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Editors

M Indra Shekhar Rao
Srinivas G Kasi

Forewords

Remesh Kumar R
Upendra Kinjawadekar
Piyush Gupta
Vineet K Saxena

JAYPEE

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Chapter 1

Immunization in India: Past, Present, and Future

M Indra Shekhar Rao, Shivananda S

INTRODUCTION

Immunization is one of the most cost-effective public health interventions and largely responsible for reduction of under-5 mortality rate and indeed, is one of the strong pillars of child survival. However, vaccine-preventable diseases (VPDs) are still responsible for over 5 lakhs deaths annually in India.

STORY SO FAR

India and China were two countries where "some form of inoculation" was practiced even before 16th century. However, modern immunization developed in India in 19th century, parallel to the Western world. The Compulsory Vaccination Act was passed in India in 1892 to ensure higher coverage with smallpox.

In 1904–1905, Central Research Institute was set up in Kasauli, Himachal Pradesh and then Pasteur Institute in Coonoor in 1907. The Pasteur Institute of India produced neural tissue antirabies vaccine in 1907, subsequently developed influenza vaccines, trivalent oral polio vaccines (OPV) and first tissue culture, and then Vero cell-derived rabies vaccine. As early as 1955–1956, the bacillus Calmette–Guérin (BCG) vaccination mass campaign was initiated in India.

In 1958, World Health Assembly (WHA) passed a resolution to eradicate smallpox; India started National Smallpox Eradication Programme (NSEP) in 1962, and universal vaccination of entire population within 3 years was planned in two phases—attack phase with 80% coverage of population followed by maintenance phase to include all newborns, infants, and children.

The last case was reported in 1975 from West Bengal, but surveillance continued thereafter. The world was declared free from smallpox on May 8, 1980 by the World Health Assembly.

The Pasteur Institute of India developed influenza vaccine in 1957, the beta-propiolactone (BPL) inactivated rabies vaccine, and trivalent OPV in 1970. There were nearly 19 vaccine-manufacturing units in public sector and 12 in private sector in 1971.

Universal Immunization Programme (UIP) is one of the largest public health programs. Routine immunization (RI) targets to vaccinate 29 million newborns each year, with all primary doses, nearly 100 million children of 1–5 years of age with booster doses of UIP vaccines and 30 million pregnant mothers are targeted for tetanus toxoid (TT) vaccination each year.

Most of the immunization sessions are focused in rural areas. 89.8% of vaccination in India is provided through public sector, while private sector contributed to only 8.7%. As per Coverage and Evaluation Survey (2009), India has an annual birth cohort of ~2.67 crores **(Table 1)**.

BACKGROUND NOTES AND PRESENT STATUS OF IMMUNIZATION

In 1978, after the Alma-Ata declaration aimed at immunizing all, the children Expanded Programme on Immunization (EPI) was launched in 1978. It was renamed as *UIP* in 1985, when its reach was expanded beyond urban areas. In 1992, it became part of Child Survival and Safe Motherhood Programme and in 1997, it was included in the ambit of National Reproductive and Child Health Programme. Since the launch of National Rural Health Mission in 2005, UIP has always been an integral part of it.

The UIP is one of the largest public health programs targeting close of 2.67 crore newborns and 2.9 crore pregnant women annually, with all primary doses, nearly 100 million children of 1–5 years of age with booster doses of UIP vaccines and 30 million pregnant mothers are targeted for TT vaccination each year.

A child is said to be fully immunized if child receives all due vaccine as per national immunization schedule within 1st year age

TABLE 1: Vaccine milestones in India.

Year	*Vaccine*	*Milestone remarks*
1985	BCG; diphtheria, pertussis, and tetanus (DPT); OPV; and measles-containing vaccine (MCV)	Universal Immunization Programme (UIP) launched with six antigens
2002	Hepatitis B—pilot	Hepatitis B vaccine launched as a pilot program in 33 districts and 14 metropolitan areas
2006–2010	Japanese encephalitis (JE)	JE vaccine added to the UIP in selected endemic districts in a phased manner
2007–2011	Hepatitis B—scale up	Hepatitis B vaccination scaled up to cover 10 additional states of India
2010	Measles-containing vaccine dose 2 (MCV2) + rubella	MCV2 (in the form of measles-rubella vaccine) added to the UIP in 21 states (in the remaining 14 states, a catchup campaign was initiated for children aged 9 months to 9 years)
2011	*Haemophilus influenzae* type b (Hib)-83	Hib vaccine introduced as the pentavalent (DPT + Hib + HepB) vaccine in two states (Tamil Nadu and Kerala)
2016	Human papillomavirus-84	Pilot program launched by state governments in Delhi and Punjab
2016–2018	Rotavirus-85	Introduced in two phases in nine states (Andhra Pradesh, Haryana, Himachal Pradesh, Odisha, Assam, Madhya Pradesh, Rajasthan, Tamil Nadu, and Tripura)
2017–2019	Pneumococcal conjugate vaccine (PCV)-86	PCV introduced in selected high-burden districts in six states (Bihar, Uttar Pradesh, Haryana, Himachal Pradesh, Rajasthan, and Madhya Pradesh)

(BCG: bacillus Calmette-Guérin; HepB: hepatitis B; OPV: oral polio vaccine)

of child. The two major milestones of UIP have been the elimination of polio in 2014 and maternal and neonatal tetanus elimination in 2015.

The new vaccines introduced in recent years are:

- Inactivated polio vaccine (IPV), November 2015–April 2016
- *Rotavirus vaccine (RVV):* In March 2016 and expanded across the country in 2019–20
- *Measles rubella (MR) vaccine:* Introduced in the country through a campaign mode in 2017, followed by two doses in RI at 9–12 months and 16–24 months
- *Pneumococcal conjugate vaccine (PCV):* Launched in May 2017 and now escalated to the entire country
- *Tetanus and adult diphtheria (Td) vaccine:* Which replaced the TT vaccine in UIP to limit the waning immunity against diphtheria in older age groups. Td vaccine to be administered to adolescents at 10 and 16 years of age and to pregnant women.

Immunization Coverage in India

The immunization coverage in India is described in **Table 2**.

THE ROAD AHEAD AND THE FUTURE

Political and Bureaucratic Will

Such an elaborate National program obviously needs political and bureaucratic support at all levels. "Inter Agency Coordination Committee" (ICC) needs to increase its focus on RI. A public–private partnership (PPP) between government of India (GoI), National Technical Advisory Group on Immunization (NTAGI), Indian Academy of Pediatrics (IAP), Indian Medical Association (IMA), development partners, Integrated Child Development Services, Ministries of Railways, Education and Defense, and key nongovernmental organizations (NGOs) involved with immunization and State representation should be strengthened and monitored funds.

TABLE 2: The immunization coverage in India.

	Coverage (%)		
Antigens/vaccines	***2000***	***2010***	***2018***
BCG	58	79	89
DTP3	—	38	89
HepB3	56	82	90
MCV1	—	—	80
MCV2	85	87	90
PAB	85	76	89
Pol3	—	—	35
Rotavirus	—	—	89
Hib3	—	—	6

(BCG: bacillus Calmette–Guérin; DTP: diphtheria; HepB: hepatitis B; MCV: meningococcal vaccine; PAB: protection-at birth; Pol: polio; Hib: *Haemophilus influenzae* type B)

Proper Monitoring of the Program

Vaccination is an essential preventive medical intervention; the vaccination program is not simply a medical modality—it is a management-dominant modality. The managerial, administrative, and governance-related inadequacies need to be addressed on a priority basis for successful flow of the program throughout the country.

Develop Effective Surveillance Systems

Universal Immunization Programme is an opportunity to establish a surveillance system for all important childhood infectious diseases as has been demonstrated by the experience of acute flaccid paralysis (AFP) surveillance network in India. Efficient surveillance systems will work even in resource-poor settings, at quite low cost relative to the cost of the intervention itself.

ADVERSE EFFECTS, DETECTION, REPORTING, AND REDRESSAL SYSTEM

Having a functional real-time adverse events following immunization (AEFI) and post-marketing surveillance system will help in generating national data and also will be useful to allow compensation claims for vaccination-related injuries and serious adverse events should the need arise, this will also provide sound basis for decisions to modify or abandon certain vaccine preparations based on reactogenicity profile.

REGULATORY AND ETHICAL ISSUES

The existing National Regulatory Authority (NRA) of the country is reliable and properly functioning. Currently, the Indian NRA, i.e., the Drug Controller General of India, though overburdened, is performing many diverse tasks including marketing authorization and licensing activities related to drugs, cosmetics, vaccines, etc. There is need to have a vaccine-specific NRA to oversee different issues related to vaccines such as licensing, postmarketing surveillance including AEFI surveillance, batch release process, laboratory support for vaccine testing, regulatory inspections of Good Manufacturing Practices (GMPs), authorization and approval of clinical trials, etc. Hence, the NRA has to be a more competent, effective, independent, and transparent body.

We need single window system to avoid regulatory delays, and strict guidelines for approval and cancellation of license must be formulated and practiced. We need clear national guidelines on the ethical conduct of clinical trials. Ethical concerns, skepticism, and low vaccination rates persist despite India's emergence as a global manufacturing leader in vaccines.

SUPPORT TO INDIGENOUS VACCINE INDUSTRY, RESEARCH AND DEVELOPMENT

Most low-cost traditional vaccines are now produced by vaccine manufacturers in India. Currently, about 43% of the global UIP vaccines come from India, and the Serum Institute is the world's leading producer of the UIP vaccines. Investment in research and

development is bound to pay rich dividends. A large number of vaccine products are currently in the pipeline and are expected to become available in near future. According to recent unpublished data, more than 80 candidate vaccines are in the late stages of clinical testing. About 30 of these candidate vaccines aim to protect against major diseases for which no licensed vaccines exist, such as malaria and dengue. Vaccines manufactured in India include—coronavirus disease (COVID) vaccines, RVVs, PCV, Japanese Encephalitis vaccines, and the 4HPV vaccine by the Serum Institute of India, which recently received market authorization.

The current national vaccine policy is supportive of the Indian vaccine industry with liberal support from government-owned institutions such as Department of Biotechnology (DBT), National Institute of Immunology (NII), and department of science, however, there is need to further empower Indian vaccine sector to meet the indigenous demand of vaccines. The time has come to develop a more effective PPP and a shared responsibility of meeting demand of local vaccine need is the need of the hour.

INTEGRATED DELIVERY OF HEALTH INTERVENTIONS

Strengthening of immunization systems so that they support and integrate with other preventive health services such as providing vitamin A supplementation, deworming, growth monitoring, and distribution of insecticide-treated bed nets offers the opportunity to create synergies and facilitate the delivery of services to bolster comprehensive disease prevention and control. Incorporating immunization into integrated primary healthcare programs may also facilitate social mobilization efforts, help to generate community demand for services, and address equity issues. The strategy of child health days, led by UNICEF, has also helped to promote RI.

CONCLUSION

India is on strong path when it comes to promoting the health, economic, and social well-being of its citizens. Indian government

will do well to dedicate itself to continue to expand its coverage, expand the number of vaccines in UIP, and expand its manufacturing industries. This must be done while managing Gavi transition and avoiding backsliding as a result. Committing to sustained investment in immunization will heap wonderful results in child health.

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Chapter 2

General Aspects of Vaccination

2.1 BASIC IMMUNOLOGY

Arun Wadhwa, Abhay Shah

IMMUNOLOGY OF VACCINATION

Vaccination: It is the act of introducing a vaccine into the body to stimulate the *immune system* to induce protection against infection or disease.

Immunization: It is a process by which a person becomes protected against a disease, generally through vaccination.

INNATE AND ADAPTIVE IMMUNE RESPONSES

Immunity may be broadly classified as innate and adaptive. 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]

TABLE 1: Differentiating features between innate and adaptive immunity.

Characteristic	*Innate*	*Adaptive*
Definition	The resistance to infection that an individual possesses by virtue of genetic and constitutional makeup; i.e., by birth	The resistance that an individual acquires in response to exposure to a foreign substance during their lifetime
Specificity	Antigen independent	Antigen specific
Time taken to respond	Immediate—hours	Late—days/weeks
Memory response	None	Present
Cells involved	Dendritic leukocyte, natural killer cells, mast cell, granulocytes/ macrophages, basophils, etc.	Predominantly lymphocytes: Killer CD8+ T cells, helper CD4+ T cells, B cells, and antigen-presenting cells
Chemical mediators	Cytokines, complement, interferon, acute phase reactants	Antibodies, cytokines

Humoral immunity is conferred by B lymphocytes, which is the principal defense mechanism against extracellular microbes and their toxins. These activated B cells differentiate into antibody (Ab) secreting plasma cells. For effective Ab production, B cells need help from T helper cells.

B lymphocytes secrete Abs 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 Abs prevent colonization, being the first step in pathogenesis by encapsulated organisms such as Hib (*Haemophilus influenzae* type b), pneumococcal, meningococcal, and organisms such as diphtheria and pertussis. Abs 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 mediated by T cells, which is the principal defense mechanism against intracellular microbes. The

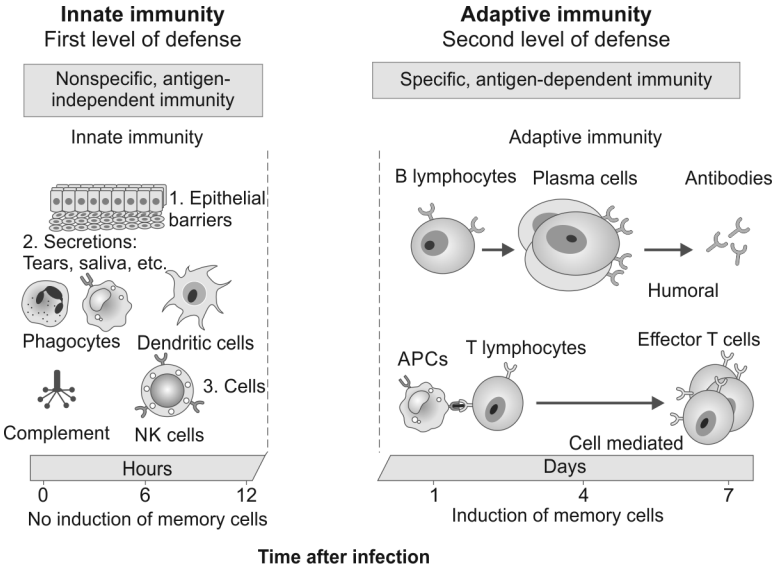

Fig. 1: Innate and adaptive immunity. (APC: antigen-presenting cell; NK cells: natural killer cells)
Source: Adapted from Vashishtha VM, Kalra A, Thacker N. FAQ on Vaccines and Immunization Practices. New Delhi: Jaypee Brothers Medical Publisher; 2011.

effectors of CMI and 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.[2]

CD4 T cells play critical roles in mediating adaptive immunity to a variety of pathogens/antigens. Naïve CD4 T cells may differentiate into one of several lineages of T helper (Th) cells, including Th1, Th2,

Th17, and iTreg, as defined by their pattern of cytokine production and function.

- Th1 cells produce interleukin-2 (IL-2) and interferon gamma and are involved with intracellular organism such as mycobacteria and induce T-cell response.
- Th2 induces IL-4, IL-5, and IL-13 cytokine-induced humoral response against extracellular organisms.
- Th17 plays a crucial role at mucosal and epithelial surfaces. Whole-cell pertussis (wP)-containing DPT (diphtheria, pertussis, and tetanus) vaccines elicit Th1 and Th17 skewed response whereas an aP containing vaccine induces Th2-skewed response.
- iTreg cells are essential to the balance between pro- and anti-inflammatory responses.

In addition to B cells and T cells, the antigen-presenting cells (APCs) have a very important role to play, in the immune response. APCs are a heterogeneous group of immune cells that mediate the adaptive immune response, by processing and presenting antigens for recognition by certain lymphocytes such as T cells. Classical APCs include dendritic cells, macrophages, Langerhans cells, and B cells.

Dendritic cells (DCs) are the only cells, capable of activating naïve T cell and play a crucial role in the induction of T-cell response. They act as messengers between the *innate* and the *adaptive immune systems*. They capture antigen, process then into small peptides, display them through major histocompatibility complex (MHC) molecules, and provide costimulation signals to activate antigen-specific T cells.

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) enter(s) the body, strong immune response is mounted. Passive immunity is conferred by maternal Abs 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 certain pathogens, e.g., rabies virus, *Clostridium tetani*, or hepatitis B virus (HBV).

TYPES OF VACCINES

Vaccines may be broadly classified as follows:

- *Live-attenuated vaccines (LAVs):* BCG, oral polio, measles, MMR (measles, mumps, and rubella), varicella, rotavirus, yellow fever, live Influenza vaccine, and live hepatitis A
- *Inactivated vaccines:*
  - *Whole-cell inactivated:* Whole-cell pertussis vaccines, rabies, inactivated poliovirus (IPV), and hepatitis A
  - *Toxoids:* Tetanus and diphtheria
  - *Sub-unit vaccines:* They differ from inactivated whole-cell vaccines, by containing only the antigenic parts which are necessary to elicit a protective immune response. They are as under:
    - *Protein vaccines:* Subunit vaccines—acellular pertussis, HBV, and some influenza
    - *Pure polysaccharide vaccines:* Typhoid, pneumococcal polysaccharide vaccine (PPSV), and meningococcal polysaccharide vaccine
    - *Conjugated polysaccharide vaccines:* Hib-CV, typhoid-CV, PCV, and meningococcal-CV
    - *Virus-like particle (VLP):* HPV
    - *DNA and RNA vaccines:* COVID-19 vaccines.

HOW DO VACCINES WORK?

Vaccines play a crucial role in prevention, disease attenuation, elimination, and eradication of vaccine-preventable diseases (VPDs).

Early protective efficacy of currently available vaccines is primarily conferred by the induction of antigen-specific Abs 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 Ab production. Other important mechanisms by which CMI works are 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 vaccine injection, the vaccine antigens attract local and systemic DCs, monocytes, and neutrophils. Innate immune responses activate these cells by changing their surface receptors, which migrate along lymphatic vessels, to the draining lymph nodes, where the activation of T and B lymphocytes takes place. The type of response elicited will depend upon the type of vaccine, its antigenic type and content, and immune status of an individual. Vaccines that stimulate innate immunity effectively are better immunogens. This can be achieved by live vaccines, adjuvants: TLRs agonists, live vectors, and DNA vaccines. Live vaccines are capable of activating innate immunity in a better way, which is helpful for subsequent induction of adaptive immune effectors. During their journey, the attenuated organisms undergo dissemination and replication and activate large number of DCs. The activated DCs migrate toward the corresponding draining lymph nodes and launch multiple foci of T- and B-cell activation. LAVs stimulate an excellent immune response as they mimic a natural infection. Large number of DCs take up vaccine antigen in multiple tissues and provide continual antigenic stimulation giving sufficient time for memory cell production.

In case of killed vaccines, there is only local and unilateral lymph node activation. 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 DCs/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 DCs is preferred over the subcutaneous route. Intradermal route recruits the abundant DCs 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 and at different time intervals, with 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,* and *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 help from antigen specific T cells, B cells activate, proliferate, and differentiate into plasma cells without undergoing affinity maturation in germinal centers (GCs). The Ab response sets in 2–4 weeks following immunization, and is predominantly IgM with low titers of low affinity IgG. The half-life of the plasma cells is short and Ab titers decline rapidly.

Additionally, the PS antigens are unable to evoke an immune response in those aged <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 Ab 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.[3,4]

Immune Response to Protein Antigens or T cell-dependent Antigens

Protein antigens 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 DCs trigger some antigen-specific B cells to migrate toward follicular dendritic cells (FDCs), initiating the GC reaction. In GCs, 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 Abs. Most of the plasma cells die at the end of GC reaction and thus decline in Ab levels is noted 4–8 weeks after vaccination. However, a few plasma cells exit in lymph nodes and 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 Abs 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 Abs that may be detected in the serum within a few days after boosting.[2,5]

Germinal Center Reaction (Fig. 2)

The development of this GC reaction requires a couple of weeks, such that hypermutated IgG Abs to protein vaccine antigens first appear in the blood 10–14 days after priming. It is the magnitude of GC responses, i.e., the quality of DC, B cell, T cell, and FDC interactions, which controls the intensity of B cell differentiation into plasma cells, and thus the peak of IgG vaccine Ab reached within 4–6 weeks after primary immunization.

Immune Response to Live Vaccines

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

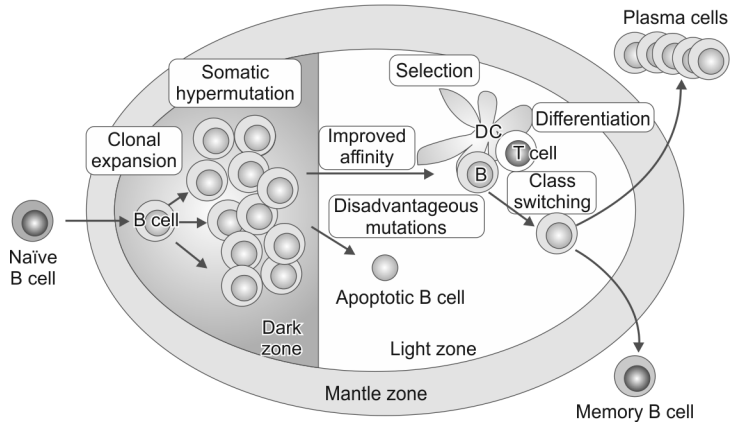

Fig. 2: The germinal center reaction. (DC: dendritic cell)

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 Abs over time). However, mumps does not follow this general principle and waning Ab levels has been demonstrated, therefore, the need for a subsequent doses.[6,7]

PRIMARY VERSUS SECONDARY IMMUNE RESPONSES

When an antigen is introduced for the first time, the immune response starts after a lag of 10 days or so. This is called primary response. In primary immune response, the antigen exposure elicits an extrafollicular response that results in the rapid appearance of low IgG Ab titers. As B cells proliferate in GCs and differentiate into plasma cells, IgG Ab titers increase up to a peak value usually reached 4 weeks after immunization. The short lifespan of these plasma cells results in a rapid decline of Ab titers, which eventually return to baseline levels.[2]

Secondary immune responses start on subsequent exposure (booster) to the same antigen. There is no lag phase, response

starts in <7 days, persists for a long time, mainly IgG type with high Ab titers. In secondary immune responses, booster exposure to antigen reactivates immune memory (memory B cells) and results in a rapid (<7 days) increase of IgG Ab titer by a rapid proliferation of memory B cells and their evolution into abundant Ab-secreting plasma cells. Short-lived plasma cells maintain peak Ab levels during a few weeks—after which serum Ab 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 Abs, which then decline with slower kinetics. This generic pattern may not apply to live vaccines triggering long-term IgG Abs for extended periods of time.[2]

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

Broadly speaking, live vaccines are superior (exception BCG and OPV) to protein antigens which in turn are superior to polysaccharide vaccines:

- *Live versus inactivated:* Higher intensity of innate responses, higher antigen content following replication, and more prolonged antigen persistence generally result into higher Abs responses to live than inactivated vaccines.
- *Protein versus polysaccharide:* Recruitment of T-cell help and induction of GCs results into higher Ab responses to protein or glycoconjugate than to PS vaccines. Hence, broadly speaking, live vaccines are superior (exception BCG and 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 Ab responses.[2] Thus, less amount of active ingredient per dose is required for an immune response similar to vaccines without adjuvant. However, adjuvants may cause some side effects.

