.indimmune.com www.lupinpharmaceuticals.com www.merckvaccines.com www.msdindia.in www.novomedi.com www.panacea-biotec.com www.paviour.org www.pfizer.com www.sunpharma.com www.samarthalifesciences.com www.sanofipasteur.com www.seruminstitute.com www.vhbgroup.com www.wockhardt.comwww. zyduscadila.com	
11.	Miscellaneous	*Indian Pediatrics*: www.indianpediatrics.net/ *Vaccines*: www.sciencedirect.com/journal/vaccine *Expert Review of Vaccines*: www.tandfonline.com/loi/ierv20 *PneumoAdip*: www.preventpneumo.org/ *ADVAC*: www.advac.org *The Pediatric Infectious Disease Journal*: www.journals.lww.com/pidj/pages/default.aspx	Information, presentations, and journal articles on vaccines and immunization practices

ANNEXURE III

Ready Reckoner for Vaccines Currently Available in India

Vaccine	*Content/dose*	*Nature and diluent*	*Storage*	*Dose, route, and site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
BCG (LAV)	Each 1 mL contains 2 × 10^6 to 8 × 10^6 CFU of viable Mycobacteria	Lyophilized, normal saline	Freezer/ 2–8°C, protect from light	0.1 mL ID, left deltoid	Single dose at birth or first contact below 5 years	0–80%	Axillary lymphadenitis	Cellular immuno-deficiency Should not be given with measles/MMR
bOPV (LAV)	Sabin strain *Type 1*: 10^6 CC ID_{50} *Type 3*: 10^6 CC ID_{50}	Liquid vaccine	Freezer/ 2–8°C	Two drops oral	Birth, 6, 10, and 14 weeks, 15–18 months, NIDs, SNIDs	10–15% per dose (India), 30% per dose (world)	Rarely VAPP	Immunodefi-cient patients and household contacts
IPV (inacti-vated)	Salk strain *Type 1*: 40 units *Type 2*: 8 units *Type 3*: 32 units	Liquid vaccine	2–8°C	0.5 mL IM or SC, thigh*/ deltoid	6, 10, and 14 weeks, booster at 15–18 months	95–100%	None	Serious hypersensitivity

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Vaccine	*Content/dose*	*Nature and diluent*	*Storage*	*Dose, route, and site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
DTwP/ DTaP	Diphtheria toxoid 20–30 Lf, tetanus toxoid 5–25 Lf, wP 4 IU/aP 3–25 mg of two to three purified pertussis antigens	Liquid vaccine	2–8°C Protect DTaP from light	0.5 mL IM thigh/ deltoid	6, 10, and 14 weeks, booster at 15–18 months, 5 years Not recommended above 7 years	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	2–8°C	0.5 mL IM thigh/ deltoid	Replacement for DTwP/DTaP in those with contraindications for pertussis vaccination, not recommended above 7 years			
TT	Tetanus toxoid 5 Lf	Liquid vaccine	2–8°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	2–8°C	0.5 mL IM thigh/ deltoid	As replacement for DTwP/DTaP/DT for catch-up vaccination in those aged above 7 years (along with Tdap), and as replacement for TT at all ages			
TdaP	Tetanus toxoid 5 Lf, diphtheria toxoid 2 Lf, 2.5–8 mg of three pertussis antigens	Liquid vaccine	2–8°C	0.5 mL IM thigh/ deltoid	Single dose at 10–12 years	90%	None	As for DTwP/ DTaP

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Vaccine	*Content/dose*	*Nature and diluent*	*Storage*	*Dose, route, and site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
Measles (LAV)	1,000 $CCID_{50}$ of Edmonston-Zagreb strain of measles virus	Lyophilized, diluent sterile water	Freezer/ 2–8°C Protect from light	0.5 mL SC thigh/ deltoid	Single dose at 9 months	80%	Mild measles like illness in <5%, rarely/ thrombocyto-penic purpura	Severely immu-nocompromised, pregnancy
Rubella (LAV)	5,000 $CCID_{50}$ of RA 27/3 strain of rubella virus	Lyophilized, diluent sterile water	Freezer/ 2–8°C	0.5 mL SC thigh/ deltoid	As for MMR, MMR preferred	95%	Mild rubella-like illness in <5%, rarely arthritis, ITP	Severely immu-nocompromised, pregnancy
MMR (LAV)	Measles 1,000 $CCID_{50}$ of Edmonston-Zagreb/Schwarz; Mumps 5,000 $CCID_{50}$ of Jeryl Lynn/Urate strain; Rubella 5,000 $CCID_{50}$ of Wistar RA 27/3	Lyophilized, diluent sterile water	Freezer/ 2–8°C Protect from light	0.5 mL SC thigh/ deltoid	Three doses at 9 months, 15–18 months and 5 years	95%	Same as measles and rubella, high fever, rarely parotid swelling aseptic meningitis	Severely immu-nocompromised, pregnancy

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Vaccine	*Content/dose*	*Nature and diluent*	*Storage*	*Dose, route, and site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
MMRV (LAV)	Measles 1,000 $CCID_{50}$ of Schwarz; Mumps 5,000 $CCID_{50}$ of Jeryl Lynn strain; Rubella 5,000 $CCID_{50}$ of Wistar RA 27/3; Varicella 1000 PFU Oka strain	Lyophilized, diluent sterile water	Freezer/ 2–8°C Protect from light	0.5 mL SC thigh/ deltoid	Two doses at 15–18 months and 5 years	95%	Same as measles and rubella, high fever, rarely parotid swelling aseptic meningitis. Febrile seizure in measles non-primed children	Severely immunocompromised, pregnancy
Hep B	20 mg/mL of HBsAg antigen	Liquid vaccine	2–8°C	<18 years 0.5 mL, >18 years 1 m IM deltoid/ thigh	Birth, 6 and 14 weeks, OR 6, 10, and 14 weeks, OR 0, 1, and 6 months	>90%	None	Serious hypersensitivity
Hib	10 mg of PRP-T or HbOC	Liquid or lyophilized, (diluent sterile water)	2–8°C	0.5 mL IM thigh/ deltoid	6, 10, and 14 weeks, booster at 15–18 months	>90%	None	Serious hypersensitivity

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Vaccine	*Content/dose*	*Nature and diluent*	*Storage*	*Dose, route, and site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
DTwP+ Hib	As for DTwP and Hib	Liquid vaccine or lyophilized Hib reconstituted with liquid DTwP	2–8°C	0.5 mL IM thigh/ deltoid	6, 10, and 14 weeks, booster at 15–18 months	As for DTwP and Hib		
DTwP+ Hep B	As for DTwP and 10 mg of Hep B	Liquid vaccine	2–8°C	0.5 mL IM thigh/ deltoid	6, 10, and 14 weeks,	As for DTwP and Hep B		
DTwP+ Hib+ Hep B	As for DTwP, Hib, 10 mg of Hep B	Liquid vaccine or lyophilized Hib reconstituted with liquid DTwP+Hep B	2–8°C	0.5 mL IM thigh/ deltoid	6, 10, 14 weeks	As for DTwP, Hib, and Hep B		
DTwP+ Hib+ Hep B+ IPV	As for DTwP, Hib, 10 mg of Hep B; IPV Salk strain *Type 1*: 40 units *Type 2*: 8 units *Type 3*: 32 units	Liquid vaccine	2–8°C	0.5 mL IM thigh/ deltoid	6 ± 10, 14 weeks and booster at 15–18 months	As for DTwP, Hib, and Hep B		

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Vaccine	*Content/dose*	*Nature and diluent*	*Storage*	*Dose, route, and site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
DTaP+ Hib+ IPV	DTaP (two component), IPV, and Hib	Liquid vaccine	2–8°C	0.5 mL IM thigh/ deltoid	6, 10, and 14 weeks and booster at 15–18 months	As for DTaP, IPV, and Hib		
DTaP+ IPV	DTaP (two component) and IPV (Types 1, 2, and 3)	Liquid vaccine	2–8°C	0.5 mL IM thigh/ deltoid	Booster 4–5 years	As for DTaP and IPV		
Vi typhoid poly-saccha-ride	25–30 mg of Vi-polysaccharide	Liquid vaccine	2–8°C	0.5 mL IM thigh/ deltoid	Above 2 years, single dose, revaccina-tion every 3 years	60%	None	Serious hypersensitivity
Vi-PS-TT con-jugate typhoid	25 µg/5 µg of Vi-polysaccharide conjugated to tetanus toxoid per 0.5 mL	Liquid vaccine	2–8°C	0.5 mL IM deltoid/ thigh	Single dose at ≥6 monthst	>90% serocon-version in >6 months to 45 years	None, only minor systemic and local side effects	Severe hypersensitivity to any constituent Pregnant and lactating mother