Antigen Nature

- *Polysaccharide antigens:* Failure to induce GCs limits 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 Ab 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 antigen.

Vaccination Schedule

The immune response improves with increasing number of doses and increased spaces between doses.

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 such as hepatitis-B vaccine. This is mainly due to adequate time interval between first few doses which act by inducing immune responses and last dose that works as boosters. Since, affinity maturation of B cells in GCs and formation of adequate numbers of memory B cells take at least 4–6 months, this schedule fulfils these requirements **(Fig. 3)**.

More than one dose is needed for better induction and recruitment of a greater number of GCs in young age considering young age limitations of immune system. A 4-week minimal interval

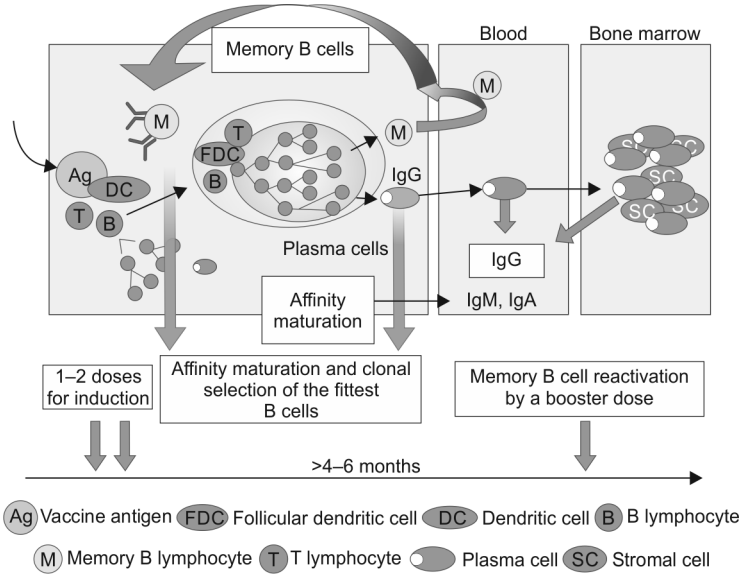

Fig. 3: Schematic presentation of various components of 0–1–6 months immunization schedule at cellular level.
Source: Adapted from Vashishtha VM, Kalra A, Thacker N. FAQ on Vaccines and Immunization Practices. New Delhi: Jaypee Brothers Medical Publisher; 2011.

between primary doses avoids competition between successive waves of primary responses.[2,6]

Other Factors

- *Genetic factors:* The capacity of antigen epitopes to associate to a large panel of MHC molecules increases the likelihood of responses in the population. MHC restriction may limit T-cell responses. Gene polymorphisms in molecules critical for B and T cell activation/differentiation are likely to affect Ab responses. 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.[2]

Secondary Immune Responses

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

- *Live versus inactivated:* Live vaccines generally induce more sustained Ab 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 preexisting Ab 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.[2]

IMMUNE MEMORY AND NEED FOR BOOSTERS

Immune memory allows one to complete an interrupted vaccine schedule without restarting the schedule. 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 Abs usually take 4–7 days. Diseases which have incubation periods shorter than this period such as Hib, tetanus, diphtheria, pertussis, and meningococcus require regular boosters to maintain protective Ab levels. However, diseases such as hepatitis A and 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 Abs and immaturity of immune system. Young age limits Ab responses to most vaccine antigens since maternal Abs inhibit Abs responses but not T-cell response, and due to limitation of B-cell responses.[8,9]

Immunoglobulin G Abs are actively transferred through the placenta, via the FcRn receptor, from the maternal to the fetal circulation. Upon immunization, maternal Abs 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 Abs 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 Abs. Hence, Ab 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 Abs increase with gestational age, e.g., with the amount of transferred immunoglobulins, and decline with postnatal age as maternal Abs wane.[2,10]

Early life immune responses are characterized by age-dependent limitations of the magnitude of responses to all vaccines. Ab 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 Abs interfere with the induction of infant Ab 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, Abs 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 Abs, as illustrated for hepatitis A or measles vaccines.

Impact of Young Age Limitations on Immunization Schedules

Disease epidemiology of 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 Abs. 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 (two doses at 6–12 months followed by a booster dose and one to two doses between 12 and 23 months for Hib and pneumococcal vaccines).

Live vaccines are even more susceptible to maternal Abs as compared to killed vaccines. However, BCG may be given as the maternal Abs 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.[2]

CORRELATES OF VACCINE-MEDIATED IMMUNITY

A given marker that is measurable, whether the Ab 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 Ab in the serum of a vaccine. Measurement of cellular components is difficult, invasive, and highly cost intensive. The correlate can be absolute, e.g., Hib (0.15 mg/mL) and hepatitis B (10 mIU/mL), which are directly protective or surrogates (indirect markers), e.g., varicella (GP Elisa units) and ROTA (IgA). Diseases such as 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.

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2.2 ELEMENTARY EPIDEMIOLOGY

Shashi Kant Dhir, Sanjay Verma

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 pinpoint 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 an assessment of the 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. Finally, 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

tuberculosis (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, as 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 depend 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, 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, and 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 more than three cases in <3 months in the same area, among those 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 and H1N1.[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*/*Haemophilus influenzae* type B (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 is attack rate in unvaccinated population, ARV is attack rate in vaccinated population, and VE is 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 bacillus Calmette–Guérin (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 three doses inactivated polio vaccine (IPV) reached 51%, 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 such as 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" does 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 such as rubella, varicella, and hepatitis A, wherein severity of disease worsens with advancing age.

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2.3 VACCINE-PREVENTABLE DISEASE SURVEILLANCE AND IDsurv

Chandra Mohan Kumar, Sanjay Verma

BACKGROUND

Disease surveillance is an essential component of public health programs. The key objectives of an efficient surveillance system are first to assess the burden of 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 to initiate investigations and control measures. Surveillance of vaccine-preventable diseases (VPDs) acquires a higher significance than all other surveillance systems, such as surveillance of noncommunicable illnesses, since most infectious diseases are now being prevented by highly effective vaccines. The number of effective vaccines will go up further in the coming time, considering the rapid advancements 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 the epidemiology of a disease
- To identify high-risk populations and regions having high transmission of the disease
- To monitor the progress of a disease control program
- To specify and monitor molecular epidemiology of infectious disease, including identification of circulating strains of the pathogen responsible for the infectious disease
- To monitor the impact of the vaccination program on overall disease epidemiology.

SURVEILLANCE: TERMINOLOGIES

- *Active surveillance*, which is done actively by designated persons at any health institutions or community. For example,

acute flaccid paralysis (AFP) surveillance was 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) and Infectious Disease Surveillance System (IDsurv).
- *Sentinel surveillance*, where clinical syndromes after laboratory confirmation are reported from selected health institutions, such as Rotavirus (Indian National Rotavirus Surveillance Network) and *Haemophilus influenzae* type b (Hib) surveillance.
- *Population-based surveillance* is conducted for selected groups with active diseases in a well-defined area/population.
- *Outbreak surveillance*, where notification is done only whenever there is a 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 such as 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 a lack of disease burden data on many important VPDs in India in the perception that the disease is not an important public health problem. Further, there is a scarcity of diagnostic tools for certain VPDs. Lack of baseline surveillance data also is a bottleneck in the 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]

VACCINE-PREVENTABLE DISEASE SURVEILLANCE SYSTEMS EXISTING IN INDIA

Following are the key surveillance systems in India:

- *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 National Institute of Virology (NIV), Pune for measles virus isolation and genotyping (Measles NetIndia).
- *AES/JE—NVBDCP (National Vector-borne Disease Control Programme) and ICMR:* Facility-based surveillance for AES in endemic areas. It is run by the Government of India under NVBDCP.
- The WHO-NPSP played a critical role in strengthening surveillance for polio that generated useful, timely, and accurate data to guide policies, strategies, and interventions until transmission of the poliovirus was interrupted in the country.

WHO-SUPPORTED SURVEILLANCE SYSTEMS

Motivated by the success of AFP surveillance, which has been active surveillance done by designated persons at any health institution or community, where the diagnosis was supported by laboratory reports. Now, this nationwide WHO-supported surveillance network will also provide surveillance for other VPDs in India.[3]

For VPD surveillance, efforts are being made to move from a passive surveillance system that includes all the diseases and conditions under national surveillance (IDSP) to active surveillance (syndromic approach) supported by laboratory investigations of each reported case on the framework of polio surveillance. Currently, this is involved in the surveillance of six diseases, which include:

1. Acute flaccid paralysis
2. Measles
3. Rubella
4. Neonatal tetanus
5. Pertussis
6. Diphtheria.

The WHO case definition for reporting of a suspected case include:
Measles/rubella:

Any person with fever and maculopapular rash (within last 3 months) with:

- Cough
- Coryza (running rose)
- Conjunctivitis (red eyes)
- Any person in whom a clinician suspects measles/rubella infection.

Diphtheria:
Any illness of upper respiratory tract characterized by:

- Laryngitis or pharyngitis or nasopharyngitis or tonsillitis
- Adherent membranes of tonsils, pharynx, and/or nose.

Pertussis:
A person with a cough lasting at least 2 weeks with at least one of the following:

- Paroxysms (i.e., fits) of coughing
- Inspiratory whooping
- Posttussive vomiting
- Apnea (only in <1 year of age)
- A person in whom a clinician suspects pertussis without other apparent cause.

All health facilities, including government, nongovernmental organizations (NGOs), private clinics, hospitals, and laboratories, should notify all cases under surveillance to District Surveillance Officer every month.

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 events following immunization) reporting system for reporting severe AEFI, known as IDsurv.org.[4]

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 the 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:

- Acute bacterial meningitis
- Chickenpox
- Diphtheria
- Dengue
- Enteric fever
- Measles
- Mumps
- Pertussis
- Pneumonia
- Hepatitis.

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2.4 PRACTICAL ASPECTS OF IMMUNIZATION

M Indra Shekhar Rao, Sanjay Srirampur

COMMUNICATING WITH PARENTS/CAREGIVERS

With several new vaccines available for use, it is an arduous task for pediatricians to offer appropriate advice to parents regarding pros and cons of each vaccine. Most of these vaccines are included in the Indian Academy of Pediatrics' (IAP's) recommendations. Thus, pediatricians are required to communicate a balanced scientific view, with clarity, to enable the parents to make the right decisions. Unfortunately, most of the educated parents would leave the choice to their pediatricians.

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 <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, three doses of measles, mumps, and rubella (MMR) vaccine, are 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

If the hands are visible dirty, they should be washed with soap and water for 2 minutes using WHO's 6-step technique. If hands are not visibly dirty, alcohol-based waterless antiseptic hand rub can be used, before every patient encounter. 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 disposable. Auto-disposable (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 are 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 needlestick 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

Vaccines are administered by oral, subcutaneous (SC), intradermal (ID) or intramuscular (IM) routes. OPV and rotavirus vaccines are administered orally, MMR, varicella, live-attenuated Japanese encephalitis (JE), live-attenuated hepatitis A vaccine (HAV), and yellow fever vaccines are administered SC, rest are administered by the IM route. Generally, vaccines meant for SC administration are valid if inadvertently administered IM. However, doses of inactivated HAV vaccine and IPV, if inadvertently administered SC, are considered valid. The IM route is crucial for HBV, HPV, and rabies vaccines and the dose should be repeated, if given SC.

Generally, 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

BOX 1: General instructions on immunization.

- Vaccination at birth means as early as possible within 24 hours after birth or at least not later than 1 week after birth
- Whenever multiple vaccinations (including two live parenteral vaccines) are to be given simultaneously, they should be administered in the same sitting or they should be administered on the same clinic day (conventionally a clinic day consists of 6 hours)
- The recommended age in weeks/months/years means completed weeks/months/years
- Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible
- There is no recommendation to wait until a vaccine reaches room temperature before administration. The vaccine should be administered as soon as it is prepared
- Immediate administration after reconstitution of a vaccine implies the reasonable time it takes to prepare, transport the vaccine to the patient to be administered and the limited documentation that may be related to this process. This interval should not exceed 30 minutes
- 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 at least 4 weeks after the early dose
- The minimum interval between two 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 and has to be repeated. This rule does not apply to live, parenteral vaccines
- Any number of antigens can be given on the same day. Two or more inactivated or inactivated and live vaccines can be administered at any interval between them. Two or more live, parenteral vaccines, should be administered on the same day or 4 weeks apart **(Table 1)**
- 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)

Contd...

Contd...

- 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 do not overlap. For older children and adults, the deltoid muscle can be used for more than one IM injection **(Table 2)**
- 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)**:
  - If vaccine leaks during administration, it may be difficult to judge how much vaccine the patient actually received. In general, it should be treated as a nonstandard injectable dose and should be repeated. If it is an inactivated vaccine, repeat the dose at the earliest
  - If it was a live vaccine, repeat the dose on the same day or 4 weeks later. If part of a dose of an oral vaccine (rotavirus) was spit out by an infant, count the dose and do not administer a second dose
  - If a person sneezes after live-attenuated influenza vaccine, the dose can be counted as valid
  - If an expired dose of a vaccine has been inadvertently administered, the dose should be repeated. If the expired dose is a live virus vaccine, it should be repeated at least 4 weeks after the previous (expired) dose was given. If the expired dose is not a live vaccine, the dose should be repeated as soon as possible. Although simply repeating the dose is preferred, serologic testing to check for immunity after certain vaccinations (e.g., measles, rubella, varicella, and hepatitis A) may be accepted
- Diluents vary widely in composition, and therefore only the diluent assigned by the manufacturer for the specific vaccine and presentation should be used. The correct temperature for long-term storage of diluents is +2°C to +8°C
- In case of space constraints in the ice-lined refrigerator (ILR)/fridge, the diluents can be stored at room temperature and kept back in the ILR/fridge, 24 hours before use

TABLE 1: Recommendations for spacing of vaccines.

Antigen combination	*Recommended interval between doses*
Two or more inactivated vaccines	May be administered or at any interval between doses
Inactivated and live vaccine	May be administered or at any interval between doses
Two or more live parenteral vaccines	May be administered on same day or at an interval of at least 28 days
Pneumococcal conjugate vaccine (PCV) 13 and Menactra (in children with functional or anatomic asplenia) should not be administered at the same visit; separate these vaccines by at least 4 weeks and administer PCV first.	

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, aspiration of the syringe is not recommended. Moreover, aspiration makes the injection procedure more painful. However, if on aspiration, blood appears in the syringe, then the procedure is to withdraw the needle and start over. The syringe, needle, and contaminated dose of vaccine should be discarded in a sharps container, and a new syringe and needle should be used to draw up and administer another dose of vaccine. This is a waste of expensive vaccine that could be avoided by simply not aspirating.

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]

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 (24% dextrose), breastfeeding, cooling of the injection site,

TABLE 2: 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 • Anterolateral thigh	• 22–25 gauge, 5/8 inch • 22–25 gauge, 1 inch	• Skin should be stretched between thumb and forefinger • 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	
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

and topical 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.

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

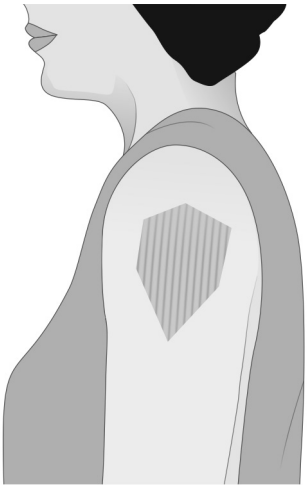


Fig. 2: Intramuscular site for administration: Deltoid muscle at upper arm.

Topical lidocaine–prilocaine emulsion should not be used on infants aged <12 months who are receiving treatment with methemoglobin-inducing agents because of the possible development of methemoglobinemia.

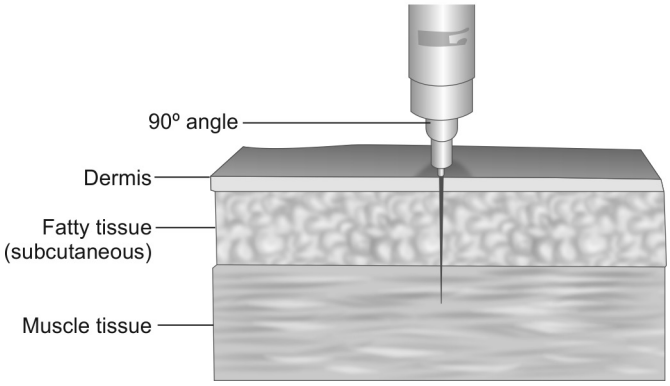


Fig. 3: Intramuscular needle insertion.

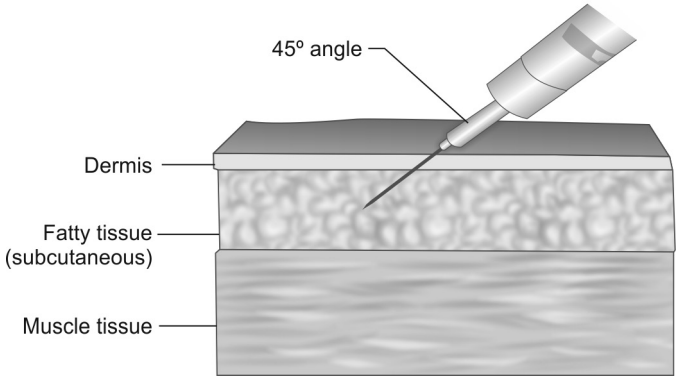


Fig. 4: Subcutaneous needle insertion.

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.

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 was given in the presence of that condition, the resulting adverse reaction could seriously harm the recipient.

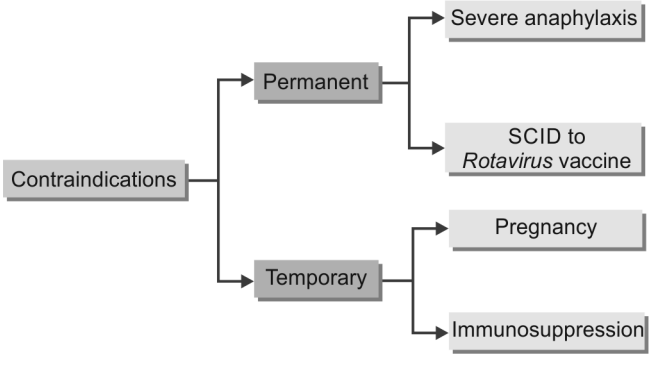
For instance, administering yellow fever to a person with a true anaphylactic allergy to egg could cause serious illness or death in the recipient. In general, vaccines should not be administered when a contraindication is present.

The only true contraindication for any vaccine is the presence of a known severe allergic reaction to a vaccine component or following a prior dose of a vaccine.

Precautions

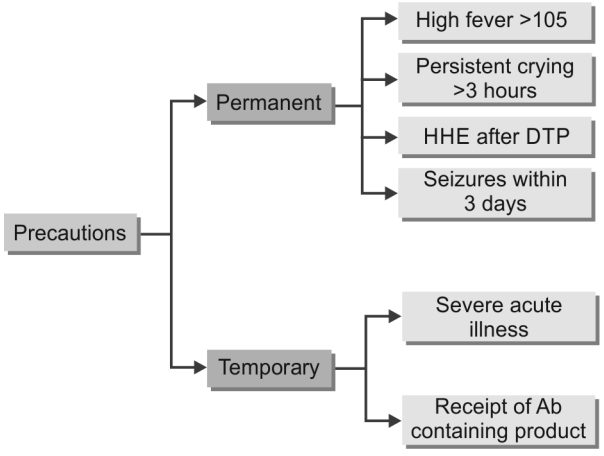
It is similar to a contraindication. A precaution is a condition in a recipient that might increase the chance or severity of a serious adverse reaction, or that might compromise the ability of the vaccine to produce immunity (such as administering measles vaccine to a person with passive immunity to measles from a blood transfusion). Injury could result, but the chance of this happening is less than with a contraindication **(Flowchart 1)**.[7] In general, vaccines are deferred when a precaution condition is present **(Flowchart 2)**. For inactivated influenza vaccines (IIVs), egg allergy other than hives, e.g., angioedema, respiratory distress, lightheadedness, recurrent emesis, or required epinephrine or another emergency medical intervention, is a precaution. IIV may be administered in an inpatient or outpatient medical setting and under the supervision of a healthcare provider who is able to recognize and manage severe allergic conditions).

Flowchart 1: Contraindications—permanent and temporary.



(SCID: severe combined immunodeficiency)

Flowchart 2: Precautions—permanent and temporary.



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

RECORDKEEPING

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. Recordkeeping is very important as guidelines issued for reporting of adverse events following immunization (AEFI) are also applicable to the private practitioners.[8]

It is necessary to record combination the brand name, type of combination [e.g., diphtheria tetanus whole-cell pertussis (DTwP)/ *Haemophilus influenzae* type B (Hib)/IPV], expiry date, date route, and site of administration.

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 caregivers should also be counseled about possible side effects,

BOX 2: Minimum resuscitative equipment.

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

their management, and danger signs before the vaccine is sent home.[8,9] **Box 2** provides the list of bare minimum equipment and drugs needed to take care of any immediate AEFI, particularly any hypersensitivity reaction to vaccine.

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2.5 VACCINE STORAGE AND HANDLING

Srinivas G Kasi, Sanjay Marathe

INTRODUCTION

By reducing the incidence of infectious diseases, immunization programs have had a major impact on the health status of the world population, especially in children. Proper vaccine storage and handling is a key component of immunization programs and is a shared responsibility from the time the vaccine is manufactured until it is administered. The majority of vaccine storage and handling errors are avoidable.

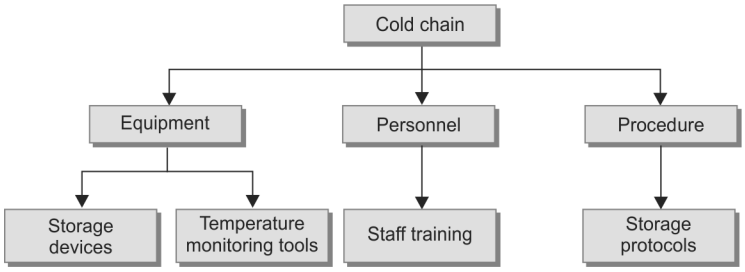
Cold chain breaches can occur even in well-designed and well-managed systems as a result of technical malfunctions; but if there are good procedures in place, problems will be detected and effectively managed so that effective protection can be extended to its recipients and vaccine losses can be prevented. 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 the recommended temperature range, from the place of manufacture to the point of administration. It has three main components:

1. Personnel
2. Equipment
3. Procedures **(Flowchart 1)**

Flowchart 1: Cold chain components.



Above three discussed components combine to ensure proper vaccine transport, storage, and handling. The optimum temperature for refrigerated vaccines is between +2 and +8°C. For frozen vaccines, the optimum temperature is –15°C to –25°C. 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 the WHO prequalified vaccines. 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 re-emergence of vaccine-preventable disease.
- Vaccines are expensive and 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.
- 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.

TABLE 1: Summary of vaccine sensitivities.

Vaccine	*Exposure to heat/ light*	*Exposure to cold*	*Storage temperature range*
Heat- and light-sensitive vaccines:			
BCG, freeze-dried	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
MR/MMR	Sensitive to heat and light	Not damaged by freezing	+2°C to +8°C
Varicella (lyophilized)	Heat sensitive	Not damaged by freezing	+2°C to +8°C
Rotavac™	Heat sensitive	Not damaged by freezing	+2°C to +8°C
Yellow fever	Heat sensitive	Not damaged by freezing	+2°C to +8°C
JE:SA-14-14-2	Heat sensitive	Not damaged by freezing	+2°C to +8°C
Live hepatitis A	Heat sensitive	Not damaged by freezing	+2°C to +8°C
Influenza: Inactivated	Heat sensitive	Damaged by freezing	+2°C to +8°C
Freeze-sensitive vaccines:			
DPT/DT/Td/ Tdap	Relatively heat stable	Freezes at −0.5 to −3°C	+2°C to +8°C
Hepatitis B	Relatively heat stable	Freezes at −3°C	+2°C to +8°C
TCV/MCV/ Hib-CV/PCV	Relatively heat stable		+2°C to +8°C
HPV	Relatively heat stable		+2°C to +8°C
Rabies	Relatively heat stable		+2°C to +8°C
JE—Inactivated	Relatively heat stable		+2°C to +8°C

(BCG: bacillus Calmette–Guérin; DPT: diphtheria, pertussis, and tetanus; Hib: *Haemophilus influenzae* type B; HPV: human papillomavirus vaccine; JE: Japanese encephalitis; MCV: meningococcal vaccine; MMR: measles, mumps, and rubella; OPV: oral poliovirus vaccine; PCV: pneumococcal conjugate vaccine; TCV: typhoid conjugate vaccine; Tdap: tetanus, diphtheria, and pertussis)

- Proper vaccine storage and management are 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.

Bacillus Calmette–Guérin (BCG), measles, mumps, and rubella (MMR), varicella DTaP (diphtheria, tetanus, and pertussis)-containing vaccines, human papillomavirus (HPV) vaccines, and rotavirus vaccines are sensitive to strong light, sunlight, ultraviolet, fluorescents (neon), and exposure of these vaccines to light should be avoided.

VACCINE STORAGE EQUIPMENT

Vaccine storage equipment can be classified into electrical and nonelectrical equipment. Electrical equipment consists of walk-in freezers, walk-in coolers, deep freezers, ice-lined refrigerators (ILRs), and the domestic refrigerators. Nonelectrical equipment includes the cold boxes and vaccine carriers.

Walk-in Freezers

Walk-in freezers (WIFs) are used for bulk storage of oral poliovirus (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 (WICs) are made up of modular and prefabricated polyurethane foam (PUF)-insulated panels with floor of either stainless steel panels or modular floor panels with aluminum-chequered plates. These cold rooms are typically controlled between 2 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 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 and front opening. Inside the ILR, there is a lining of water containers (ice packs or tubes) fitted all around the walls and held in place by frame. While the refrigerator is operating, the water in the containers freezes and if the electricity supply fails, the ice lining keeps the temperature inside 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 irregular power supply. In the ILR, vaccines should be stored in baskets to avoid direct contact with the sides and the bottom. Since the bottom of the ILR is its coldest part, the most heat-sensitive vaccines should be stored at the bottom and the most heat-resistant vaccines in the top compartment. This is reverse of the domestic refrigerator.

- *Bottom:* Measles, MR, MMR, BCG, OPV, yellow fever (YF), live Japanese encephalitis (JE), varicella, rotavirus, live-attenuated hepatitis A vaccine.
- *Middle and upper:* All the pertussis containing combination vaccines, inactivated hepatitis A vaccines, typhoid conjugate vaccine (TCV), pneumococcal conjugate vaccine (PCV), meningococcal vaccine (MCV), inactivated influenza vaccine, HPV, rabies, and inactivated JE vaccines **(Figs. 1 to 3)**.

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

Fig. 1: Ice-lined refrigerator.

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

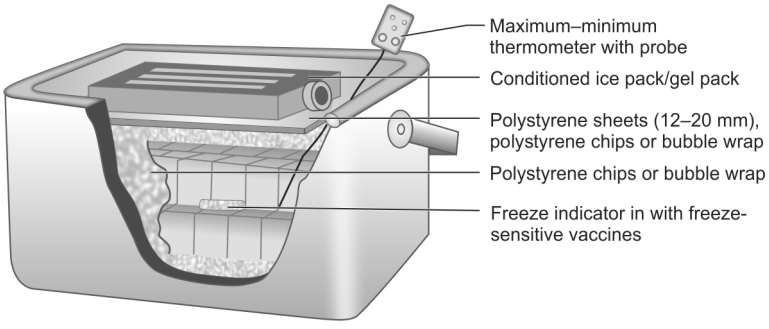


Fig. 3: Vaccine storage in cooler ice-lined refrigerator.

primary health center (PHC). In an emergency, they can also be used to store vaccines and frozen ice packs. Before placing vaccines in the cold boxes, conditioned ice packs are placed at the bottom and sides of the cold box. The vials of diphtheria, pertussis, and tetanus (DPT), diphtheria and tetanus (DT), hepatitis B, and tetanus toxoid (TT) vaccines should not be placed in direct contact with ice packs, they should be placed in a cartoon or plastic bag. Vaccines can be kept in a 5-L cold box for 90 hours and a 20-L cold box for 6 days when the ambient temperature is 43°C, provided that the boxes are fully functional and not opened during this period.

Vaccine Carriers

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

Icepacks

Icepacks are flat, leak-proof plastic containers, of standard dimensions that should be filled with tap water to fill about 80% of the capacity. They are kept in deep freezers at –25°C, till they are frozen. When removed from the freezers, the temperature of the frozen icepacks is –20°C, which can damage freeze-sensitive vaccines. The frozen ice packs have to undergo a process known as "sweating" to make it suitable for use. Sweating is done in the following way: the icepacks are placed on a table. The icepacks are shaken every few minutes till the ice is noted to move around in the icepacks. This may take a few minutes to an hour. They are now ready for use in vaccine carriers and cold boxes.

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

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 poliovirus vaccine; DPT: diphtheria, pertussis, and tetanus; DT: diphtheria and tetanus; Hep B: hepatitis B; TT: tetanus toxoid; ILR: ice-lined refrigerator)

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.

Direct cool refrigerators are to be avoided as there is uneven temperature distribution and formation of ice from the water vapor inside the refrigerator.

However, if domestic refrigerator is the only alternative to store the vaccines, 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. Do not store food, drinking water, or other medications in vaccine refrigerators.
- The refrigerator compartment temperature is maintained between 2 and 8°C and freezer compartment temperature 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*:
  - Should be placed away from direct sunlight and away from doors and windows

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

- A distance of 10 cm should be maintained all around to permit air circulation.
- Should be placed on a stand at least 5 cm in height
- The electric socket should be switchless or the switch should be taped to avoid accidental switching off.

- Accessibility should be restricted only to the vaccination staff so as to minimize unnecessary door opening and preventing accidental switch off of power supply
- A chart should be pasted on the door displaying the location of the vaccines in the refrigerator
- *Stabilize the temperature of the new refrigerator before stocking:*
  - When the refrigerator is first installed, set the thermostat to +2°C and +5°C. Once the daily temperature range remains consistently between +2 and +8°C, the thermostat is correctly adjusted and the setting should not be changed, even if electrical power is lost. The thermostat should not be readjusted if the temperature occasionally rises a degree or so above +8°C after a power cut, or in very hot weather. In a new refrigerator, allow 1 week of twice-daily refrigerator and freezer temperature recordings before using the unit to store vaccines. Once the temperature recorded on two consecutive days of temperatures is within the recommended range, the unit is stable and ready for use.

Avoid unnecessarily opening the refrigerator door. The WHO recommends door openings be minimized to not more than four times a day.

- *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)**.
- *Increase cool mass*:
  - Place water bottles in the door or the lowest shelf of the refrigerator and/or ice packs/gel packs in the freezer

Fig. 4: Temperature monitoring.

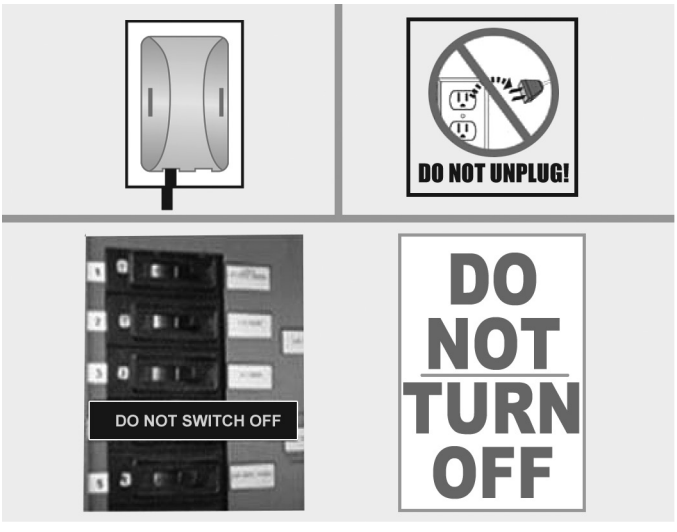


Fig. 5: Safeguard the power source.

Fig. 6: Water bottles to increase cool mass.

compartment 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 minimize 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, JE (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, Hep B, DTP/Hep B, DTP/Hep B/Hib, DTP/Hep B/Hib/IPV Hib, PCV, HPV, rotavirus, and/or any other freeze-sensitive vaccines in the middle shelf.
- 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

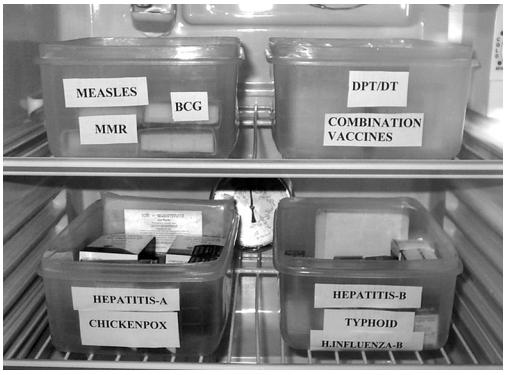


Fig. 7: Vaccine storage pattern.

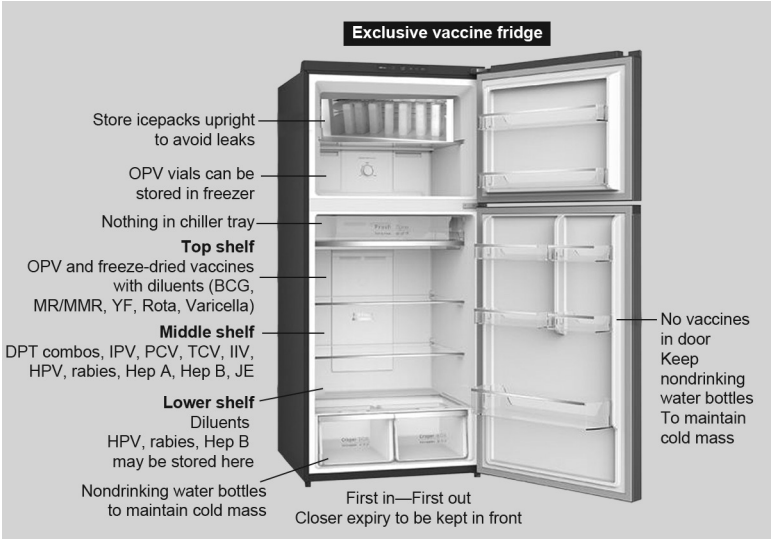


Fig. 8: Storage protocol in domestic fridge. (BCG: bacillus Calmette–Guérin; DPT: diphtheria, pertussis, and tetanus; HPV: human papillomavirus vaccine; Hep: hepatitis; JE: Japanese encephalitis; MMR: measles, mumps, and rubella; OPV: oral poliomyelitis vaccine; YF: yellow fever; IIV: inactivated influenza vaccine; IPV: inactivated polio vaccine; PCV: pneumococcal conjugate vaccine; TCV: typhoid conjugate vaccine)

labeled so they can be easily identified to their matching vaccine. Heat-stable vaccines (PCV, HBV, TCV, HPV, and rabies) can be stored in the lowest shelf for short periods.

- *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 **(***see* **Table 3)**.
  - When necessary, 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 cold box with conditioned ice packs or gel packs.

Purpose-built Vaccine Refrigerator

Purpose-built vaccine refrigerator is preferred refrigerator for vaccine storage. It is used by hospitals, pharmacies, and larger

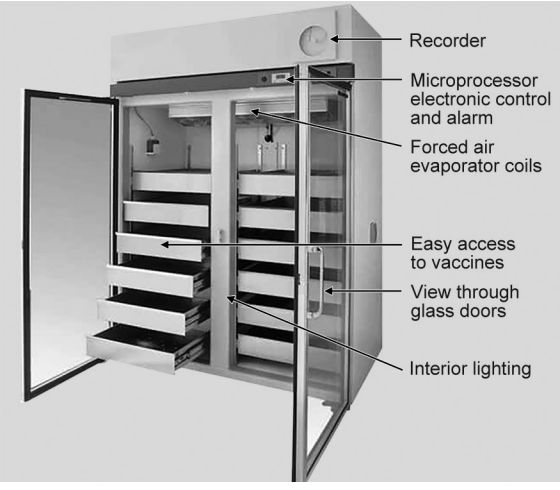


Fig. 9: Purpose-built vaccine refrigerator.

general practices. It has following advantages over the domestic refrigerator **(Fig. 9)**:

- No need to modify for vaccine storage
- Programmed to maintain an internal temperature between 2 and 8°C
- Cabinet temperature is not affected by ambient temperature and is stable and uniform
- Evaporator operates at 2–8°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.

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 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 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. It is 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.

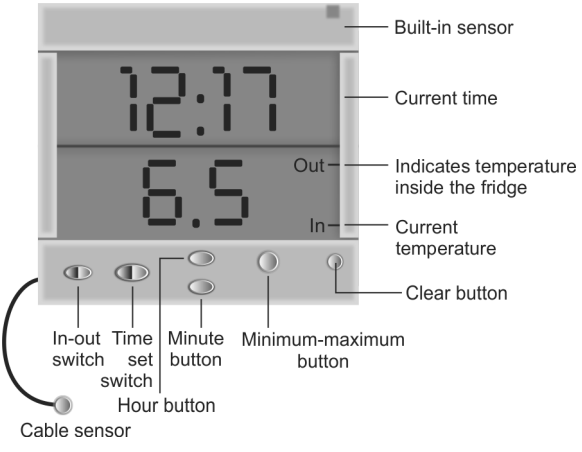


Fig. 10: Minimum/maximum thermometer.

- *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.

Temperature of ILRs/freezers used for storage of vaccines must be recorded twice daily, at 10 AM and 4 PM. This should be recorded in a logbook.

All cold chain temperature monitoring devices should be calibrated once in 6 months or earlier, if necessary.

Vaccine Vial Monitor

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

Fig. 11: Vaccine vial monitor.

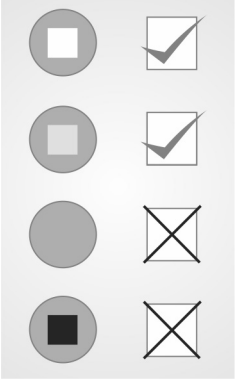


Fig. 12: Decision to use vaccine(s) based on vaccine vial monitor sensitivity.

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 such as 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)**. The refrigerator temperature needs to be stabilized before starting the use of refrigerator for vaccine storage.

In multidose vials, where the VVM is attached over the label, the vaccine vial once opened can be used for next 28 days (liquid or freeze-dried). When the VVM is attached anywhere other than label (cap or neck of ampoule), the vaccine vial, once opened, must be discarded after immunization session or within 6 hours of opening, whichever comes first.

Electronic freeze indicators: These are devices used to monitor the exposure of vaccines to freezing and are used with freeze-sensitive vaccines (DPT containing vaccines, Hep B, TT containing vaccines).

The most commonly used type of freeze indicator is the *freeze-tag* **(Fig. 13)**. This consists of an electronic temperature measuring circuit with a LCD. A small blinking dot of light in the corner of the display shows that the freeze-tag is functioning correctly.

If the freeze-tag is exposed to a temperature below 0°C for more than 60 minutes, the display will change from the "good status" (✓) to the "alarm status" (×).

Vaccines that have been exposed to freezing may have been damaged and should be checked by using the shake test.

3M™ Freeze Watch™ indicators **(Fig. 14)** consist of a highly sensitive indicating liquid inside a specially designed ampoule to monitor exposure of temperature-sensitive products to freezing temperatures.

Fig. 13: Freeze-tag.

Fig. 14: Freeze Watch.

When exposed to freezing temperatures, the ampule fractures, releasing a liquid. The liquid irreversibly stains a paper behind the ampule, indicating that product has been exposed to unacceptable temperatures.

Vaccines that have been exposed to freezing may have been damaged and should be checked by using the shake test.

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 (about 1 month's requirement) to meet the needs of the vaccination unit
   - Ensure that the ordered vaccine stock is delivered when the vaccination unit is open. Vaccines should be delivered when staff is available to unpack and store.
   - Store vaccines at the recommended temperatures, immediately on arrival, refrigerated vaccines between 2 and 8°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 are 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 such as 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 staffs have 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.

Electronic Vaccine Intelligence Network (eVIN): Electronic Vaccine Intelligence Network is an IT-based system aimed at strengthening vaccine supply chain systems across the country. First introduced in 2015, eVIN enables real-time monitoring of vaccine stocks and storage temperatures in multiple locations across the country. All cold chain handlers are provided smartphones having an application that allows for the digitization of vaccine inventory, real-time stock and temperature vaccine requirement, emergency management, consumption patterns, route planning and stock reallocation. SIM-enabled temperature loggers are attached to the cold chain equipment and capture temperature information through digital sensors placed in the ILRs. Temperature data is recorded every 10 minutes and updated at interval of 60 minutes on the server via General Packet Radio Service (GPRS). In case of a temperature breach, the logger alarms and sends mail and SMS alerts to the concerned technicians and management managers.

It has been implemented in all 36 states and 733 districts with over 29,000 storage centers or cold chain points which are live on eVIN. eVIN has achieved a vaccine availability rate of over 99% at all cold chain points and over 80% reduction in instances of vaccine stock-outs.

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2.6 ADVERSE EVENTS FOLLOWING IMMUNIZATION

M Indra Shekhar Rao, Harish Kumar Pemde

INTRODUCTION

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 (AEFI). As vaccine-preventable infectious diseases continue to decline, the risks associated with vaccines have become increasingly noticeable and a matter of concern.

An 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]

WHAT IS THE IMPORTANCE OF AEFI REPORTING?

- It helps in identifying or better understanding the safety issues relating to newly introduced vaccines.
- It helps in monitoring AEFI rates and trends across the country.
- It helps in identifying problems with manufacture, storage, delivery, or administration.

TABLE 1: Some serious adverse events following immunizations with 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	4–30 days	2–4/1,000,000
DTwP	Prolonged crying and seizures	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	1/1000,000

(BCG: bacillus Calmette–Guérin; DTwP: diphtheria, tetanus, and whole cell pertussis; HHE: hypotonic hypo-responsive episode; OPV: oral poliovirus vaccine)

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 diphtheria, tetanus, and pertussis (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 inactivated poliovirus vaccine (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. These include:
  - Transmission of infection by contaminated multidose vial or reuse of disposable syringes and needles.
  - *Reconstitution error:* Vaccine reconstituted with the incorrect diluent.
  - *Injection administered at incorrect site*: Bacillus Calmette–Guérin (BCG) given subcutaneously (SC), rabies, or hepatitis B vaccine given SC or DPT administered SC.
  - *Improper storage and transport of vaccine*: Vaccines frozen during storage and administered, can give rise to sterile abscess. These vaccines are also ineffective.
  - *Contraindication is ignored*: Live vaccine administered to an immunosuppressed subject.
  - *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.

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, (5) where the vaccine quality is suspicious.
- *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. They are caused when recipient's immune system reacts to antigens, adjuvants, stabilizers, preservatives contained in the vaccine. They are very rarely life-threatening nor do they cause any disability although there is some risk of morbidity. The patient may not be hospitalized and will not have sequelae.
- *Minor AEFI:* Minor AEFIs usually occur within a few hours of injection, resolve after short period of time, and pose little danger. Minor AEFIs can be local reactions (pain, swelling, and redness) or systemic reactions (fever > 38°C, irritability, malaise, etc.), which can be managed with antipyretics and anti-inflammatory and resolve within 2–3 days.

Cluster of AEFIs is considered serious AEFI. A cluster is defined as two or more cases of the same AEFI related in time, place, or vaccine administered. A cluster usually occurs with a particular healthcare provider or a facility.