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Vaccine	*Content/dose*	*Nature and diluent*	*Storage*	*Dose, route, and site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
HPV Bivalent	L1 protein of serotypes 16 and 18	Liquid vaccine	2–8°C	0.5 mL IM thigh/ deltoid	9–14 years, 0 and 6 months; 15–45 years, 0, 1, and 6 months	>90% against serotype-specific cervical cancer	None	Serious hypersensitivity pregnancy
Quad-rivalent	L1 protein of serotypes 6,11, 16, and 18				9–14 years, 0 and 6 months; 14–45 years, 0, 2, and 6 months			
Nonava-lent	L1 protein of serotypes 6, 11, 31, 33, 45, 52, and 58	Liquid vaccine	2 to 8°C	0.5 mL IM thigh/ Deltoid	10–26 years, 0, 2, and 6 months	>90% against serotype specific cervical cancer	None	Serious hypersensitivity pregnancy

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Vaccine	*Content/dose*	*Nature and diluent*	*Storage*	*Dose, route, and site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
PCV10	Capsular polysaccharide of serotypes 1, 4, 5, 6B, 7F, 9V, 14, and 23F linked to protein D (NTHi), 18C linked to TT and 19F to diphtheria toxoid	Liquid vaccine	2–8°C	0.5 mL IM thigh/ deltoid	6, 10, and 14 weeks, booster at 15–18 months	95% against serotype-specific invasive disease	None	Serious hypersensitivity
PCV13	Capsular polysaccharide of serotypes 4, 6B, 9V, 14, 18C, 19F, 23, 1, 5, 6A, 7F, and 3 linked to CRM 197	Liquid vaccine	2–8°C	0.5 mL IM thigh/ deltoid	6, 10, and 14 weeks, booster at 15–18 months	95% against serotype-specific invasive disease	None	Serious hypersensitivity
PPSV23	Capsular	Liquid vaccine	2–8°C	0.5 mL SC/IM thigh/ deltoid	Single dose after 2 years Revaccination only once after 3–5 years	70% against invasive disease in high-risk children	None	Serious hypersensitivity

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Vaccine	*Content/dose*	*Nature and diluent*	*Storage*	*Dose, route, and site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
Inacti-vated Hep A	HM 175 strain Composition varies with brands/age	Liquid vaccine	2–8°C	Below 15–18 years (as per brand) 0.5 mL IM deltoid/ thigh	Two doses 6 months apart, 18 months onward	>95%	None	Serious hypersensitivity
Hep A and Hep B	Composition varies with age	Liquid vaccine	2–8°C	Below 18 years 0.5 mL	0, 1, and 6 months, 18 months onward	>95%	None	Serious hypersensitivity
Live attenu-ated Hep A	6.5 log particles of H2 strain	Lyophilized, sterile water	2–8°C	1 mL SC deltoid/ thigh	Two doses 6 months apart 18 months onward till 15 years	>95%	None	Immunodeficient patients
Varicella	At least 1,000 PFU of Oka strain (varies according to product)	Lyophilized, sterile water	2–8°C Protect from light	0.5 mL SC deltoid/ thigh	Two doses, first dose after 15 months and sec-ond dose after 3 months of first dose or at 5 years	70–90% with one dose >95% with two doses	Varicella-like rash in 5%	Pregnancy, severely immuno-compromised

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Vaccine	*Content/dose*	*Nature and diluent*	*Storage*	*Dose, route, and site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
Rotavirus Human Monovalent (LAV)	Human rotavirus stain 89-12 (G1P8)	Lyophilized, sterile water-based specific liquid diluent	2–8°C Protect from light	1 mL orally	Two doses, first dose at 6–15 weeks, second to be completed by 32 weeks and not to be initiated after 15 weeks	85–98% against severe rotavirus diarrhea	None	Acute gastroenteritis, history of intussusception, beyond 6 months
Rotavirus Human Bovine Pentavalent vaccine (LAV)	Five rotavirus reassortant strains G1, G2, G3, G4, and P1A (8)	Liquid vaccine	2–8°C	2 mL orally	Three doses, first dose at 6–15 weeks and then at 4 weeks of interval schedule to be completed by 32 weeks	85–98% against severe rotavirus diarrhea	None	Beyond 32 weeks age, history of intussusception