The following AEFIs should be reported:

- All serious AEFI
- Signals and events associated with a newly introduced vaccine
- AEFI that may have been caused by an immunization error
- Significant events of unexplained cause occurring within 30 days after vaccination
- Events causing significant parental or community concern.

The list of reportable AEFIs with timelines is shown in **Table 2**.

TABLE 2: Reportable adverse event following immunizations with timelines.

Timeline	*Event*
Occurring within 24 hours of immunization	• Anaphylactoid reaction (acute hypersensitivity reaction) • Anaphylaxis • Persistent (more than 3 hours) inconsolable screaming • Hypotonic hypo-responsive episode • Toxic shock syndrome
Occurring within 5 days of immunization	• Severe local reaction • Sepsis • Injection site abscess (bacterial/sterile)
Occurring within 15 days of immunization	• Seizures, including febrile seizures (6–12 days for measles/MMR; 0–2 days for DTP) • Encephalopathy (6–12 days for measles/MMR; 0–2 days for DTP)
Occurring within 3 months of immunization	Acute flaccid paralysis (4–30 days for OPV recipient; 4–75 days for contact)
Occurring between 1 and 12 months after BCG immunization	• Lymphadenitis • Disseminated BCG infection • Osteitis/Osteomyelitis
No time limit	Any death, hospitalization, or other severe and unusual events that are thought by health workers or the public to be related to immunization

(BCG: bacillus Calmette–Guérin; DTP: diphtheria, tetanus, and pertussis; MMR: measles, mumps, and rubella; OPV: oral poliovirus vaccine)

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 sends it to the State Immunization/Expanded Programme of Immunization (EPI) 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 (see Annexure).

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 **(Fig. 1)**. 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

Fig. 1: The adverse event following immunization (AEFI) reporting circle.

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 **(Fig. 2)**. A proportion of cases causally assessed by the states are further causally assessed by the National AEFI Committee.

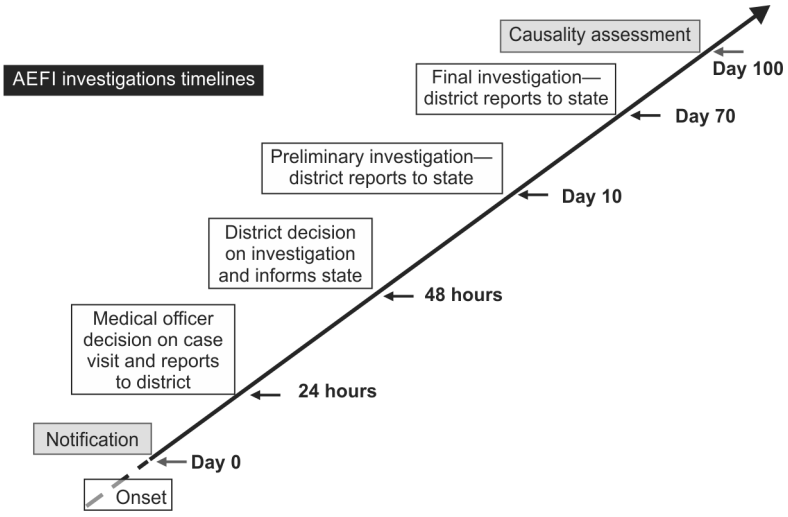


Fig. 2: Adverse event following immunization (AEFI) investigations timelines.

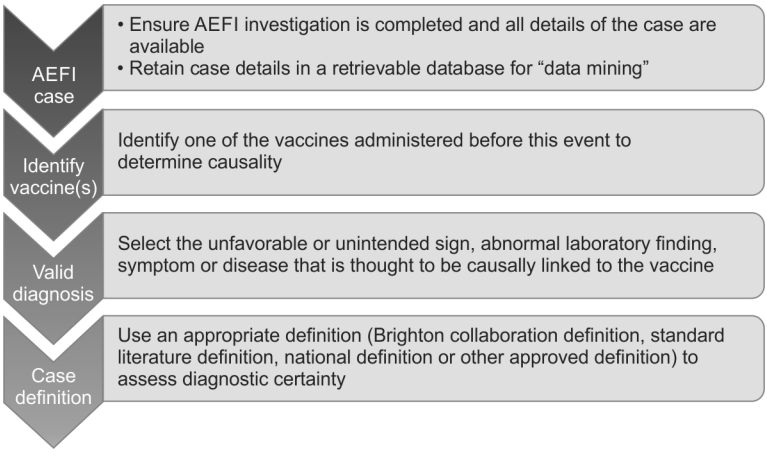
CAUSALITY ASSESSMENT

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. It should be noted that causality assessment is not the responsibility of the reporting pediatrician. 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 include 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

Flowchart 1: Eligibility for causality assessment.



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/laboratory finding **(Flowchart 1)**.

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 (Table 3)

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

TABLE 3: 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.)?	☐☐☐☐	

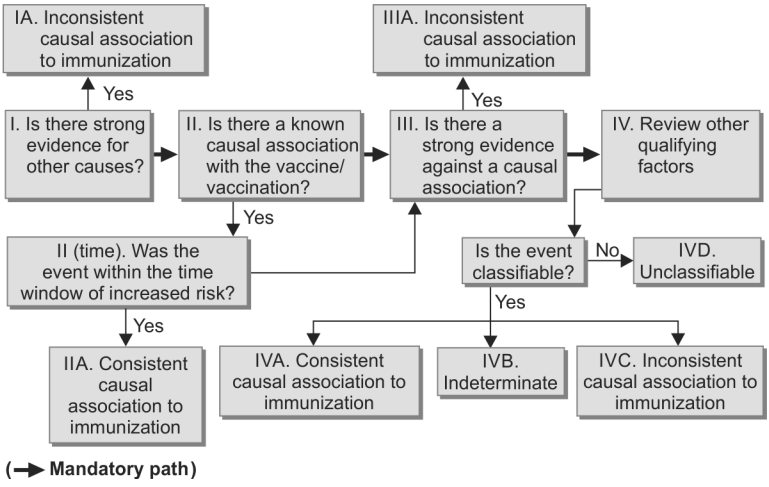
Contd...

Contd...

Immunization anxiety (Immunization Triggered Stress Response - ITSR)		
10. In this patient, was the vaccine administered incorrectly (e.g., wrong dose, site or route of administration; wrong needle size, etc.)?	☐☐☐☐	
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: not applicable; GACVS: Global Advisory Committee on Vaccine Safety)

Flowchart 2: Causality assessment algorithm.



The Causality Assessment Algorithm

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
  - 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)
  - 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).

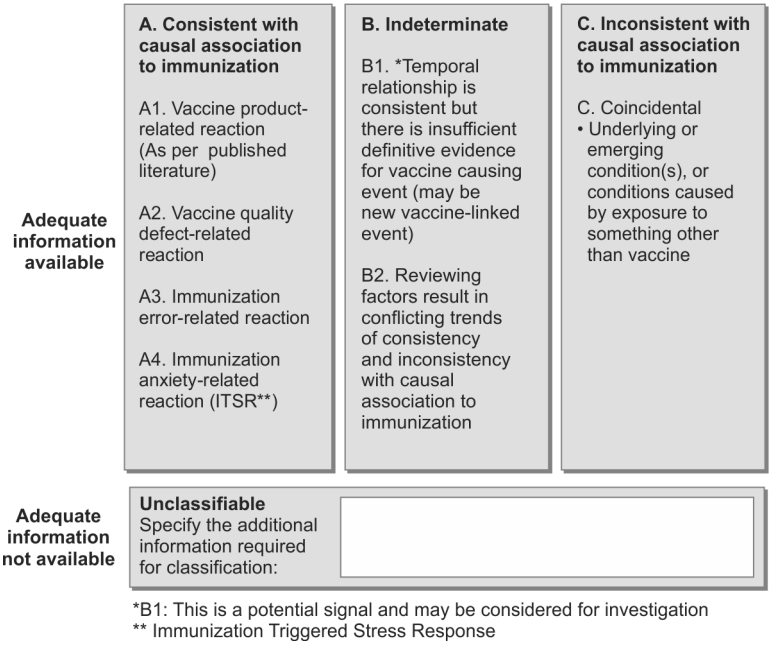


Fig. 3: Causality assessment classification.

Causality Assessment Classification (Fig. 3)

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 4**.

Steps after Causality Assessment

After causality assessment, the results need to be shared with all stakeholders for taking relevant action **(Table 4)**. 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 be informed. Training and capacity building including intensification of supervision and monitoring is required

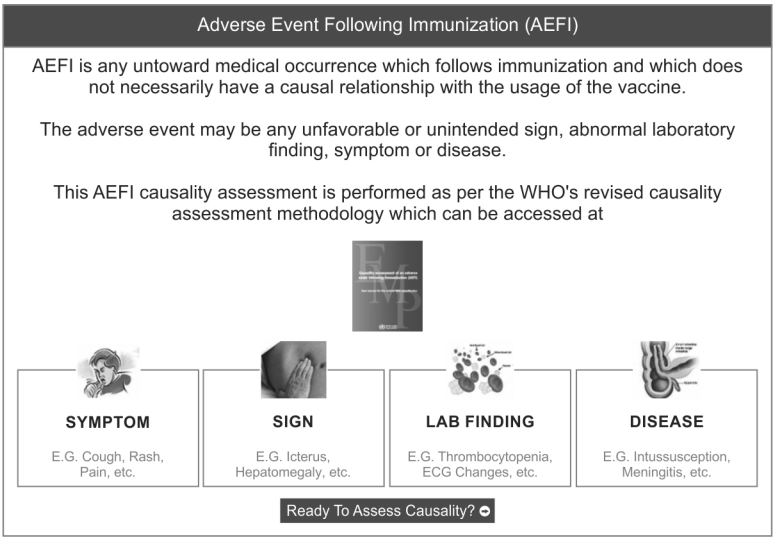


Fig. 4: WHO software for causality assessment.

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

TABLE 4: 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]

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 Indian Academy of Pediatrics (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 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.

BOX 1: Emergency management of anaphylaxis.

- Administer epinephrine (1:1,000 solution) 0.01 mL/kg/dose (maximum 0.5 mL) intramuscular (IM) in anterolateral thigh
- Set up intravenous (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

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 that are not included in the Universal Immunization Programme (UIP) in India are provided by the private sector only. AEFI reporting from private sector will provide vital information on the safety of new vaccines in India. In rural areas, serious AEFI occurring in the clinic of a pediatrician should be immediately reported to the medical officer in-charge of nearest PHC or other health facility. In the urban areas, it should be reported to either the 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 "Case Reporting 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

IDsurv.org is an infectious disease surveillance and AEFI reporting system developed by IAP.

The objectives of IDsurv are:

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

Members have to register on the website and create an account with a password.

When an AEFI case is reported on IDSurv, real-time notification is sent to IAP AEFI surveillance committee, the State EPI officer, and

to the Nodal Person in MoHFW, Government of India. Subsequently, the Government authorities will take over the investigation of the case.

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2.7 SCHEDULING OF VACCINES

Arun Wadhwa, Harish Kumar Pemde

INTRODUCTION

Main objectives of scheduling of vaccines are to achieve maximum effectiveness using recommended vaccines for a country while minimizing the number of healthcare 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 changes, and has become more complex.[1] Traditionally, the 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 in the 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 or even eradicate it, as has 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 vaccine-preventable diseases (VPDs). An optimal but not necessarily the best immunological

response may be considered appropriate 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 which include:

- *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 germinal centers (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 and sometimes even beyond.
- *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 passive antibodies (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. Antibodies against the injected live vaccine may interfere with replication. If a live-injectable vaccine [measles, mumps, and rubella (MMR), varicella, or combination measles, mumps, rubella, and varicella (MMRV)] must be given around the time that immunoglobulins are given, the two must be separated by enough time so that the antibodies do 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 antibodies are 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 their specific antibodies. 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.[3]

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, diphtheria, pertussis, and tetanus (DPT) combination was a standard for a long time, so was MMR. Logical additions to DPT were *Haemophilus influenzae* type B (Hib), injectable polio, and hepatitis B. The preservation of efficacy needs to be evaluated by trials and monitored by post-launch 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, and competing priorities)
- Recipient (age, cohort size, and vulnerability)
- Vaccine (local production, availability, cost, efficacy, safety, and 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. 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 their immunization schedule. The National Immunization Schedule (UIP) is shown in **Table 1**.

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 inactivated 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, inactivated poliovirus vaccine (IPV), Hib, pneumococcal conjugate, hepatitis A, hepatitis B, human papillomavirus (HPV), 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 the vaccines prescribed for adolescent immunization in India by Indian Academy of Pediatrics (IAP) **(Table 2)**.[4]

TABLE 1: National Immunization Schedule.

National Immunization Schedule for pregnant women, infants, and children (Vaccine-wise)				
Vaccine	***When to give***	***Dose***	***Route***	***Site***
For pregnant women:				
Tetanus and adult diphtheria (Td)	Early in pregnancy	0.5 mL	Intramuscular	Upper arm
Td-2	4 weeks after Td-1	0.5 mL	Intramuscular	Upper arm
Td-booster	If received 2 TT/Td doses in a pregnancy within the last 3 years*	0.5 mL	Intramuscular	Upper arm
For infants:				
Bacillus-Calmette Guérin (BCG)	At birth or as early as possible till 1 year of age	0.1 mL (0.05 mL until 1 month 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 mid-thigh
Oral polio vaccine (OPV)-0	At birth or as early as possible within the first 15 days	2 drops	Oral	Oral
OPV-1, 2, and 3	At 6 weeks, 10 weeks and 14 weeks (OPV can be given till 5 years of age)	2 drops	Oral	Oral

Contd...

Contd...

Vaccine	*When to give*	*Dose*	*Route*	*Site*
Pentavalent 1, 2, and 3	At 6 weeks, 10 weeks, and 14 weeks (can be given till 1 year of age)	0.5 mL	Intramuscular	Anterolateral side of mid-thigh
Pneumococcal conjugate vaccine (PCV)	Two primary doses at 6 and 14 weeks followed by booster dose at 9–12 months	0.5 mL	Intramuscular	Anterolateral side of mid-thigh
Rotavirus (RVV)	At 6 weeks, 10 weeks, and 14 weeks (can be given till 1 year of age)	5 drops (liquid vaccine) 2.5 mL (lyophilized vaccine)	Oral	Oral
Inactivated polio vaccine	Three fractional doses at 6–14 weeks and 9 months	0.1 mL	Intradermal two fractional dose	*Intradermal:* Right upper arm
Measles-rubella (MR) 1-dose	9 completed months–12 months. (Measles can be given till 5 years of age)	0.5 mL	Subcutaneous	Right upper arm
Japanese encephalitis (JE)-1	9 completed months–12 months	0.5 mL	• Subcutaneous (Live-attenuated vaccine) • Intramuscular (Killed vaccine)	• Left upper Arm (Live-attenuated vaccine) • Antero-lateral aspect of mid-thigh (Killed vaccine)

Contd...

Contd...

Vaccine	*When to give*	*Dose*	*Route*	*Site*
Vitamin A (1-dose)	At 9 completed months with MR	1 mL (1 lakh IU)	Oral	Oral
For children:				
Diphtheria, pertussis, and tetanus (DPT) booster-1	16–24 months	0.5 mL	Intramuscular	Anterolateral side of mid-thigh
MR-2-dose	16–24 months	0.5 mL	Subcutaneous	Right upper arm
OPV booster	16–24 months	2 drops	Oral	Oral
JE-2	16–24 months	0.5 mL	• Subcutaneous (Live-attenuated vaccine) • Intramuscular (Killed vaccine)	• Left upper arm (Live-attenuated vaccine) • Antero-lateral aspect of mid-thigh (Killed vaccine)
Vitamin A (2nd to 9th dose)	16–18 months. Then one dose every 6 months up to the age of 5 years	2 mL (2 lakh IU)	Oral	Oral
DPT booster-2	5–6 years	0.5 mL	Intramuscular	Upper arm
Td	10 years and 16 years	0.5 mL	Intramuscular	Upper arm

*One dose if previously vaccinated within 3 years.

Note:

- Japanese encephalitis vaccine is introduced in select endemic districts after the campaign.
- The 2nd to 9th doses of vitamin A can be administered to children 1–5 years old during biannual rounds, in collaboration with ICDS.

TABLE 2: Indian Academy of Pediatrics immunization schedule 2020–21.

Vaccine	*Age in completed weeks/months/years*															
	Birth	*6 w*	*10 w*	*14 w*	*6 m*	*7 m*	*9 m*	*12 m*	*13 m*	*15 m*	*16–18 m*	*18–24 m*	*2–3 y*	*4–6 y*	*9–14 y*	*15–18 y*
BCG																
Hepatitis B	HB 1[a]	HB 2	HB 3	HB 4[b]												
Polio	OPV	IPV 1[c]	IPV 2[c]	IPV 3[c]							IPV[c] B1			IPV[c] B2		
DTwP/DTaP		DPT 1	DPT 2	DPT 3							DPT B1			DPT B2		
Hib		Hib 1	Hib 2	Hib 3							Hib B1					
PCV		PCV 1	PCV 2	PCV 3				PCV B								
Rotavirus		RV 1	RV 2	RV 3[d]												
Influenza					Dose 1[e]	Dose 2		Annual Vaccination								
MMR							Dose 1			Dose 2				Dose 3		
TCV																
Hepatitis A								Dose 1				Dose 2[f]				
Varicella										Dose 1		Dose 2[g]				
Tdap[h]/Td																
HPV															1 & 2[i]	1, 2 & 3[j]

Contd...

Contd...

Vaccine	Age in completed weeks/months/years															
	Birth	*6 w*	*10 w*	*14 w*	*6 m*	*7 m*	*9 m*	*12 m*	*13 m*	*15 m*	*16–18 m*	*18–24 m*	*2–3 y*	*4–6 y*	*9–14 y*	*15–18 y*
Meningococcal[k]							Dose 1	Dose 2								
JE								Dose 1	Dose 2							
Cholera								Dose 1	Dose 2							
PPSV 23																
Rabies																
Yellow Fever																

Recommended age | Vaccines in special situations | Catch up age range

[a]Fourth dose of hepatitis B permissible for combination vaccines only
[b]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
[c]b-OPV, if IPV booster (standalone or combination) not feasible
[d]Third dose not required for RV1. Catch-up to 1 year of age in UIP schedule
[e]Live-attenuated hepatitis A vaccine: single dose only
[f]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
[g]2nd dose of varicella vaccine should be given 3–6 months of age after dose 1. However, it can be administered anytime 3 months after dose 1 or at 4–6 years
[h]Tdap should not be administered as the second booster of DPT at 4–6 years. For delayed 2nd booster, Tdap can be given after 7 years of age. A dose of Tdap is necessary at 10–12 years, irrespective of previous Tdap administration. If Tdap is unavailable/unaffordable, it can be substituted with Td
[i]Before 14 completed years, HPV vaccines are recommended as a 2-dose schedule, 6 months apart
[j]From 15th year onwards and the immunocompromised subjects at all ages, HPV vaccines are recommended as a 3-dose schedule, 0–2–6 (HPV4); HPV9 is licensed till 26 years.
[k]Menactra is approved in a 2-dose schedule between 9 and 23 months. Minimum interval between two doses should be 3 months. Menveo is recommended as a single dose schedule after 2 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

WORLD HEALTH ORGANIZATION RECOMMENDATIONS

The World Health Organization (WHO) monitors vaccination schedules across the world, noting what vaccines are included in each country's program, the coverage rates achieved, and various auditing measures.[5] 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 is regularly updated.[5] WHO further subclassifies the vaccines as: (1) recommendations for all individuals (BCG, hepatitis B, DPT, polio, Hib, PCV, rotavirus, measles, rubella, HPV); (2) recommendations for individuals residing in certain regions [Japanese encephalitis (JE), yellow fever, and tick-borne encephalitis]; (3) recommendations for individuals in some high-risk populations (typhoid, cholera, meningococcal, hepatitis A, and rabies); and (4) recommendations for individuals receiving vaccinations from immunization programs with certain characteristics (mumps and influenza).[6]

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Chapter 3

Licensed Vaccines

3.1 BACILLUS CALMETTE–GUÉRIN VACCINE

Kripasindhu Chatterjee, Shivananda S

EPIDEMIOLOGY

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

Tuberculosis occurs most commonly in children <5 years. While pulmonary tuberculosis (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, of which, about 1 million were children. 10% 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] TB 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 1st 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. BCG vaccination is recommended in countries or settings with a high incidence [TB notification rate >40 TB cases (all forms) per 100,000 population per year] of TB and/or high leprosy burden.

VACCINE

Bacillus Calmette–Guérin vaccine is one of the oldest vaccines, first used in humans in 1921. BCG vaccine is derived from the bovine TB 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 TB. 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 2–8°C for up to 12 months without losing its potency. Diluent, supplied with the vaccine, 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 postexposure 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 formation of a wheal of 5 mm. BCG vaccine should be injected in a clean, healthy area of skin. The vaccine should be given preferably in the lateral aspect of the left 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. Absence of scar formation does not indicate a failure of take of the vaccine. The standard dose of reconstituted vaccine is 0.05 mL for infants aged <1 month and 0.1 mL for those aged >1 month. BCG is given till 1 year of age as per National Immunization Schedule (NIS) and till 5 years of age as per Indian Academy of Pediatrics–Advisory Committee on Vaccines and Immunization Practices (IAP-ACVIP). BCG vaccine is not available in combination with other vaccines.

IMMUNOGENICITY, EFFICACY, AND EFFECTIVENESS

BCG Vaccine Efficacy and Effectiveness against Pulmonary Tuberculosis

The efficacy and effectiveness of BCG vaccination against TB have been found to differ considerably 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 of different subgroups. Among different variables studied included: age at

vaccination, prior tuberculin skin test (TST) positivity, distance from the equator, and study quality. Among those vaccinated as neonates, protection against PTB was 59% [RR: 0.41, 95% confidence interval (CI): 0.29–0.58]. In studies where BCG was given in childhood and with stringent TST screening, protection against PTB was 74% (RR: 0.26, 95% CI: 0.18–0.37). Protective efficacy was apparently higher in settings further away from the equator. But this higher apparent protection against PTB in settings further from the equator was reduced in the multivariable analysis ($p < 0.054$). The authors suggested the remaining persistence of a latitudinal effect could be due to the fact that TST screening may not exclude exposure to all environmental mycobacteria.[8]

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 in one study. Protection was found to vary by age, with neonatal vaccination providing 82% protection against PTB (RR: 0.18, 95% CI: 0.15–0.21) as compared to 64% (RR: 0.36, 95% CI: 0.30–0.42) in TST-negative schoolchildren. The same review also evaluated eight case–control studies which revealed 54% neonatal BCG vaccine effectiveness (VE) from seven studies (OR: 0.46, 95% CI: 0.40–0.52), but found only one study in older children, which reported minimal protection. These observational studies of VE, therefore, support findings from RCTs of high protection against PTB from BCG vaccination of neonates, and moderate protection of school-age TST-negative children.[9]

BCG Vaccine Efficacy and Effectiveness against Meningeal and Miliary Tuberculosis

Evidence from a meta-analysis of six 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), and among school-age children who were TST-negative, with 92% reduction of severe disease (RR: 0.08, 95% CI: 0.03–0.25).