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Vaccine	*Content/dose*	*Nature and diluent*	*Storage*	*Dose, route, and Site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
Rotavirus Human Bovine Monovalent vaccine (LAV)	One rotavirus reassortant strain 116E	Liquid vaccine	2–8°C	0.5 mL orally	Three doses, first dose at 6–15 weeks and then at 4 weeks of interval schedule to be completed by 32 weeks	85–98% against severe rotavirus diarrhea	None	Beyond 32 weeks of age, history of intussusception
Rotavirus Human Bovine Pentavalent vaccine (LAV)	Five rotavirus reassortant strains G1, G2, G3, G4, and G9	Lyophilized, sterile water-based specific liquid diluent	25°C (thermostable)	2.5 mL orally	Three doses, first dose at 6–15 weeks and then at 4 weeks of interval schedule to be completed by 32 weeks	85–98% against severe rotavirus diarrhea	None	Beyond 32 weeks age, history of intussusception

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Vaccine	*Content/dose*	*Nature and diluent*	*Storage*	*Dose, route, and site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
Inactivated Kolar strain JE vaccine (JENVAC)	Inactivated, Kolar strain, 821564XY JE vaccine 5.0 µg per 0.5 mL	Liquid vaccine	2–8°C	0.5 mL intramuscular deltoid/thigh	Two doses at 4 weeks interval from 1 year of age and onward (up to 50 years) Booster may be needed	>90% seroconverts and seroprotection after one dose in 1–50 years	None, only fever and local side effects	Severe hypersensitivity to any constituent
Inactivated SA-14-14-2 strain JE vaccine (JEEV)	3 µg and 6 µg per 0.5 mL of inactivated Vero cell culture derived SA 14-14-2 JE vaccine	Liquid vaccine	2–8°C	1–3 years: 3 µg 3–18 years: 6 µg IM; deltoid/thigh	Two doses at 4 weeks interval Booster may be needed	>90% seroconversion	None, only fever, and local side effects	Severe hypersensitivity to any constituent
Live JE vaccine, SA-14-14-2	5.4 log PFU of SA 14-14-2 strain of JE virus	Liquid vaccine	2–8°C	0.5 mL SC thigh/deltoid	Two doses at 9 month and 15–18 months	>90%	None	Immunodeficient patients and their household contacts

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Vaccine	*Content/dose*	*Nature and diluent*	*Storage*	*Dose, route, and site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
MPSV	Bivalent (A + C) Quadrivatent (A + C + Y + W135)	Lyophilized, diluent sterile water	2–8°C	0.5 mL SC or thigh/ deltoid	If indicated, single dose above 2 years, re-vaccination once after 3–5 years	90%	None	Serious hypersensitivity
MCV4 Quad-rivalent	4 µg of Meningo-coccal group A, C, Y and W0135 polysaccharides conjugated to 48 µg of diphtheria toxoid	Liquid vaccine	2–8°C	0.5 mL IM deltoid	Single dose from >2–55 years	Effective-ness: 80–85%	None, no extra risk of GBS amongst vaccine	Severe hypersensitivity to any constituent
Flu vaccine trivalent (IIV3)	15 µg of HA of two Type A and one Type B (differs according to Northern/ Southern Hemisphere and usually yearly) inactivated influenza virus	Liquid vaccine	2–8°C	0.25 mL IM thigh/ 0.5 mL IM thigh/ deltoid	Two doses below 8 years, single dose yearly. 0.25 mL for 6 months to 3 years; 0.5 mL for above 3 years	Effective-ness: 80–85%	None	Severe hypersensitivity to any constituent

Contd...

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Vaccine	*Content/dose*	*Nature and diluent*	*Storage*	*Dose, route, and site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
Flu vaccine Quadrivalent (IIV4)	15 µg of HA of two Type A and two Type B (differs according to Northern/ Southern Hemisphere and usually yearly) inactivated influenza virus	Liquid vaccine	2–8°C	0.25 mL IM thigh/0.5 mL IM thigh/ deltoid	Two doses below 8 years, single dose Yearly. 0.25 mL for 6 months to 3 years; 0.5 mL for above 3 years	*Effectiveness*: 80–85%	None	Severe hypersensitivity to any constituent
Flu vaccine Live attenuated influenza (LAIV)	107 EID 50 of two Type A and 106.5 EID 50 of one Type B (differs according to Northern/ Southern Hemisphere and usually yearly) inactivated influenza virus	Lyophilized, sterile water-based specific liquid diluent	2–8°C	0.25 mL in each nostril	Single dose above 2 years of age	*Effectiveness*: 80–85%	None	Severe hypersensitivity to any constituent, less than 2 years or above 50 years, h/o asthma, GBS, on antiflu medications or aspirin

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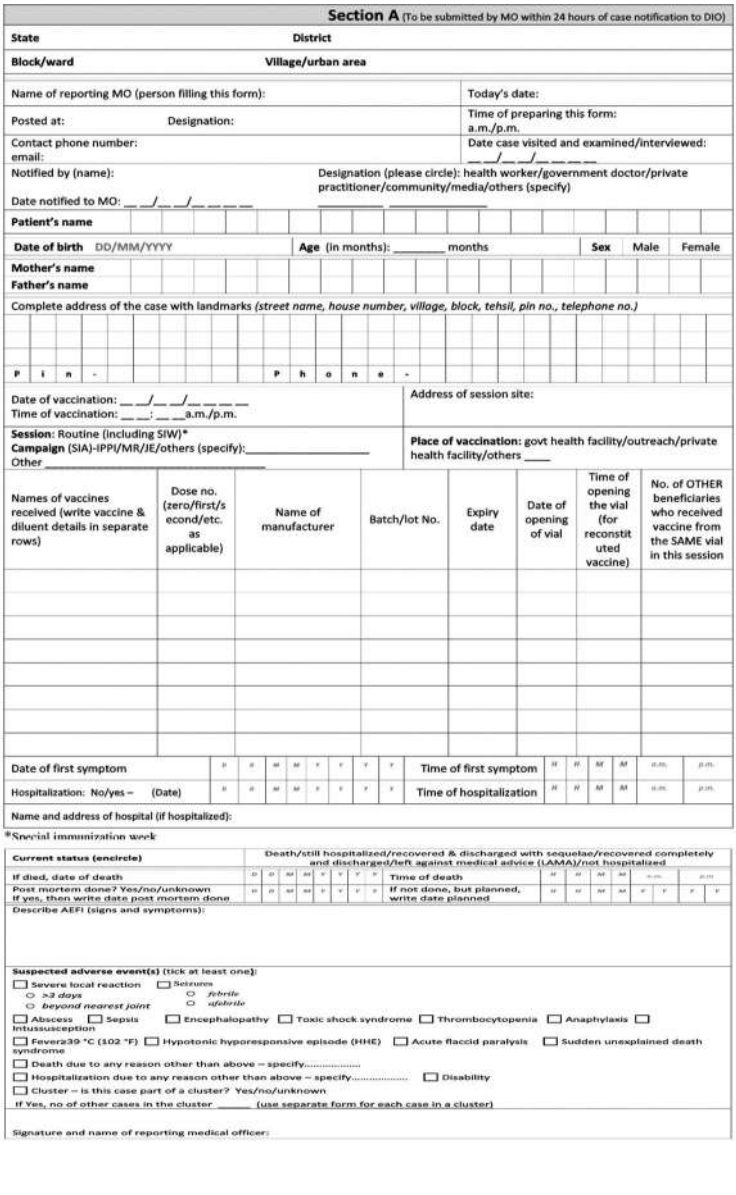
Vaccine	*Content/dose*	*Nature and diluent*	*Storage*	*Dose, route, and site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
Yellow fever vaccine	17D strain of yellow fever virus	Lyophilized, sterile diluent	2–8°C	0.5 mL SC thigh/ deltoid	Single dose, revaccination every 10 years if needed	>90%	Rarely neurologic/ visoerotropic disease	Below 6 months, serious egg allergy severe immunodeficiency, thymus disease
Cholera	1.5 mL contains killed bivalent (O1 and O139) strains of *V Cholerae*	Liquid vaccine	2–8°C	1.5 mL po	Two doses above 1 year and 2 weeks apart	60%	None	None