Vaccination of school-age children or older individuals who were not stringently TST screened revealed little evidence of protection

against severe disease. However, the numbers of severe TB cases were very small (0–3 cases) to be statistically relevant.[8]

A systematic review and meta-analysis 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 four of the studies in Asia and Latin America. These studies confirm previous evidence of high degree of protection of BCG vaccination against severe forms of TB.[10]

Emerging Evidence of BCG Vaccine Protection against Primary Infection with *M. Tuberculosis*

A systematic review and meta-analysis,[11] conducted to examine protective effect of BCG against primary infection by interferon-gamma release assay (IGRA) tests, showed that BCG-vaccinated children exposed to persons with open PTB had 19% less infection than unvaccinated children (95% CI: 8–29).

BCG Vaccine Efficacy and Effectiveness against Other Mycobacterial Diseases

Two recent systematic reviews,[12] analyzing the efficacy and VE of BCG against leprosy, revealed that BCG was effective in preventing leprosy, with an overall pooled RR of 0.45 (95% CI: 0.34–0.56).

Systematic review[13] on effect of BCG vaccination on Buruli ulcer and other nontuberculous mycobacterial infections showed that BCG vaccination has ~50% efficacy (RR: 0.5, 95% CI: 0.37–0.69) in African settings against Buruli ulcer and that BCG is protective against nontuberculous mycobacteria (NTM) lymphadenitis in children.[13-15]

Nonspecific Effects of BCG including COVID-19

In observational studies, it was observed that the severity of COVID-19 and its mortality were lesser in the countries who had long-term national BCG vaccination policy than those who did not or those who previously used to give BCG but have discontinued later.[16-18]

The nonspecific effects of BCG vaccination, "Trained Innate Immunity", result from metabolic and epigenetic changes expressing genetic regions encoding for proinflammatory cytokines, leading to more cytokine release such as interferon-γ (IFN-γ) and interleukin-1β (IL-1β), that play vital role in prevention of viral infection against heterologous diseases.[19-21]

A study from Guinea-Bissau[22] and Spain[23] has shown that BCG-vaccinated children suffered less from neonatal sepsis, respiratory infection, and fever than those who did not receive BCG. This lower incidence of respiratory infection was not found in children who received vaccines other than BCG proving that the infection-lowering effect was due to BCG itself.[22]

DURATION OF PROTECTION

A systematic review concluded that protection after primary infant BCG vaccination could last for up to 15 years in some populations.[9] Longer duration of protection has been reported from some western countries.[24-26]

BCG REVACCINATION IN ADOLESCENTS AND ADULTS

Different studies have shown little or no evidence of an effect of BCG revaccination in adolescents and adults after primary BCG vaccination in infancy, either on protection against *M. tuberculosis* infection or on TB disease.[27-32] However, a study in Malawi[30] found that revaccination with BCG in both children and adults conferred an additional 49% protection (95% CI: 0–75%). Such differences between studies and populations may reflect different patterns of natural exposure to a variety of mycobacterial species and other confounding factors.

VACCINE SAFETY

In general, BCG vaccination is safe.

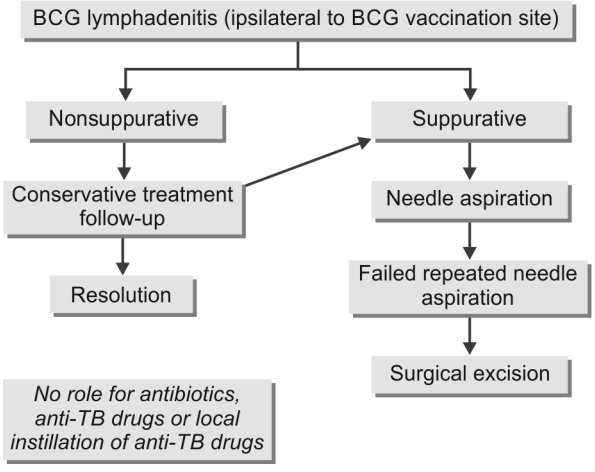
About 95% of BCG vaccine recipients experience a reaction at the injection site characterized by a papule which may progress to become ulcerated, with healing after 2–5 months leaving a superficial scar. This is considered normal.

Mild reactions are mostly local with or without regional manifestations. Local adverse effects include abscess, injection site reaction, lymphadenopathy, and delayed healing of the ulcer at site of vaccination.[13,33] Batch-related variation in the adverse event following immunization (AEFI) rates has been noted.[34-36]

The BCG lymphadenitis is diagnosed when ipsilateral axillary, supraclavicular, or lower cervical lymph node enlargement develops after BCG vaccination and is severe enough to arouse significant concern from the child care provider to seek medical attention. The incidence of suppurative lymphadenitis due to BCG vaccination is 100–1,000 per million doses administered.

There are two forms of BCG lymphadenitis—nonsuppurative and suppurative. The nonsuppurative form has a benign clinical course. Generally, the lymph node does not exceed 15 mm in size, is firm in consistency, and the lesion resolves spontaneously without any sequelae over a period of weeks. No treatment is indicated except a periodic reassessment. The suppurative form is marked by the progressive enlargement of the ipsilateral regional lymph nodes with softening, fluctuation, and overlying skin changes of induration and erythema. If untreated, the suppuration progresses to rupture, persistent caseous discharge, and sinus formation. Wound healing may take takes several months **(Flowchart 1)**.

Flowchart 1: Algorithm for management of BCG lymphadenitis.



(BCG: bacillus Calmette–Guérin; TB: tuberculosis)

Other severe complications caused by BCG are osteitis/osteomyelitis and disseminated BCG infection, with incidence rates of 1–700 cases, and 2 cases per 1 million vaccinations, respectively.

Disseminated BCG infection is diagnosed definitively based on the presence of the following features:

All three of the following conditions should be met:

1. BCG cultured and identified by culture, biochemical methods
2. Dissemination evidenced by either A or B:
   A. Positive blood or bone marrow culture
   B. Evidence of infection at two or more anatomic sites beyond the region of vaccination
3. A systemic syndrome compatible with mycobacterial disease, e.g., fever, weight loss, anemia, and death.

The occurrence of disseminated BCG infection warrants investigations for immunodeficiency states including severe combined immunodeficiencies (SCIDs), chronic granulomatous disease (CGD), complete DiGeorge syndrome, and Mendelian susceptibility to mycobacterial disease (MSMD) with underlying genetic defects, NF-kappa B essential modulator (NEMO), tyrosine kinase 2 (TYK2), and HIV.[37,38]

The BCG-induced osteitis or osteomyelitis is a serious AEFI following BCG vaccination, usually affects the long bones and the reported incidence varies from 0.01 to 30 per million doses, varying by batch and has a good prognosis.[39] Defects of the innate immune response should be suspected in any infant with BCG osteitis. There are no controlled studies regarding the treatment of BCG osteitis. Apart from surgical management, which is necessary in most cases, chemotherapy involves using three to four anti-TB drugs selected from the group consisting of isoniazid, rifampicin, ethambutol, streptomycin, and clarithromycin. Pyrazinamide is not effective against *Mycobacterium bovis*, and is not included in most regimes.[40]

SPECIAL POPULATIONS

HIV-infected Infants

In general, populations with high prevalence of HIV infection also have high burden of TB; in such populations, the benefits of

preventing severe TB outweigh the risks associated with the use of BCG vaccine.

Evidence shows 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. Early initiation of antiretroviral therapy (ART), before immunological and/or clinical HIV progression, has been shown to substantially reduce the risk of BCG-immune reconstitution inflammatory syndrome (BCG-IRIS) regional adenitis. Observational data from a cohort study in South Africa with 12,748 children receiving ART who developed lymphadenitis following BCG confirmed a low risk: 0.6%.[13,41] The risk of TB in people living with HIV is 15–22 times higher than people without HIV.[42]

The HIV-exposed infants, who are asymptomatic, like all other infants, should be given BCG at birth. If BCG has not been given at birth, or for neonates with HIV infection confirmed by early virological testing, BCG vaccination should be delayed until ART has been started and the infant confirmed to be immunologically stable (CD4 > 25%). If HIV-infected individuals, including children, are receiving ART, are clinically well and immunologically stable (CD4% > 25% for children aged <5 years or CD4 count ≥200 if aged >5 years), they should be vaccinated with BCG.[43]

Preterm Infants and Low-birth Weight Infants

Bacillus Calmette–Guérin vaccination at birth in healthy preterm infants born after 32–36 weeks of gestation was found to be safe and effective.[13,44-49] Evidence from three RCTs conducted in the same high TB-endemic setting in West Africa found that early BCG vaccination of low birth weight (LBW) infants weighing down to ~1,500 g has a beneficial effect on overall infant mortality; however, safety and efficacy studies were not reported.[13,50-52] For BCG vaccination of very LBW and extremely LBW infants, there are insufficient data to assess safety, immunogenicity, and efficacy. Based on current evidence, early BCG vaccination is recommended in stable infants who are preterm and/or LBW.[53,54]

Neonates Born to Mothers with Pulmonary TB[55]

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. BCG vaccination should be given at birth.

ABSENCE OF SCAR FOLLOWING NEONATAL BCG VACCINATION

Scar failure rate following BCG neonatal vaccination of 8.6%.[56] and 10% has been reported in Indian studies. In a study of 655 children, 591 (90.2%) showed presence of scar. Of 64 children who failed to develop a scar, positive in vitro response to PPD was demonstrated in 88.2%, 94.7% and 80% of infants who received BCG at 0–1 day, 2–30 days and 31–90 days. Thus, failure of formation of BCG scar at the site of BCG vaccination may not necessarily imply failure of immunization because majority of them elicit positive in vitro lymphocyte migration inhibition (LMI) response.[57]

The presence of BCG scar is the only simple way of determining previous vaccination in clinical settings as well as in health surveys to assess vaccine uptake in spite of studies indicating that scar development is not a reliable indicator of the immunological response to BCG. Hence, a single repeat dose of BCG may be administered to infants who fail to demonstrate a scar beyond 6 months of vaccination. If there is a failure of scar formation after the second vaccination, no further doses are warranted. Pre-BCG Mantoux test is not necessary.

The BCG vaccine can be safely coadministered with diphtheria–pertussis–tetanus (DPT), polio, hepatitis B, *Haemophilus influenzae* type b (Hib), and measles and rubella vaccines.[13] There is no evidence to suggest reduced immunogenicity, and no safety concerns have been reported.

CONTRAINDICATIONS FOR BCG VACCINE

- Anaphylaxis after any component of a TB vaccine
- Children with known or suspected HIV infection, who are symptomatic or have laboratory evidence of immunosuppression

- Children on corticosteroids or other immunosuppressive therapy, including monoclonal antibodies against tumor necrosis factor (TNF)-alpha, such as infliximab, etanercept, and adalimumab
- Infants born to mothers who were treated with biologic response modifiers in the 3rd trimester of pregnancy. These medicines include TNF-alpha-blocking monoclonal antibodies, rituximab
- Children people with congenital cellular immunodeficiencies, including specific deficiencies of the interferon-γ pathway
- Children with malignancies involving bone marrow or lymphoid systems.

Pregnant women: BCG vaccine has not been shown to harm the fetus, but receiving live vaccines in pregnancy is not recommended.

PRECAUTIONS

Bacillus Calmette–Guérin vaccination should be deferred in the following groups:

- Neonates who are medically unstable, until the neonate is in good medical condition and ready for discharge from hospital
- Infants born to mothers who are suspected or known to be HIV-positive, where testing facilities are available, until HIV infection of the infant can be confidently excluded
- People with active skin disease such as eczema, dermatitis, or psoriasis at or near the site of vaccination
- People can receive BCG vaccine at any time before or after receiving immunoglobulins or any antibody-containing blood product.

IAP/ACVIP RECOMMENDATIONS

A single dose of BCG vaccine should be given to all healthy neonates at birth. If missed in the neonatal period, the vaccine should be administered at the earliest opportunity.

Bacillus Calmette–Guérin should be administered intradermally, on the left shoulder, at the insertion of the deltoid, in a dose of 0.05 mL to those <1 month of age and 0.1 mL in those >1 month of age.

Bacillus Calmette–Guérin can be coadministered with hepatitis B vaccine.

Catch up vaccination can be done till 5 years of age. Pre-BCG Mantoux test is not recommended till this age.

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3.2 POLIO VACCINE

Bhaskar Shenoy, Sunil Kumar Agarwalla

INTRODUCTION

While polio cases have fallen 99.9% since 1988, polio remains a Public Health Emergency of International Concern (PHEIC) and persistent barriers in reaching every child with polio vaccines and the pandemic have contributed to an increase in polio cases. In the year 2022, 596 cases of all forms of polio were recorded compared to 698 in 2021.[1,2]

In 2014, India was officially declared "Polio Free" by the World Health Organization (WHO). India is one of the 11 countries in the Southeast Asian region which have been certified as being free of the wild poliovirus (WPV). This achievement makes the South-East Asia Region, the fourth WHO Region to be certified as polio free, after the Region of the Americas in 1994, the Western Pacific Region in 2000 and the European Region in 2002.

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 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.

At one time, poliovirus infection occurred throughout the world. Vaccination resulted in reduced circulation of WPV and its elimination from the United States in 1979. A polio eradication program conducted by the Pan American Health Organization led to elimination of polio in the Western Hemisphere in 1991.

In 1988, more than 125 countries had WPV transmission with 350,000 of paralytic polio cases. This motivated the 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. Type 2 and 3 WPVs have been eradicated worldwide and endemic circulation of type 1 WPV persists only in two countries.

Polio remains endemic in two countries—Afghanistan and Pakistan. Globally, as of December 27, 2022, 30 cases of confirmed polio due to wild poliovirus type 1 (WPV1)[1] and 566 cases due to circulating vaccine-derived poliovirus (cVDPV),[2] from AFP cases, have been reported this year. Incidentally, both UK and USA have reported one case each of cVDPV, from AFP cases.[4] In 2022, cVDPV cases have been reported in 23 countries, with 482 out of the 566 cases being cVDPV2.[2] Until poliovirus transmission is interrupted in these countries, all countries remain at risk of importation of polio, especially vulnerable countries with weak public health and immunization services and travel or trade links to endemic countries.

The Polio Eradication Strategy for 2022–2026 outlines measures including increased government accountability and wider use of novel oral poliovirus vaccine type 2 (nOPV2) that are needed to avoid new emergences of cVDPV2 during outbreak responses.[3] In 2021, approximately 136 million nOPV2 doses have been released in eight countries approved for initial use (Benin, Chad, Congo, Liberia, Niger, Nigeria, Sierra Leone, and Tajikistan). SIAs continue to be affected by the COVID-19 pandemic in 2021. Gradually, nOPV2 is brought into wider use to ascertain whether it can replace mOPV2.

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 guidelines rely on acute flaccid paralysis (AFP) cases below 15 years to identify the cases of polio. All children

with AFP should be reported and tested for WPV within 48 hours of onset.

To test for polio, fecal specimens are analyzed for the presence of poliovirus. Because shedding of the virus is variable, two specimens, taken 24–48 hours apart, are required.

Since the highest concentrations of poliovirus in the stools of infected individuals are found during the first 2 weeks after onset of paralysis, stools samples should be collected as soon as possible.

Stool specimens must be sealed in containers and stored immediately inside a refrigerator or packed between frozen ice packs at 4–8°C in a cold box. Undue delays or prolonged exposure to heat on the way to the laboratory may destroy the virus. Specimens should arrive at the laboratory within 72 hours of collection. Otherwise, they must be frozen (at –20°C), and then shipped frozen, ideally packed with dry ice or cold packs. The procedure is known as the "reverse cold chain".[5]

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, 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.[6]

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.[5]

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 is now not available. mOPV will be stockpiled for future outbreaks.[5]

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: (1) mOPV1, mOPV2, or mOPV3; and (2) bOPV containing types 1 and 3. The tOPV containing types 1, 2, and 3 has been discontinued globally.

Seroconversion with mOPV1 is approximately threefold higher than that of the type 1 component of tOPV. A clinical trial in India confirmed that the antibody response to types 1 and 3 with bOPV was superior that induced by tOPV.

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 (SAGEs) recommended the cessation of use of type 2 OPV, switch from tOPV to bOPV, and use of mOPV2 for outbreaks response.

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 and +8°C for a maximum of 6 months. Vaccine vial monitor 2 (VVM2) gives a visual indication of whether the vaccine has been kept at the correct temperature conditions. OPV is contraindicated in immunodeficient children. 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.[6]

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 have 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 occurs 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.[7,8] 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%.[9,10] The reduced antibody response to OPV in children in low-income settings is 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). 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 does not carry the risk of inducing 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.[8]

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.[5] 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 polioviruses. 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.[11]

Persistence of Mucosal Immunity

Recent data reveals that mucosal immunity does not last >1 year.[11] 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.[10]

Duration of Protection

After induction of active immunity either by vaccination or exposure to poliovirus, usually measured by circulating antibody titer, protection against paralytic polio is almost life-long and protective immunity will not decrease even if the antibody titers decline over time and 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), and/or rotavirus vaccines. While some reduction in antibody response to rotavirus vaccine has been demonstrated when administered simultaneously with OPV, studies have shown no decrease in protective efficacy of rotavirus vaccine in infants receiving concurrent OPV.

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.

Safety Issues of OPV

The main safety issues of OPV are VAPP and cVDPV.

Vaccine-associated Paralytic Poliomyelitis

Vaccine-associated paralytic poliomyelitis is paralytic polio occurring in a vaccinee or a close contact, which is caused by a strain of poliovirus that has genetically changed in the intestine, from the original attenuated vaccine strain contained in OPV. VAPP is defined as:

- A case of AFP with residual paralysis (compatible with paralytic poliomyelitis) lasting at least 60 days
- Occurring in an OPV recipient between 4 and 40 days after the dose of OPV was administered
- In a person who has had known contact with a vaccine recipient between 7 and 60–75 days after the dose of OPV was administered
- Isolation of vaccine-related poliovirus from any stool samples and no isolation of WPV was frequently used as criteria.

Vaccine-associated paralytic poliomyelitis is indistinguishable from paralytic polio caused by the wild virus. 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.[12,13] 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 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 maternal antibodies, birth dose of OPV, early immunization with OPV, and most importantly lower "take" of the vaccine. 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%). The exact burden of VAPP in India is not known, as VAPP is classified as nonpolio AFP.

Vaccine-derived Poliovirus

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. Such mutated viruses can circulate in a community for an extended period of time and cause paralysis, which is known as cVDPV. 90% of reported cVDPV are due to type 2 polio virus.[14]

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.

These viruses are further subdivided into three categories:

1. Circulating VDPVs, 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

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 continues to circulate for >6 months following detection, which represents programmatic failures to contain the cVDPV, then they are known persistent cVDPVs.[14]

In July 2015, the GPEI revised the definition of cVDPV to enhance its sensitivity.[14] In the new guidelines, cVDPVs are defined as genetically linked VDPVs isolated from: (1) at least two individuals—not necessarily AFP cases—who are not household contacts; (2) one individual and one or more environmental surveillance (ES) samples; or (3) 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 >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.

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 is 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. IPV is available as 10-dose, 5-dose, and single dose vials; IPV vials can be used up to 28 days after opening the vial. IPV is also available as a component of combination vaccines.

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.[15] 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 vaccines usually retain seroprotective titers until the first booster is given during the 2nd year of life, and this third or fourth injection gives a marked anamnestic response with booster dose.

Intradermal Inactivated Polio Vaccine

Fractional doses of IPV, one-fifth of a full dose, reduce the cost and allow 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 **(Fig. 1)**. 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)[16] and in Bangladesh (6 and 14 weeks),[17] 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 who, in 1990, using the modern cIPV, demonstrated that one-fifth of the intramuscular (IM) dose is immunogenic in humans when delivered intradermally (ID). Several trials have shown that two consecutive doses of

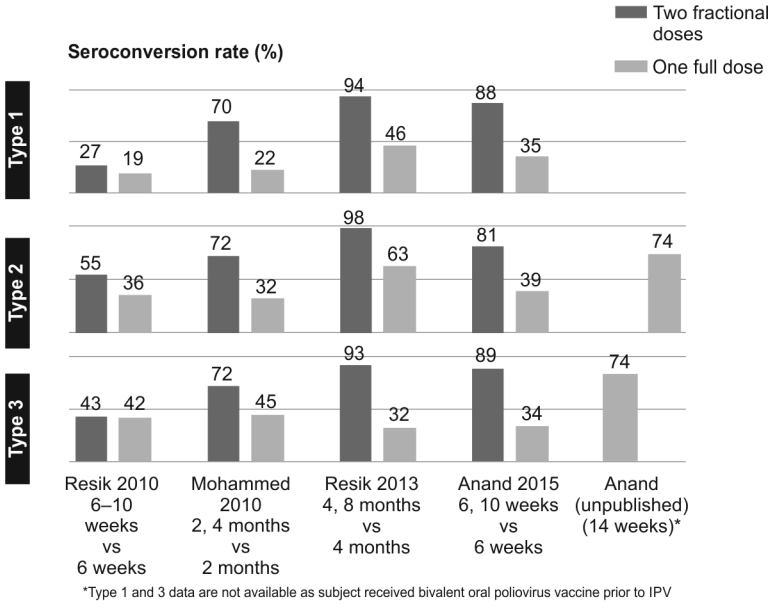

Fig. 1: Comparison of two fIPV doses with one full intramuscular dose across five studies.

fractional ID IPV compared well to one dose of full 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.[16-18] 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.

In early 2016, the WHO announced a global shortage of inactivated poliovirus vaccine. *In response, WHO's Strategic Advisory Group of Experts on Immunization recommended that countries with good immunization systems and coverage consider administering two fractional inactivated poliovirus vaccine doses of 0.1 mL each ID instead of a single, IM, full dose of 0.5 mL.*[19]

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.[3] 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, Hungary, and USA. Such schedules also reduce the number of doses of IPV.

Concurrent IPV and OPV

In developing country settings, the concurrent administration of OPV and IPV has induced uniformly high antibody responses to all three poliovirus types, as evidenced from the studies from Thailand and Pakistan.[20,21] 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.[11]

OPV Followed by IPV

A recent study in India assessed a schedule with bOPV only 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).[4]

Mucosal Immunity/Protection

In a study done in India, 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.

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

No data is 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.

A single dose of cIPV demonstrated excellent immunogenicity and led to higher increases in antibodies to all three polio types than did an additional dose of bOPV. There is some suggestion 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.[20]

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 WPV 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. IPV 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 vaccines who have not seroconverted, particularly against type 2 after bOPV. 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 VDPVs.

It is not possible to say when IPV usage will cease. 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.[22]

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.[23]

As discussed above, two doses of fIPV at 6 and 14 weeks results in better seroconversion rates against type 2 as compared to a single dose of IM-IPV at 14 weeks. Moreover, the fIPV schedule is dose sparing.

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 (3+1 schedule).

Sequential IPV–OPV Schedule

In 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 should 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.

Studies, examining the long-term persistence of antibodies following IPV vaccination in the absence of a booster vaccination

given after the first 2 years of life, are lacking. Persistence of antibodies only up to the school-entry age has been demonstrated, as all IPV using countries recommend a school age booster. All infant and toddler schedules result in persistence of detectable polio antibodies at least till the school age booster with the highest titers with the 3+1 schedule.[24]

A study assessing the persistence of antibodies against diphtheria, tetanus, pertussis, poliomyelitis, and *Haemophilus influenzae* type b (Hib) in 5–6-year-old French children, after primary vaccination and first booster with a pentavalent combined aP/wP vaccine in the 2nd year, had shown persistence of SPR but a significant fall in antibody titers just before the preschool booster. A booster resulted in SPR rising to 100% and GMTs rising 32–55-fold for all the three serotypes.

There are no studies regarding the long-term persistence of antibodies with the schedule of 6–10–14 weeks or two fractional doses intradermal inactivated polio vaccine (ID–IPV).

Mucosal immunity to polio vaccines is important for interruption of poliovirus transmission. It is well established that IPV is less effective than OPV in stimulating mucosal immunity.

Some studies have suggested an inverse correlation between circulating levels of preexisting homotypic antibodies and excretion of poliovirus types 1, 2, and 3 following the feeding of trivalent OPV. This association was found to be strongest for type 1 and less for types 2 and 3. Reduced excretion of type 1 was demonstrated from the stools, with titers <1:8 having the highest excretion rates and titers >1:128 having the lowest excretion rates.[25]

Advisory Committee on Vaccines and Immunization Practice Recommendations

The Advisory Committee on Vaccines and Immunization Practices (ACVIP) recommends a birth dose of bOPV, followed by an all IPV schedule at 6–10–14 weeks, an IPV booster at 15–18 months, and a second booster of IPV at 4–6 years. The second booster dose can be given as either standalone IPV or as a combination with DPT (DTwP/DTaP) vaccines.

The Universal Immunization Programme (UIP) recommends two dose of fIPV at 6 and 14 weeks, to be administrated ID at the insertion of the deltoid, on the right arm and a booster dose of fIPV at 9 months on the left arm.

Those who have received two doses of fIPV as part of the UIP schedule may be offered a single dose of IM-IPV at least 8 weeks after the last dose of fIPV.

For those who have received only bOPV, one dose of IM-IPV may be offered followed by a second dose after 8 weeks.

All children <5 years of age should receive bOPV on all SIA days.

National Immunization Days

The objective of national immunization days (NIDs) is to reduce the widespread transmission of wild polio in the endemic countries. The NIDs are conducted once or 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 may be 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.

Mopping-up Campaigns

Mopping-up campaigns usually target children <5 years of age wherein 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

Stopping all Poliovirus

Today, the two countries of focus are *Afghanistan* and *Pakistan* as they have never stopped transmission of endemic WPV.

Surveillance

Polio surveillance underpins the entire polio eradication initiative. Without surveillance, it would be impossible to pinpoint where and how poliovirus is still circulating. Polio surveillance identifies new cases and detects any circulation of poliovirus.

Preparing for a Polio-free World

A polio-free world requires updated vaccination policies, including the phased withdrawal of OPV, appropriate containment of the poliovirus in facilities, certification that polio has been eradicated, and planning for the transition of knowledge and infrastructure to serve other health goals.

Various strategies are being studied to make IPV more affordable. These include:

- *Reduce the volume of each dose:* ID delivery: discussed above.
- *Reduce the antigen content of each dose by use of adjuvants:* An investigational trivalent aluminium adjuvanted IPV (IPV-Al) vaccine, containing approximately one-tenth of the amount of each antigen in the IPV vaccine, adjuvanted to aluminum hydroxide (0.5 mg aluminum), was shown to be noninferior to cIPV. This vaccine was licensed in 2019 and WHO prequalified in 2020.
- *Reduce the number of IPV doses:* Studies have shown that administration of a 2-dose IPV schedule at 6 weeks to 9 months or 14 weeks to 9 months had ≥99% cumulative immune response to all three PV types. Schedules that provide two early doses with DPT1 and DPT3 may achieve higher population coverage and higher immune response for a younger age, but schedules that provide a second dose at least 4 months after the first will overall achieve a higher immune response though by a later age.
- *Sabin IPV (sIPV) to reduce the cost of vaccine manufacture:* The inherent safety of the attenuated Sabin strains used in OPV vaccines has led to use of these strains for use in manufacturing IPV. IPV manufacture needs BSL-IV levels and hence cannot be manufactured by Developing Countries Vaccine Manufacturers (DCVMs), thus increasing the cost of the vaccine. Since, sIPV does not contain WPV, it requires BSL-I–II, for manufacture, which is available with DCVMs, so its manufacture is less expensive.

IAP recommendations.

- *Polio vaccine schedule:* Birth OPV, IPV 6, 10, 14 weeks, booster 1 at 18 months, booster 2 at 4–6 years.
- OPV primed/incomplete fIPV vaccinated children must be given at least 1 IM IPV at least 8 weeks after the last fIPV dose.
- bOPV schedule at birth, 6–10–14 weeks without any IPV should be strongly discouraged.
- No child should be left without at least 1 dose of IPV.
- All IAP/UIP immunized children should receive OPV on all SIA days till 5 years of age.

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3.3 HEPATITIS B VACCINE

Srinivas Kalyani, Srinivas G Kasi

BACKGROUND

Hepatitis is the main manifestation of hepatitis viral infection in humans, is caused by five virus species—(1) hepatitis A virus (HAV), (2) hepatitis B virus (HBV), (3) hepatitis C virus (HCV), (4) hepatitis D virus (HDV), and (5) hepatitis E virus (HEV). Together these viruses caused 1.34 million deaths in 2015.[1] All hepatitis viruses cause acute hepatitis; HBV frequently causes 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, thus placing India in the intermediate endemicity zone.[2] Infection with HBV may occur perinatally (vertical transmission), during early childhood (horizontal transmission), through sexual contact, or nosocomially. In India, 1.6–4% of the populations carry this virus in their blood. 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 (HepB). The seropositivity of HepB was found to be 2.9% among pregnant women in India.[3] The risk of infection in a child born to a HepB-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 HepB vaccination.[4]

VACCINES

Hepatitis B virus immunization before HBV exposure is the most effective means to prevent HBV transmission. The active substance in the HepB vaccine is the viral surface protein HBsAg (hepatitis B surface antigen). The currently available vaccine, containing the surface antigen of HepB, is produced by recombinant technology in yeast and adjuvanted with aluminum salts and preserved with thimerosal (thimerosal-free vaccines are also available). This vaccine is available since 1986. HepB 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. HepB vaccines are relatively heat stable.[5] HepB vaccines are available as monovalent formulations and in combination with other vaccines including diphtheria, tetanus, and pertussis (DTP), *Haemophilus influenzae* type b (Hib), and inactivated polio vaccine (IPV).[4,5]

Hepatitis B vaccine is also available in combination with hepatitis A vaccine. Each dose of this vaccine contains 20 μg of HbsAg and 720 EU of hepatitis A vaccine. The schedule is 0–1–6 months for those >18 years of age.

Immunogenicity, Efficacy, and Effectiveness

The protective efficacy of HepB vaccination is related to the induction of antibody to hepatitis B surface antigen (anti-HBs) antibodies and 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] The WHO recommends a minimum interval of 4 weeks between the three doses. Schedules with these minimum intervals have seroconversion rates that are similar to schedules with longer intervals between doses, but the antibody concentrations after completion of the schedule are lower with schedules with shorter intervals between doses.

Dosage and Administration

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

Hepatitis B vaccines are administered intramuscularly, in the anterolateral thigh (for children <3 years) or deltoid (for children ≥3 years). HepB administered at any site other than the deltoid or anterolateral thigh should not be counted as valid and should be repeated.[7,8] Injections in the gluteal region should be avoided due to low immunogenicity.

Inadvertent administration of the adult dose to a child is safe.[9] The vaccine is extremely safe and well tolerated.

Interchangeability

The same brand of vaccine should be used whenever it is feasible, particularly for the first three doses in the series.[10] However, monovalent HepB vaccine brands may be interchanged within an immunization series.

Till additional data is available, the primary series of an acellular pertussis-containing HepB combination vaccine should not be interchanged, as far as feasible and the same brand should be used for completing the series.[11]

Immunization Schedules

Infants

The classical schedule is 0, 1, and 6 months. The vaccine is highly immunogenic and seroconversion rates are >90% after a three-dose schedule. However, seroprotection rates >90% are seen with any schedule, consisting of three doses, given at an interval of at least 4 weeks between doses. 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, although there are no specific dosage recommendations made for children.[5] Four doses may be given for programmatic reasons and the additional dose is not harmful. It should be noted that delaying the administration of the birth

dose to infants of chronically infected mothers increases the risk of perinatal HBV transmission. As of now, none of the above schedules needs a booster.

Schedules with a birth dose are necessary in all areas of high and moderate endemicity to prevent perinatal transmission. The birth dose should be administered as soon as possible after birth, ideally within 24 hours. If administration within 24 hours is not feasible, a late birth dose has some effectiveness. Although effectiveness declines progressively in the days after birth, after 7 days, a late birth dose can still be effective in preventing horizontal transmission and, therefore, remains beneficial.

Antibody titers >10 mIU/mL signify a response and are considered protective.[6]

The HepB vaccine series does not need to be restarted, if it was interrupted.[10]

Adverse Reactions

Hepatitis B vaccines are safe. The most frequently reported side effects are pain at the injection site in 3–29%, erythema in 3%, and fever >37.7°C (99°F) in 1–6%.[1] Administration of the first dose during the birth hospitalization has not been associated with increased rates of newborn sepsis evaluations.[12] In a large cohort, the risk of anaphylaxis after a HepB-containing vaccine was 1 per 1.1 million doses [95% confidence interval (CI): 0.1–3.9].[13]

Contraindications

The contraindication is severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component (e.g., yeast). Pregnancy and lactation are not contraindications for vaccination.

Duration of Protection

The standard three-dose HepB 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. The higher the peak of anti-HBs concentrations following immunization, the longer it 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.[14] Furthermore, observational studies have shown the effectiveness of a primary series of HepB vaccine in preventing infection up to 22 years postvaccination of infants.[5,19] Studies have shown long-term protection against developing primary liver cancer (efficacy 84%, 95% CI: 23–97), mortality from infant fulminant hepatitis (efficacy 69%, 95% CI: 34–85), and severe end-stage liver disease (efficacy 70%, 95% CI: 15–89).[15]

However, HepB 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 HepB 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 yearly and booster vaccination given whenever levels drop to below protective levels. Children with cystic fibrosis, liver disease, or celiac disease should be managed as above, as they may not respond as well to HepB vaccine.

Coadministration

Hepatitis B vaccines do not interfere with the immune response to any other vaccine and vice versa. The immune responses and safety of HepB-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 HepB vaccine in management of perinatal/occupational/sexual exposures to HepB 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. HepB vaccine and HBIG should be administered at different anatomic sites and regardless of birth weight or maternal antiviral therapy for high HepB viral loads during pregnancy. HBIG provides temporary protection lasting 3–6 months. HBIG should never be given intravenously.

The HBIG is also used alone following exposure to HepB in patients who are nonresponders to HepB vaccination (genetic reasons/immunocompromised status). In this situation, two doses of HBIG, 1 month apart, are indicated.

Infants who receive appropriate immunoprophylaxis may be breastfed immediately after birth.

Prevaccination 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]

However, in patients at high risk of HBV infection, prevaccination serology may identify acute or chronic HBV infection or immunity to HBV infection, preventing unnecessary vaccination. In most cases, the first dose of vaccine should be administered immediately after blood is obtained for serology (i.e., without waiting for results). When serologic testing and HepB vaccination are to be performed on the same day, blood for serology should be obtained before immunization. Transient HBsAg positivity (<21 days) has been reported following HepB vaccination.[16]

Postvaccination Testing

Serologic testing to assess antibody response to HepB vaccine usually is not necessary for immunocompetent children and

adolescents. However, it should be performed at least 1 month after completion of the immunization schedule, in specific populations, including:[10]

- Patients on hemodialysis
- People with HIV infection
- Immunocompromised patients (e.g., hematopoietic stem-cell transplant recipients or people receiving chemotherapy)
- People at occupational risk of exposure from percutaneous injuries or mucosal or nonintact skin exposures (e.g., certain healthcare and public safety workers)
- Sexual partners of HBsAg-positive people
- Infants born to HBsAg-positive women.

Both HBsAg and antibody to HBsAg (anti-HBs) should be obtained after receiving ≥3 doses of HepB vaccine, at least 4 weeks after the last dose of the HepB vaccine. Levels of anti-HBs decreases with increasing intervals from the last dose of HepB vaccine and hence may result in unnecessary revaccination when serology is obtained later that showed nonprotective titers.[17-19]

Older Children and Adolescents

Hemodialysis Patients

Serologic testing (anti-HBs) 1–2 months after administration of the last dose of the primary HepB vaccine series is recommended to determine the need for revaccination.[10]

Annual anti-HBs testing is recommended for hemodialysis patients and administration of a booster dose of HepB vaccine should be done, when the anti-HBs concentration is <10 mIU/mL.[10]

Immunocompromised patients: The immune response to HepB vaccine is reduced in children who are immunocompromised.[20-22] Annual testing for anti-HBs and provision of a booster dose of HepB vaccine when anti-HBs concentration is <10 mIU/mL are a reasonable strategy for prevention of HBV infection in immunocompromised children and adolescents with ongoing risk of HBV exposure and is suggested by the Advisory Committee on Immunization Practice (ACIP) and American Academy of Pediatrics (AAP).[10]

Nonresponders

Vaccine recipients who do not develop a serum anti-HBs response (≥10 mIU/mL) after a primary vaccine series should be tested for HBsAg to rule out the possibility of a chronic infection as an explanation of failure to respond to the vaccine. Such individuals should receive a 2nd series of three doses in 0–1–6 months schedule and retested for anti-HBs response, 1–2 months after the last dose.

A nonresponder is defined as a vaccine recipient who does not develop a serum anti-HBs response (≥10 mIU/mL) after two series of three doses of a HepB vaccine each, administered according to recommendations.

Such individuals should be administered two doses of HBIG, 1 month apart, after every significant exposure to HepB.

Healthy individuals in whom the lack of response appears to be genetically determined: Immunogenetic studies have demonstrated that certain individuals lack a dominant response gene that controls the production of anti-HBs. The absence of this gene may be marked by two extended human leukocyte antigen (HLA) haplotypes.[23] In a study from the United States, an increased incidence of individuals homozygous for the extended HLA haplotype B8, SC01, and DR3 was found among nonresponders.[23]

Among the responders, individuals homozygous for this haplotype developed a lower antibody level compared with heterozygotes.

In another study of 52 nonresponders from Sweden, the HLA haplotype (DQB1*0604; DQA1*0102DRB1*1302) was more frequent in nonresponders.[24]

VACCINE-INDUCED HBV S ESCAPE MUTANTS

Hepatitis B virus *S* gene mutants have been described in infants who were infected with HBV despite an adequate anti-HBs response to HepB vaccination. These mutants have been observed in many parts of the world including China, Singapore, Taiwan, Japan, Italy, and Africa.[25]

The most common mutation involves a glycine to arginine substitution at codon 145 in the "a" determinant of HBsAg. This mutation decreases binding of HBsAg to anti-HBs and may explain why these infants develop "escape" infection.[26,27]

Most reports found that the HBV S mutations were not detected in the maternal carriers, suggesting that the mutations were selected by immune pressure (vaccine and/or HBIG).[28]

The benefits of conventional HepB vaccine far outweigh the concerns of HBV S escape mutants, and vaccination programs should not be deterred because of these concerns. There is clearly a need for further research to develop vaccines that are more effective and capable of circumventing these mutations.

Management of an Infant Born to Hepatitis B-positive Mother[29]

The risk of perinatal transmission among infants born to HBsAg-positive mothers is as high as 90% without immunoprophylaxis.[29,30] Pregnant women should be counseled and encouraged to opt for HBsAg screening. If the mother is known to be HBsAg negative, HepB vaccine can be given in the recommended schedule. If the mother's HBsAg status is not known, it is important that HepB 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 HepB vaccine within 12 hours of birth, using two separate syringes and separate sites for injection at the same time (i.e., same day, same clinic visit).[30] The injections may be administered in any order. There is no minimum interval between administration of HepB vaccine and HBIG, if they are not administered at the same time.

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 HepB vaccine should be administered at 6–10–14 weeks as part of combination vaccines.

If HBIG is not available (or is unaffordable), HepB 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 HepB vaccine is 85–95% and that with HepB vaccine alone (first dose at birth) is 70–75%.[31] 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.[32] Following neonatal administration of HBIG and HepB vaccination in

the first 4–6 months of age, the ideal time to perform serology is after 9 months of age, because HBIG may still be present in the blood, if done earlier and may result in detection of HBIG and not the anti-HBs produced by the baby. It should not be performed sooner than 4 weeks after the last dose of HepB vaccine because of the possibility of transient (<21 days) HBsAg-positivity related to the vaccine.[16]

In case of infants born to HbsAg-positive mothers, who received HBIG and the complete schedule of HepB vaccine, postvaccination serology [both HBsAg and antibody to HBsAg (anti-HBs)] should be obtained usually at 9–12 months of age, because HBIG may still be present in the blood and, if done earlier, may result in detection of HBIG and not the anti-HBs produced by the baby.[10]

Infants who are HBsAg-positive at any time during postvaccination testing should be referred for evaluation of chronic liver disease. Household contacts who have not been vaccinated against HBV should be vaccinated.

Infants who are HBsAg-negative and have anti-HBs concentration ≥10 mIU/mL are immune to HBV. Additional doses of HepB vaccine and serologic testing are not necessary.

Infants whose anti-HBs is <10 mIU/mL remain susceptible to HBV. For infants who remain susceptible after the primary infant series, the recommendation is to administer three doses of HepB vaccine (at 0, 1–2, and 6 months) followed by measurement of anti-HBs and HBsAg 1–2 months after the third dose.

The HBsAg-negative children whose anti-HBs levels remain <10 mIU/mL after two complete series of HepB vaccines are considered to be "nonresponders" and susceptible to HBV. Available data do not suggest a benefit from additional doses of HepB vaccine.[19]

Caregivers of nonresponders should receive information about precautions to prevent HBV infection, and the nonresponders should receive appropriate postexposure prophylaxis, if they are exposed (HBIG: 0.06 mL/kg, to be given within 72 hours and a repeat dose after 1 month).[33]

In a meta-analysis of three randomized trials, compared with placebo/no intervention, the combination of HepB vaccine and HBIG reduced HBV infection in infants born to HBsAg-positive women [4% vs. 57%, relative risk (RR) 0.08, 95% CI: 0.03–0.17].[34]

IMMUNIZATION OF PRETERM INFANTS

Preterm infants and low-birth weight infants with birth weight <2,000 g have a decreased response to HepB 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 **(Table 1)**.[4,5,32]

TABLE 1: Hepatitis B immunization management of preterm infants weighing <2,000 g, by maternal hepatitis B surface antigen (HBsAg) status.

Maternal HBsAg status	*Recommendation*
Positive	• Administer HBIG + single-antigen hepatitis B vaccine within 12 hours of birth • Do not count the birth dose as part of the vaccine series • Administer three additional hepatitis B vaccine doses at 6, 10, and 14 weeks • Test for HBsAg and antibody to HBsAg 1–2 months after completion of >3 doses of a licensed hepatitis B vaccine series (i.e., at age 9–18 months, generally at the next well-child visit). Testing should not be performed before the age of 9 months nor within 4 weeks of the most recent vaccine dose
Unknown	• Administer HBIG + single-antigen hepatitis B vaccine within 12 hours of birth • Test mother for HBsAg • Do not count the birth dose as part of the vaccine series • Administer three additional hepatitis B vaccine doses at 6, 10, and 14 weeks
Negative	A birth dose of hepatitis B vaccine can be given to low birth weight and premature infants. For these infants, the birth dose should not be counted as part of the primary three-dose series; the three doses of the standard primary series should be given according to the national vaccination schedule

(HBIG: hepatitis B immunoglobulin)

Recommendations for Preterm Infants

A birth dose of HepB vaccine can be given to low birth weight and premature infants. For these infants, the birth dose should not be counted as part of the primary three-dose series; the three doses of the standard primary series should be given according to the national vaccination schedule.

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

Hepatitis B vaccination should be routinely offered to persons in high-risk settings that include healthcare 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.[35]

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.[32] HepB 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 needlestick 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.

In addition, HBV has been demonstrated to survive in dried blood at room temperature on environmental surfaces for at least 1 week. The risk of HBV infection in the exposed HCP is primarily related to the degree of contact with blood in the workplace and also to the 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 2**.

TABLE 2: 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[†] × 1 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

Contd…

Contd…

*Vaccination and antibody response status of exposed persons**	*Treatment*		
	Source is HBsAg positive	*Source is HBsAg negative*	*Source is unknown on not tested*
Fully vaccinated and known responder‡	No treatment	No treatment	No treatment
Vaccinated with three doses and known nonresponder‡	HBIG† × 1 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	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† × 1 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 immunoglobulin (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 Centers for Disease Control and Prevention. 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.

IAP/ACVIP Recommendations for Use

Individual Use

All infants, irrespective of the birth weight or gestational age, should be administered the first dose of HBV within 24 hours and three more doses along with combination vaccines at 6–10–14 weeks.

The Indian Academy of Pediatrics (IAP) Advisory Committee on Vaccines and Immunization Practices (ACVIP) committee stresses the significance and need of a birth dose (within 12–24 hours). The birth dose can reduce perinatal transmission by 18–40%.

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 HepB vaccine or whose vaccination status is not known or where the administration was inappropriate. 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 HepB vaccine are equally safe and effective and any may be used.

All infants, irrespective of the birth weight or gestational age, of HBsAg-positive mothers, should receive HBIG 0.5 mL IM followed by the first dose of HepB vaccine, within 12 hours of birth (HBIG and vaccine should be administered on different limbs), followed by three doses of a HepB containing combination vaccine at 6–10–14 weeks. Postvaccination testing for HBsAg and anti-HBs should be done at 9–12 months of age.

PUBLIC HEALTH PERSPECTIVES

Hepatitis B vaccination is great public health significance. Though the Government of India (GoI) initiated HepB vaccination since 2002, the IAP–ACVIP believes that all infants should receive their first dose of HepB 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 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.[4]

Delivery of HepB 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.

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3.4 DIPHTHERIA, TETANUS, AND PERTUSSIS VACCINES

Srinivas G Kasi, Abhay Shah

BACKGROUND

Since the introduction of the whole-cell pertussis, diphtheria, and tetanus vaccines in Expanded Programme for Immunization (EPI), the morbidity and mortality due to diphtheria, tetanus, and pertussis (DTP) have reduced significantly in India. The 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] It needs to be stressed that completion of the primary schedule and boosters are necessary for complete protection against the target diseases.

EPIDEMIOLOGY

Diphtheria

The use of DTP vaccines has had significant impact on the burden of diphtheria. However, the disease is still persisting in India and published reports of the disease indicate outbreaks, secular trends, and a shifting epidemiology over the years.[2-5] Outbreaks have been reported in medical college hostels.[6] Due to waning vaccine-induced immunity and poor uptake of booster doses, majority of outbreaks and cases are observed in schoolgoing children, adolescents, and adults **(Table 1)**.[5]

TABLE 1: Age distribution of cases of Diphtheria, in states of India with case-based surveillance 2016.

State	*Total cases*	*Under 5 years*	*5–10 years*	*Over 10 years*
Bihar	71	41%	34%	25%
Haryana	59	27%	53%	20%
Kerala	556	8%	18%	74%
Uttar Pradesh	844	25%	53%	22%
Total	**1,530**	**20%**	**39%**	**41%**

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.[7]

Pertussis

In India, the incidence of pertussis declined sharply after launch of Universal Immunization Programme (UIP). Prior to UIP, India reported 200,932 cases and 106 deaths in the year 1970 with a mortality rate of <0.001%. In 2020, 12,566 cases were reported, reflecting a decline of >90%.[8] Among different states, MP, Jharkhand, Assam, UP, WB, and Dadra And Nagar Haveli reported the maximum cases in 2017, of which only 6 deaths were reported.[9] A prospective multinational serosurveillance study of *Bordetella pertussis* infection, among 10–18 years subjects from 8 Asian countries, was carried out, with 200 subjects from India. High titers of anti-PT immunoglobulin G (IgG) > 62.5 IU/mL (which is indicator for B petitions infection within 12 months prior) were found in 18% of subjects.[10] 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 *B. pertussis* infection rates in the community that may be responsible for appearance of typical pertussis disease in infants and children.[11]

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.[8] In a sero-survey of schoolchildren, 7–17 years of age, in Hyderabad, only 64% were immune to tetanus.[12] In May 2015, neonatal maternal tetanus was declared as eliminated in India based on figures of incidence of <1 case per 1,000 live births in all districts of the country for 2 consecutive years.[8]

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 to 30 Lf that of tetanus toxoid (TT) varies from 5 to 25 Lf per dose and whole cell pertussis >4 IU 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 (IM) 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 exceed 95%. There is no known immune correlate of protection against pertussis. 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.[11,12] For higher efficacy trials, the efficacy estimates vary from 83 to 98% and 36 to 48% in lower efficacy trials. According to a systematic review done in 2003, the pooled-efficacy of wP vaccine against pertussis in children was 78%.[13] The efficacy of wP alone ranged from 61 to 89%, and the efficacy of combination DTwP vaccines ranged from 46 to 92%.[13] 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 such as pain, swelling, and redness at the local site, fever, fussiness, anorexia, and vomiting are reported in almost half the vaccines 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 >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.[14] The frequency of systemic reactions reduces and that of local reactions increases with increasing number of doses. Serious adverse 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, without any other cause, 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 >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.[14]

Recommendations for Use

The standard schedule is three primary doses at 6, 10, and 14 weeks and two boosters at 15–18 months and 4–6 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 an increased reactogenicity. 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 most 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 **(Table 2)**.[15] Nearly 2-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

TABLE 2: 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	25 µg	25 µg	25 µg	25 µg	2.5 µg	8 µg
Filamentous hemagglutinin	25 µg	25 µg	25 µg	25 µg	5 µg	8 µg
Pertactin	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)

tetanus and pertussis are 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.[11]

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%.[11] However, a few countries such as Japan, Denmark, and Sweden 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.[15] This is the reason why direct comparison of protective efficacy of different aP vaccines in human is not possible.

Different researchers 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 five-component aP vaccine had an estimated efficacy of 88.7% [95% confidence interval (CI): 79.4–93.8%].[16] 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 one- and two-components (67–70%).[13] A Cochrane review by Zhang et al.[17] 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. 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,[14] the available evidence[11] is not sufficient to establish any significant difference in vaccine effectiveness of aP vaccines with differing numbers of components.[14]

The effectiveness of vaccination programs on a national level depends not only on the efficacy of the vaccine but also on 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 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.[18] 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 **(***see* **Table 2)**.

Recommendations for Use

The vaccines should be stored at 2–8°C and the recommended dose is 0.5 mL IM. 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 such as USA, UK, Australia, Chile, Brazil, Colombia, and Pakistan employing both aP and wP vaccines despite having very high-vaccination coverage.[14] 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.[14] 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.[16,17,19-22]

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).[14]

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).[14] 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 years 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.[14]

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.[11] Many later trials have also hinted that the efficacy of the aP vaccine may not be as robust as reported in the initial studies.[19-22] 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.[24-26] Recent data from US and Australia have suggested reduced durability of vaccine-induced immunity after the aP vaccination in comparison of wP vaccines.[16,22] 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 aP vaccine

series was significantly less effective and durable than one that contains at least one dose of the traditional whole cell vaccine."[23]

Original wP and aP priming generates comparable protective immunity in the first few years after vaccination. However, wP/aP priming induces different T cell phenotypes, which have been shown to persist for at least 15 years. Adults who received a Tdap booster and who had received either wP or aP priming followed by multiple aP boosters, the aP primed group showed increased interleukin 4 (IL-4), IL-5, IL-13, IL-9, and transforming growth factor-β (TGF-β) (Th2 response) and decreased interferon-γ (IFN-γ) and IL-17 production (Th1 and Th17 response), defective in their ex vivo capacity to expand memory cells, and less capable of proliferating in vitro. Pertussis-specific IgG4 antibodies were significantly elevated in aP compared with wP individuals.[24-31] While IgG1 antibodies are potent neutralizing antibodies, IgG4 antibodies are less effective in neutralization and are more tolerizing in nature.

The current evidence is tilted in favor of wP vaccines as far as effectiveness of the pertussis vaccines is concerned.[11] 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.[11] **Table 3** 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 and also serves as a reservoir for disease transmission to unvaccinated or partially vaccinated young infants.[11] 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.[14] 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.[32] There is a paucity of robust data on the incidence of adolescent and adult pertussis in India but is perceived to be significant, especially in those states where childhood immunization

Table 3: 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

coverage is good and reduced natural circulation of pertussis leads to infrequent adolescent boosting.[11] In a study of pertussis infection among 10–18 years subjects from 8 Asian countries, with 200 subjects from India, high titers of anti-PT IgG > 62.5 IU/mL, indicative of *B. pertussis* infection within the past 12 months, were found in 18% of subjects.[10]

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).[11] 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. Hence, 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 2 provides details of available Tdap vaccines in India. The vaccine should be stored between 2 and 8°C, and must not be frozen. The dose is 0.5 mL 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 such as 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.[14] 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.[11] 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.[28] 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 Advisory Committee on Immunization Practices (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.[28-33]

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.[11] Several strategies such as 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.[11] 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.[10]

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.[34] Even three to six 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.[35]

There are a few concerns regarding maternal immunization, they include ultimate titers 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.[11] 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.[36] 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.[19] 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.[11]

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 (ACVIPs) of the Indian Academy of Pediatrics 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.[11]

Individual Use: IAP Recommendations

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.[14]

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

- *Primary immunization*: The primary series should be completed with three doses of either wP or aP vaccines, irrespective of the number of components. The schedule should begin at 6 weeks of age, with three doses administered at an interval of 4 weeks. wP vaccine is definitely superior to aP vaccine in terms of efficacy and duration of protection but more reactogenic. In view of parental anxiety and concerns for its reactogenicity, aP vaccine can also be administered in the primary series. The primary aim is to increase the vaccination coverage with either of the vaccines.

There is strong evidence of effectiveness and real-life performance of wP vaccines from India where their widespread use has markedly reduced the incidence of pertussis after the launch of UIP.

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 or aP vaccines. However, considering the higher reactogenicity, aP vaccine/combination **(***see* **Table 2)** 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 IM 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 16–18 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: If the series is started after 1 year of age, 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 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 10–11 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 persons aged 7–10 years, who receive a dose of Tdap as part of the catch-up series, an adolescent Tdap vaccine dose should be administered at age 11–12 years.
- A single dose of Tdap may also be used as replacement for Td/TT booster in adults of any age, if they have not received Tdap in the past.
- Tdap can 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.

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

Tetanus toxoid, and reduced quantity diphtheria, and aP during pregnancy: Immunization of pregnant women (maternal immunization) is an effective approach to protect very young infants and neonates. IAP recommends 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).[34-36]

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.[14]

TETANUS AND DIPHTHERIA VACCINE

Background

Antibodies to tetanus and diphtheria decline over time, resulting in increasing susceptibility of adolescents and adults to diphtheria. Hence, regular boosting is needed to ensure adequate levels of antibodies during any apparent or inapparent exposure to tetanus bacilli/toxin.[37]

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 tetanus and diphtheria every 10 years.

Vaccine

Tetanus and diphtheria contain 5 Lf of TT and only two units of diphtheria toxoid are stored at 2–8°C and are administered IM in a dose of 0.5 mL. 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.

Tdap/Td in Pregnancy

The WHO has evolved exhaustive guidelines for administration of Tdap/Td in pregnant women,[38,39] which are endorsed by IAP.

- *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, in the schedule mentioned earlier.

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 prevent anaerobic environment which is conducive to tetanus toxin production. The indications for Tdap/Td and tetanus immunoglobulin (TIG) are as below **(Table 4)**.

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

TABLE 4: Tetanus prophylaxis in wound management.

	Doses of TT	***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 >10 years since last dose.
[‡]Yes, if >5 years since last dose.
(Tdap: tetanus toxoid and reduced quantity diphtheria and acellular pertussis; TT: tetanus toxoid)

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.

IAP recommendations: Diphtheria and tetanus toxoids and pertussis 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

(DTaP: diphtheria, tetanus, and acellular pertussis; DTwP: diphtheria, tetanus and whole cell pertussis; Tdap: tetanus and diphtheria toxoids and acellular pertussis)

IAP recommendations: Tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine.

Routine vaccination:
- *Recommended schedule:* One dose of Tdap to all adolescents aged 10 years through 12 years
- Adacel™ is approved for use for 11–64 years
- Boostrix™ is approved for use >4 years of age
- The IAP/ACVIP does not recommend use of Tdap before the age of 7 years
- 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

Contd…

Contd…

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
- If the last dose of Tdap has been administered >9 years, the adolescent booster of Tdap is not necessary
- Persons aged 11 years through 18 years who have not received Tdap vaccine should receive a dose followed by tetanus and diphtheria toxoids (Tds) booster doses every 10 years thereafter
- Tdap vaccine can be administered regardless of the interval since the last tetanus and diphtheria toxoid-containing vaccine

(DTaP: diphtheria, tetanus, and acellular pertussis; DTwP: diphtheria, tetanus and whole cell pertussis)

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3.5 *HAEMOPHILUS INFLUENZAE* TYPE B CONJUGATE VACCINES

Sanjay Lalwani, Shivananda S

BACKGROUND

Haemophilus influenzae type b (Hib) organisms are divided into capsulated and noncapsulated strains. Capsulated *Haemophilus influenzae* has six serotypes of which type b is most important. 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 2 years of life before natural protective immunity is acquired by the age of 3–4 years. Noncapsulated (nontypeable strain—NTHi) Hib causes bronchitis, otitis media, sinusitis, and pneumonia, is not amenable to prevention at present, and can occur at all ages. *Haemophilus influenzae* spread by respiratory droplet infection and also by fomites contaminated with respiratory secretions. 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. It was estimated that there were 29,500 Hib deaths (18,400–40,700) in HIV-uninfected children and an additional 1,000 deaths in HIV-infected children aged 1–59 months in 2015. Hib deaths declined by 90% (78–96) from 2000 to 2015. Most children who died of Hib (76%) presented with pneumonia. India (15,600 deaths, 9,800–21,500), Nigeria (3,600 deaths, 2,200–5,100), China (3,400 deaths, 2,300–4,600), and South Sudan (1,000 deaths, 600–1,400) had the greatest number of Hib deaths in 2015. An estimated 340,000 episodes (196,000–669,000) of severe Hib occurred globally in children in 2015.[2]

Global estimates of burden of disease caused by Hib in children <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 (247,000–527,000) 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 1st 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. Among

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 highlight the burden of Hib disease in the prevaccine era 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 *Corynebacterium 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 PRP-T is 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 and 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 2nd 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 2nd year of life. A booster dose with diphtheria, tetanus, and whole-cell pertussis (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

Following the recommendations of the Hib and pneumococcal subcommittee of National Technical Advisory Group on Immunization (NTAGI) in India, in April 2008, Hib-CV as part of a pentavalent combination vaccine was introduced in a phased manner in 2011, in a three-dose schedule of 6–10–14 weeks, without any booster dose and subsequently escalated to the rest of the country. All the reported serious AEFIs were investigated by a special causality subcommittee formed by the National AEFI Committee, which concluded that these AEFIs were not causally related to pentavalent vaccine. IAP had conducted a scientific study among around 1,000 pediatricians and found that >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.[12]

According to a meta-analysis, in 2000, there were almost 883,000 (517,000–1,750,000) cases of severe Hib disease in India. Following the introduction of Hib in the UIP, the number of cases of severe Hib estimated in 2015 had reduced to 236,000 (138,000–468,000) cases, a significant reduction of over 75%. The estimated number of deaths has dropped from 82,600 (52,300–112,000) in the year 2000 to 15,600 (9,800–21,500) in the year 2015.

Following introduction of pentavalent vaccine in the UIP, significant reductions in the role of Hib as the causative pathogen in cases of meningitis have been reported.[13-15]

INDIVIDUAL USE

Indian Academy of Pediatrics Advisory Committee on Vaccines and Immunization Practices (ACVIP) recommends use of Hib vaccine for all children below the age of 5 years.

SCHEDULE AND DOSES

Monovalent Hib-CV is no longer available. Hib-CV is available in combination with DPT/HBV/IOPV as a quadrivalent or pentavalent or hexavalent combinations.

The vaccination schedule for Hib is as follows:

- *<6 months:* Three doses at an interval of at least 4 weeks and one booster at 16–18 months
- *6–12 months:* Two doses at an interval of 4 weeks and 1 booster at 16–18 months
- *12–15 months:* One dose and a booster at 16–18 months
- *>15 months:* One dose only.

Catch-up vaccination is not recommended for healthy children >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/Hepatitis B/inactivated poliomyelitis vaccine (IPV).

Haemophilus influenzae type B (Hib) conjugate vaccine.

Routine vaccination:

- *Minimum age:* 6 weeks
- Primary series includes 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 one 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

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3.6 PNEUMOCOCCAL VACCINES

Rajendra Khadke, Abhay Shah

INTRODUCTION

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 <5 years of age. Furthermore, *"the recent development of widespread microbial resistance to essential antibiotics underlines the urgent need for more efficient pneumococcal vaccines."*[1]

EPIDEMIOLOGY

Pathogen

Streptococcus pneumoniae is gram-positive, catalase-negative, facultatively anaerobic diplococci. The polysaccharide capsule surrounding the cell wall is responsible for virulence, type-specific identification, and stimulation of protective antibodies in the host.

Host

The causative agent, *S. pneumoniae*, frequently colonizes the nasopharynx and is transmitted mainly through respiratory droplets. Infants and young children are thought to be the main reservoir of this agent with the prevalence 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). Less common PDs include soft tissue infections, pyogenic arthritis, osteomyelitis, primary peritonitis and salpingitis, and endocarditis. Pneumococcal bacteremia in patients with compromised immune status causes a rapidly progressive, fulminant course marked by abrupt onset, progressive purpura, disseminated intravascular coagulation, and death in 24–48 hours. The spectrum resembles

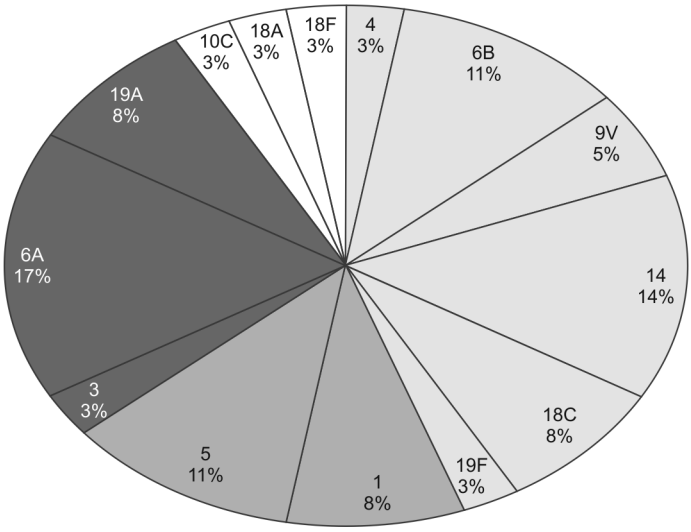

Fig. 1: Serotype distribution.[15]

Waterhouse–Frederickson syndrome.[2] Rare complications of pneumococcal infection include hemolytic–uremic syndrome and rhabdomyolysis.

A review of >70 studies has shown that out of >90 serogroups, only 10 serogroups are responsible for most pediatric infections **(Fig. 1 and Table 1)**.[3] After the introduction of pneumococcal conjugate vaccine (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]

Burden of Pneumococcal Diseases

Disease occurs in all age groups, with the highest rates of disease in children under 2 years of age and among the elderly. 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 <2 years. 90% of bacteremia, 30–50% of severe pneumonia, are caused by pneumococcus.[12,13] *Streptococcus pneumoniae* is the leading cause of pneumonia in children under 5 and it was responsible for 52% of all fatal pneumonia cases in children in 2016.[13]

TABLE 1: Characteristics of different serotypes.[5-11]

Serotypes	
1, 5, and 14	• 28–34% of IPD • 30% of IPD in 20 of the world's poorest countries • Serotype 14 is antibiotic resistant
3	• OM, pneumonia, especially complicated necrotizing pneumonia • Usually causes noninvasive disease
6A	• NP carriage, an important cause of IPD • Antibiotic resistant
6B	Antibiotic resistant
7F	Important in India, increased case fatality rates
19A	• Most prevalent in the US, in India (8–13%) • IPD, AOM, mastoiditis • Antibiotic resistant
19F and 23F	• Responsible for 9–18% cases globally • Antibiotic resistant

(AOM: acute otitis media; IPD: invasive pneumococcal disease; NP: nasopharyngeal carriage)

Global Burden

As per WHO (2018)[11] of the estimated 5.83 million deaths among children <5 years of age globally in 2015, 294,000 were estimated to be caused by pneumococcal infections. Pneumonia accounts for 14% of all deaths of children under 5 years old, killing 740,180 children in 2019.

Indian Scenario

Pneumococcal disease is also the number one vaccine-preventable cause of death in children under 5 years, globally and in India.[14] There is no robust data on the burden of milder pneumococcal illnesses, such as sinusitis and otitis media.

The burden of pneumococcal diseases: There is no nationally representative study of IPD incidence in the community. Most of the available data on PDs is from hospitals and on meningitis. According to a 2-year prospective study at three Bengaluru hospitals

in south India, the 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.[15]

Pneumonia burden: India accounts for 23% of global pneumonia burden and 36% of total WHO regional burden. 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.[16-18]

Meningitis burden: There is also a lack of community-based incidence of ABM in India. 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.[19] In a hospital-based sentinel surveillance for bacterial meningitis in <5 years children prior to the introduction of the PCV-13 in India, between March 2012, and September 2016 in eleven hospitals, *S. pneumoniae* accounted for 74.2%.[20]

Mortality Data

Global

World Health Organization estimates that pneumonia killed 740,180 children <5 years of age in 2019 out of estimated 5.3 million global annual deaths with PD being the major cause of pneumonia.

India

Pneumonia causes an estimated 408,000 deaths among under-5 contributing to 19% of child mortality in India. 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.[21] These results highlight the need to improve access to care and increase coverage and equity of pneumonia-preventing vaccines.

Drug Resistance

Antimicrobial-resistant serotypes in *S. pneumoniae* have been evolving with the 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 the increasing prevalence of multidrug resistance in pneumococci.[22] Penicillin-resistant isolates may be cephalosporin-resistant and commonly exhibit resistance to non-β-lactam antibiotics such as trimethoprim–sulfamethoxazole and macrolides.

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 (PPSV23) 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 a normal saline solution with either phenol or thiomersal as a preservative. It is stored at 2–8°C. Not more than two-lifetime doses are recommended, as repeated doses may cause immunologic hyporesponsiveness to subsequent doses.

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 IgG2 subclass. Though the total antibodies, as measured using the ELISA, 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.[23-25] 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.[26] One study in Uganda in HIV-infected adults showed an increased risk of pneumonia among those vaccinated with PPSV23.[26]

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 *Haemophilus influenzae* type B (Hib) vaccines.

Vaccines' Composition

The serotypes and conjugating proteins in PCVs available in India **(Table 2)**.

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 ≥0.35 μg/mL measured by the WHO reference assay (or an alternative)
- The serotype-specific IgG geometric concentration ratios.

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

TABLE 2: Serotype composition and conjugating proteins of PCVs.

	Serotypes												
PCV-13	4	6B	9V	14	18C	19F	23F	1	5	7F	3	6A	19A
Conjugating protein	CRM^{197}												
PCV-10 GSK	4	6B	9V	14	18C	19F	23F	1	5	7F	XX	XX	XX
Conjugating protein/s	Protein D (NTHi)				TT	DT	Protein D (NTHi)						
PCV-10v SII	X	6B	9V	14	XX	19F	23F	1	5	7F	XX	6A	19A
Conjugating protein	CRM^{197}												

(CRM: cross-reactive material; PCV: pneumococcal conjugate vaccine)

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

- *Invasive pneumococcal disease:* IPD was the primary outcome for the pivotal clinical trials of PCV. While the trials used different formulations of the vaccine administered in infants in either a 6-, 10-, and 14-week schedule or a 2-, 4-, and 6-month 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).[27]
- *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. Given the diversity in vaccine formulations and vaccination schedules used and in the populations in which the vaccines were tested, the results were remarkably consistent. Based on the studies of PCV-7, PCV-9, and PCV-11, according to Cochrane systemic review, the pooled estimate of vaccine efficacy against radiologically defined pneumonia was found to be 27% (95% CI: 15–36%, $p < 0.0001$).[27-31] The impact of PCV was observed in both WHO defined radiological pneumonias and the pneumonias which do not satisfy the criteria for this definition.[31]
- *Otitis media:* Two Cochrane database of systematic reviews (CDSR), done in 2019 and revised in 2020, examined the effect of PCVs on AOM.[32,33] These studies did not include any data on PCV-13.

For PCV-7 administered in early infancy, a relative risk reduction (RRR) of –5% (95% CI: –25–12%) in high-risk infants and 6% (95% CI: 4–9) in low-risk infants, on all-cause AOM was seen. A RRR of 20%

(95% CI: 7–31%) in pneumococcal AOM and 9% (95% CI: –12–27%) to 10% (95% CI: 7–13%) reduction in recurrent AOM was also seen.

For PCV-10 (GSK), the RRR on all-cause AOM varied from 6% (95% CI: –6–17%) to 15% (95% CI: –1–28%) in healthy infants and 53% (95% CI: 16–74%) RRR in pneumococcal AOM was seen.

No beneficial effect was seen on all-cause AOM, with PCV-7, in children aged 1–7 years with a history of respiratory illness or frequent AOM.

A systematic review of the efficacy, effectiveness, and impact of high-valency pneumococcal conjugate vaccines on otitis media was published recently.[34]

In children aged <2 years, impact studies reported reductions of all-cause OM (primary care, outpatient, ambulatory, emergency department visits) between 47–51% for PCV-13 and 34–43% for PHiD-CV compared to periods before PCV introduction. These studies were not conducted in comparable settings and the results cannot be directly compared.

The RRR of PCV-13 and PHiD-CV on complex, complicated, recurrent, and hospitalized otitis media (OM) varied from 9 to 62%, with the highest impact seen in those <1 year. Greater RRR was seen for hospitalized OM/complicated OM.

Only four studies allow some degree of direct comparison between PCV-13 and PHiD-CV. These studies suggest PHiD-CV may offer better protection against some OM outcomes than PCV-13, but present data is inconclusive.

It is very difficult to establish the microbial diagnosis in AOM as it is not ethical and feasible to do a middle ear tap for middle ear fluid culture specimens. *In a* Finish study, the PCVs (PCV-7 and PCV-10 GSK) 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.[35,36] However, the PCV-7-CRM[197] was observed to protect against recurrent or more severe forms of AOM, including otitis requiring tympanostomy tube placement.[37-39] 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.[40] In this trial, significant protection was also observed against AOM caused by NTHi with observed efficacy of 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.[40] 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. A prospective study on AOM using PCV-13 in Israel showed a decrease in AOM significantly from 12.2 per 1,000 to 6 per 1,000 children and that caused by NTHi from 5.7 to 3.8 per 1,000 children.

Vaccine Effectiveness

Many countries in which PCVs were introduced as part of routine immunization have shown a 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 a reduction in nasopharyngeal carriage and transmission of the organism.[40-42] 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.[43-46] After the introduction of PCV-13 in the US, there was 90% decline in the 6 serotypes driven predominantly by 19A and 7F.[45] Following the introduction of PCV-13 into the national immunization programs of Australia,[46,47] Uruguay,[48] and United Kingdom,[49] reductions in hospitalized chest X-ray-confirmed pneumonia and empyema cases were noted. Similarly, following PCV-13 introduction in Nicaragua—a low-to-middle income country,[50] a reduction in hospitalization and outpatient visits for pneumonia was found in children 1 year of age. Finland introduced PCV-10 in its national immunization program in 2010. The vaccine efficacy was found to be 98% against vaccine serotypes.[51]

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.[35]

Effectiveness of Incomplete Series

Significant effectiveness against vaccine-type IPD in children <5 years was reported for PCV-13 in 3+1 (86–96%) and 2+1 schedule (67.2–86%) and for PCV-10 for 3+1 (72.8–100%) and 2+1 schedule (92–97%). In pivotal clinical trials, the effectiveness of one dose of PCV-13 was estimated at 48%, two doses 87%, and 2+1 doses at 100%. One dose catch-up for toddlers showed 83% effectiveness.[36]

Safety

The safety of PCV has been well studied and all formulations are considered to have an excellent safety profile in various studies.[37,38] The main adverse events (AEs) observed are injection-site reactions, fever, irritability, decreased appetite, and increased, and/or decreased sleep which were reported in 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]

Pneumosil™

Serum Institute of India has now introduced a new 10vPCV marked at Pneumosil in India. This 10-valent PCV is focusing on the serotypes prevalent in 70.4% of the affected population [Asia, Africa, LAC (Latin America and the Caribbean), and India].

New 10vPCV (SIIPL-PCV) Clinical Data

Pneumosil (10-valent) has been extensively evaluated in five randomized controlled trials (RCTs) and has demonstrated comparable safety and immunogenicity against licensed

pneumococcal vaccines across diverse populations of India and Africa when administered to adults, toddlers, and infants using different vaccination schedules.

In the phase 1/2 study done in the Gambia, in infants, seroprotection rates (SPRs) of >90% were observed for all serotypes with PCV-13 following the primary immunization, whereas SPR of >90% was observed for all serotypes except serotypes 6A and 6B, following SIIPL-PCV. Serotype-specific IgG geometric mean concentrations (GMCs) estimates after the primary series were above 1 mg/mL for all serotypes following both vaccines. The IgG GMC was higher following PCV-13 for seven (6A, 6B, 7F, 9V, 19A, 19F, and 23F) of the 10 serotypes.[39]

The serotype-specific OPA GMTs following the primary series were comparable for the two vaccines for six (1, 5, 6B, 14, 19F, and 23F) of 10 serotypes, the responses were higher with PCV-13 for the four remaining serotypes.

A substantial booster response was observed for all serotypes following PCV-13 and for all serotypes except serotype 5 following SIIPL-PCV.

The magnitude of the booster response was greater for five serotypes (1, 6B, 9V, 19A, and 23F) following SIIPL-PCV and for serotype 5 following PCV-13.

The persistence of antibodies was seen for all serotypes till 1 year of follow-up.

The serotype-specific OPA GMTs following the primary series were comparable for the two vaccines for six (1, 5, 6B, 14, 19F, and 23F) of 10 serotypes, while the responses were lower following SIIPL-PCVTM for the remaining 4 serotypes.[52] A significant booster response (except for type 5) was noted with both vaccines in children primed at 6–10–14 weeks with the SIIPL-PCV and the comparator vaccines. The magnitude of the booster response was higher for 1, 6B, 9V, 19A, and 23F with SIIPL-PCVTM, while it was higher for 5, 19A, and 19F with PCV-13. The OPA GMTs following the booster vaccination in toddlers were generally comparable with both vaccines. In comparison with Synflorix, both vaccines elicited a significant booster immune response for all 10 serotypes except serotype 5, while the OPA GMTs showed a booster response for all

10 serotypes. The persistence of antibodies was seen for all serotypes till 1 year of follow-up.

A phase-3, randomized, double-blind study of the safety, tolerability, lot-to-lot consistency, immunogenicity, and non-interference with concomitant vaccinations of Serum Institute of Pneumosil, was done in healthy infants (6–8 weeks of age) in The Gambia, who received three doses of either Pneumosil (three groups receiving vaccine from different lots) or Synflorix (one group) at 6, 10, and 14 weeks of age.[53]

Among the shared serotypes, the GMCs for serotypes 1, 5, 7F, 14, and 23F were higher after SIIPL-PCV than after PHiD-CV, while the seroresponse for serotype 19F was higher after PHiD-CV. The immune response to SIIPL-PCV compared with PHiD-CV was confirmed. The seroresponse rates and GMCs to serotypes 6A and 19A in SIIPL-PCV were superior to the cross-reactive responses to serotypes 6B and 19F generated by PHiD-CV.

Compared with after PHiD-CV, OPA GMTs after SIIPL-PCV were higher for serotypes 1, 5, 6B, and 23F and lower for serotypes 9V and 19F.

In both groups, a significant booster response was demonstrated for all serotypes except serotype 5 on the basis of IgG GMC ratios, and for all serotypes, on the basis of OPA GMT ratios.

Post-booster IgG GMCs were higher in the SIIPL-PCV group for serotypes 1, 5, 6B, 7F, 14, and 23F and were higher in the PHiD-CV group for serotypes 9V and 19F. The OPA GMTs were higher in the SIIPL-PCV group than in the PHiD-CV group for serotypes 1, 6B, 7F, 14, and 23F.

Safety and Side Effects

All injection-site AEs were mild (grade 1) to moderate (grade 2). fever was the most frequent and was observed in more than half of the participants. Altogether, five (0·7%) of 751 participants had any grade 3 systemic reaction. The rates of local and systemic reactions were lower after the booster.

The Drugs Controller General of India (DCGI) has approved it for active immunization against invasive disease and pneumonia caused by *S. pneumoniae* serotypes 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, and 23F

in infants from 6 weeks of the age group for three-dose regimen (dosing schedule: 6, 10, and 14 weeks).[54] The WHO has approved it for active immunization against invasive disease, pneumonia, and acute otitis media caused by *S. pneumoniae* serotypes 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, and 23F, till the age of 2 years.[55]

Serotype Replacement

Early observations, which showed that though PCV reduced nasopharyngeal carriage with vaccine serotypes, a carriage with nonvaccine serotypes increased, led to concerns about replacement disease due to serotypes not contained in the vaccines. 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

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 **(Fig. 2)**. The vetted average difference is >11%.[52]

In the new 10vPCV from SII, there is no serotype 3 unlike PCV-13, and it does not have serotypes 4 and 18C which are there in previous PCVs. New 10vPCV also contains 6A and 19A serotypes like PCV-13. This amounts to nearly 74% of Indian serotypes coverage presently prevailing in India.

IAP/ACVIP RECOMMENDATIONS[56]

Pneumococcal Conjugate Vaccines

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. New 10vPCV (SII) is licensed for active immunization for the prevention of PDs caused by the respective vaccine serotypes in children from

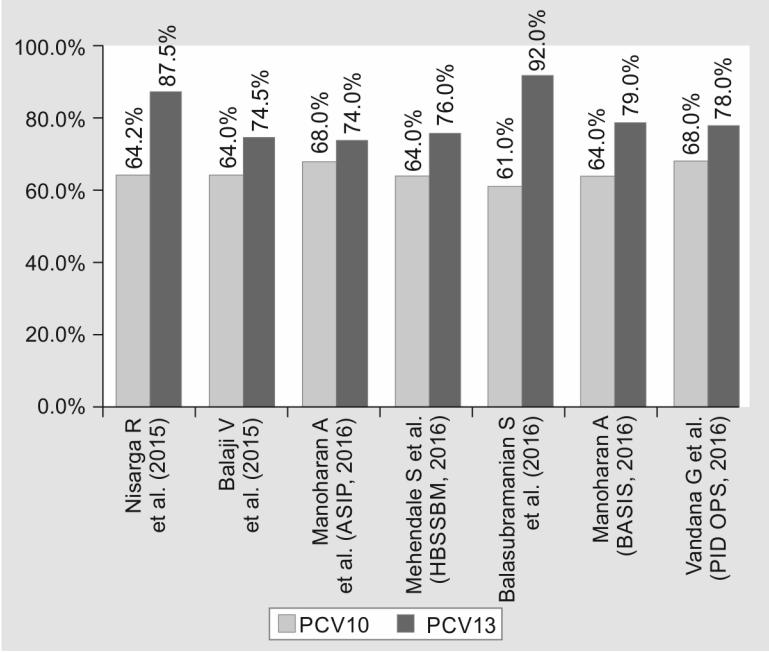

Fig. 2: Serotype coverage difference between PCV-10 and PCV-13 in different studies.[15,52,55] (PCV: pneumococcal conjugate vaccine)

6 weeks to 2 years of age only and not beyond. In addition, PCV-13 is also licensed for the prevention of PD in healthy immunocompetent children beyond 6 years and adults of all ages. PCV-13 has been licensed by the DCGI for the age group of 6–17 years. However, the disease burden in this age group is questionable and Advisory Committee on Vaccines and Immunization Practices (ACVIP) does not recommend it for this population **(Table 3)**.

Interchangeability: When primary immunization is initiated with one of these vaccines, the remaining doses should be administered with the same product. However, if it is not possible to complete the series with the same type of vaccine, the other PCV product should be used.

The PCV-13 is administered intramuscularly as a 0.5 mL dose and is available in latex-free, single-dose, and prefilled syringes. PCV-13 can be administered at the same time as other routine childhood

TABLE 3: Schedule for PCVs.

Age at first dose	*Primary series PCV-13*	*Primary series PCV-10*	*Primary series 10vPCV-10*	*Booster dose All PCVs*
6 weeks to 6 months	3 doses	3 doses	3 doses	One dose* 12–15 months
7–11 months	2 doses*	2 doses*	2 doses*	One dose* during 2nd year
12–23 months	2 doses†	2 doses†	2 doses†	Not applicable
24–59 months	1 dose	2 doses†		Not applicable

*At least 6 months after the third dose.
†At least 8 weeks apart.
Notes:
- Routine use of PCV-10/13 is not recommended for healthy children aged >5 years.
- Minimum age for administering the 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).
- The DCGI has approved 10vPCV-10 SII for active immunization in infants from 6 weeks of the age group for three-dose regimen (dosing schedule: 6, 10, and 14 weeks). The WHO has approved it for active immunization, till the age of 2 years. ACVIP endorses WHO recommendation of its use till the age of 2 years.

(PCV: pneumococcal conjugate vaccine)

vaccinations if administered in a separate syringe at a separate injection site. Concurrent administration of PCV-13 and PPV-23 is not recommended.

B. High-risk group of children ***(Table 4)***

Immunocompetent children (high risk):

- 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 leaks
- Cochlear implant.

TABLE 4: Recommendations for pneumococcal immunization with PCV13 and/or PPSV23 vaccine for children at high risk or presumed high risk of pneumococcal disease.[57]

Age	*Previous dose of any pneumococcal vaccine*	*Recommendations*
<23 months	Nil	Age-appropriate recommendations
24–71 months	4 doses of PCV-13	• Dose 1 of PPSV23 at least 8 weeks after last dose of PCV13 • Dose 2 of PPSV23, 5 years after dose 1
24–71 months	3 previous doses of PCV13 before 24 months of age	• Dose 1 of PPSV23 at least 8 weeks after last dose of PCV13 • Dose 2 of PPSV23, 5 years after dose 1
24–71 months	<3 doses of PCV 13	• 2 doses of PCV13 at least 8 weeks apart • Dose 1 of PPSV23 at least 8 weeks after last dose of PCV13 • Dose 2 of PPSV23, 5 years after dose 1
24–71 months	1 dose of PPSV23	• 2 doses of PCV13 at least 8 weeks apart and 8 weeks after last dose of PPSV23 • 1 dose PPSV23, 5 years after dose 1 and 8 weeks after PCV13
6–18 years with medical conditions	Nil	• 1 dose of PCV13 • Dose 1 of PPSV23, 8 weeks later • Dose 2 of PPSV23, 5 years after dose 1
	1 dose of PCV13	• 1 dose PPSV23 • 2nd dose PPSV23, 5 years later
	>1 dose of PPSV23	• 1 dose PCV13, >8 weeks later • 1 dose PPSV23, 5 years later

- A second dose of PPSV23, 5 years after the first dose is recommended only for children who have functional or anatomic asplenia, HIV infection, or other immunocompromising conditions.
- All other children with underlying medical conditions should receive one dose of PPSV23.
- No more than two doses of PPSV23 are recommended.

(HIV: human immunodeficiency virus; PCV: pneumococcal conjugate vaccine; PPSV: pneumococcal polysaccharide vaccine)

Children with functional or anatomic asplenia (very high risk):

- Sickle cell disease and other hemoglobinopathies
- Chronic or acquired asplenia
- Splenic dysfunction.

Children with immunocompromising conditions (very high risk):

- 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 immunodeficiency [includes B- (humoral) or T-lymphocyte deficiency; complement deficiencies, particularly C1, C2, C3, and C4 deficiency; and phagocytic disorders (excluding chronic granulomatous disease)].

When elective splenectomy, immunocompromising 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.

- Prematurity (PT) and very low birth weight (VLBW) are considered 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]

Pneumococcal polysaccharide vaccine (PPSV23):

- *Minimum age:* 2 years
- 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 high-risk medical conditions
- 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 the prevention of PDs amongst high-risk individuals.*

Direct versus cross-protection by PCVs: 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.[58]

PUBLIC HEALTH PERSPECTIVES

As of March 2021, a total of 148 countries have introduced PCV into their national immunization program (NIP), which includes 60 Gavi-eligible countries. 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).[59]

On May 13th, 2017, PCV-13 was launched by the Union Health Ministry of India under the Universal Immunization Programme (UIP) and introduced in a phased manner and by November 2021, was rolled out in the entire country. The schedule consists of two primary doses at weeks 6 and 14, followed with a booster dose at 9 months.[60] Presently, the SII-PCV-10 is being used in the UIP.

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 >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 a high risk of disease, e.g., those with asplenia, should also be targeted for vaccination.[61]

RECENT UPDATES IN PNEUMOCOCCAL VACCINES (TABLE 5)

BE 14v-PCV

On August 29, 2022, the Subject Expert Committee (SEC) of the Central Drugs Standard Control Organization (CDSCO) has recommended the grant of permission to Biological E Limited to manufacture the 14-valent investigational vaccine against *S. pneumoniae* infection.[62]

The BE's PCV14 contains 14 serotypes, 12 of them the same as in Prevnar. In addition, it contains serotypes 22F and 33F:

Each dose of 0.5 mL contains:[63]

- Pneumococcal polysaccharide serotype 1.....3.0 μg
- Pneumococcal polysaccharide serotypes 3, 4, 5, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F .....2.2 μg
- Pneumococcal polysaccharide serotype 6B.....4.4 μg
- Adsorbed onto aluminum phosphate, as Al+++.....≤0.75 mg
- Polysaccharide conjugated to.....20–50 μg of CRM[197]
- *Other ingredients:* Polysorbate 20, succinic acid.

The single-dose vial is preservative free, while the multidose vial has 2-phenoxyethanol as a preservative.

In phase-3 studies, BE 14v-PCV demonstrated noninferiority to PCV-13 for the 12 common serotypes (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) and noninferiority of 22F and 33F against the lowest performing serotype 3, in PCV-13. Noninferiority was demonstrated for OPA titers. The safety comparison shows that BE-PCV-14 vaccine was well tolerated and found to be safe in comparison with Prevenar 13 vaccine.

PCV-15: Vaxneuvance™ is indicated for active immunization for the prevention of invasive disease caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F in individuals 6 weeks of age and older. The schedule is the same as PCV-13. It is not marketed in India.[64,65]

TABLE 5: Serotype composition of newly introduced PCVs compared to existing PCVs.

PCV-10 GSK	1		4	5	6A	6B	7F	9V	14	18C		19F	23F
PCV-10 SII	1			5	6A	6B	7F	9V	14		19A	19F	23F
PCV-13	1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
PCV 14 (BE)	1	3	4	5		6B	7F	9V	14	18C	19A	19F	23F
												22F	33F
PCV-15 (MSD)	1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
												22F	33F
PCV-20 (Pfizer)	1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
							22F	33F	8	10A	11A	12F	15B/C

(PCV: pneumococcal conjugate vaccine)

20-Valent Pneumococcal Vaccine (20vPnC-Prevenar 20)[66]

PCV-20: Prevnar 20 is a vaccine indicated for active immunization for the prevention of pneumonia and invasive disease caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F in adults 18 years of age and older. For >19 years, it is indicated for those with certain chronic conditions. It is preferred as a single 0.5 mL dose for those >65 years of age.

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3.7 ROTAVIRUS VACCINES

Shashi Kant Dhir, Srinivas G Kasi

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]

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% of deaths 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 128,000 (range: 104,500–155,600) in 2016.[4] 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.[5]

ROTAVIRUS MORBIDITY, MORTALITY, AND BURDEN IN INDIA

National estimates of rotavirus attributable deaths among children under 5 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 rotavirus deaths under age of 5 years in 2013. Indian Academy of Pediatrics (IAP) carried out

a systematic review of burden of rotavirus diarrhea in under-5 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.[6]

It is difficult to estimate the impact of rotavirus diarrhea on under-5 mortality in India. In the Million Death Study, 3,053 (13.2%) of 23,152 deaths among children <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.[7] The prevalence of rotaviral diarrhea among Indian children aged <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).[8] 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% 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 of 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.[9]

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.[10]

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%).[11]

PATHOGEN

Rotavirus is an icosahedral ribonucleic acid virus and seven serogroups have been described (A–G); Group A rotaviruses cause most of the illness in humans. 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 carried out by IAP, a total of 51 studies could be identified which dealt with serotyping of rotavirus.[6] Overall, G1 was the most common serotype isolated in Indian studies (32%), followed by G2 (24%), and G-untypeable (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-untypeable 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 untypeable strains.[11]

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.[12] 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 ($p = 