(BCG: Bacillus Calmette–Guérin; LAV: live attenuated vaccine; bOPV: bivalent oral poliovirus vaccine; IPV: inactivated polio vaccine; ID: intradermal; MMR: measles, mumps, and rubella; NID: National Immunization Days; SNID: sub-National Immunization Days; VAPP: vaccine-associated paralytic polio; SC: subcutaneously; IM: intramuscularly; DTwP: diphtheria, tetanus and whole-cell pertussis; DTaP: diphtheria, tetanus and acellular pertussis; DT: diphtheria and tetanus; HHE: hypotonic-hyporesponsive episode; TT: tetanus toxoid; Td: tetanus and diphtheria; Tdap: diphtheria toxoid and acellular pertussis; $CCID_{50}$: cell culture infectious dose 50%; ITP: immune thrombocytopenic purpura; MMRV: measles, mumps, rubella, and varicella; Hep B: Hepatitis B; Hib: *Haemophilus influenzae* type b; PRP-T: polyribosylribitol phosphate-tetanus; HbOC: *Haemophilus influenzae* oligosaccharide CRM197 conjugate; HPV: human papillomavirus; PCV: pneumococcal conjugate vaccine; PPSV23; pneumococcal polysaccharide vaccine; PFU: plaque-forming unit; JE: Japanese encephalitis; MPSV: meningococcal polysaccharide vaccine; MCV: meningococcal vaccine; IIV: inactivated influenza vaccine; EID: emerging infectious diseases; GBS: Guillain-Barré syndrome)

ANNEXURE IV

AEFI Reporting Form



Section A (To be submitted by MO within 24 hours of case notification to DIO)

State **District**

Block/ward **Village/urban area**

Name of reporting MO (person filling this form): | Today's date:

Posted at: Designation: | Time of preparing this form: a.m./p.m.

Contact phone number: email: | Date case visited and examined/interviewed: __ __/__ __/__ __ __ __

Notified by (name): Designation (please circle): health worker/government doctor/private practitioner/community/media/others (specify)

Date notified to MO: __ __/__ __/__ __ __ __ _____ _____

Patient's name

Date of birth DD/MM/YYYY | **Age** (in months): _____ months | **Sex** Male Female

Mother's name

Father's name

Complete address of the case with landmarks *(street name, house number, village, block, tehsil, pin no., telephone no.)*

P i n - P h o n e -

Date of vaccination: __ __/__ __/__ __ __ __
Time of vaccination: __ __: __ __a.m./p.m.

Address of session site:

Session: Routine (including SIW)*
Campaign (SIA)-IPPI/MR/JE/others (specify):_____
Other _____

Place of vaccination: govt health facility/outreach/private health facility/others ____

Names of vaccines received (write vaccine & diluent details in separate rows)	Dose no. (zero/first/second/etc. as applicable)	Name of manufacturer	Batch/lot No.	Expiry date	Date of opening of vial	Time of opening the vial (for reconstituted vaccine)	No. of OTHER beneficiaries who received vaccine from the SAME vial in this session

Date of first symptom D D M M Y Y Y Y | Time of first symptom H H M M a.m. p.m.

Hospitalization: No/yes – (Date) D D M M Y Y Y Y | Time of hospitalization H H M M a.m. p.m.

Name and address of hospital (if hospitalized):

*Special immunization week

Current status (encircle) Death/still hospitalized/recovered & discharged with sequelae/recovered completely and discharged/left against medical advice (LAMA)/not hospitalized

If died, date of death D D M M Y Y Y Y | Time of death H H M M a.m. p.m.

Post mortem done? Yes/no/unknown
If yes, then write date post mortem done D D M M Y Y Y Y | If not done, but planned, write date planned D D M M Y Y Y Y

Describe AEFI (signs and symptoms):

Suspected adverse event(s) (tick at least one):

☐ Severe local reaction ☐ Seizures
○ *>3 days* ○ *febrile*
○ *beyond nearest joint* ○ *afebrile*

☐ Abscess ☐ Sepsis ☐ Encephalopathy ☐ Toxic shock syndrome ☐ Thrombocytopenia ☐ Anaphylaxis ☐ Intussusception

☐ Fever≥39 °C (102 °F) ☐ Hypotonic hyporesponsive episode (HHE) ☐ Acute flaccid paralysis ☐ Sudden unexplained death syndrome

☐ Death due to any reason other than above – specify.....

☐ Hospitalization due to any reason other than above – specify..... ☐ Disability

☐ Cluster – Is this case part of a cluster? Yes/no/unknown

If Yes, no of other cases in the cluster _____ (use separate form for each case in a cluster)

Signature and name of reporting medical officer: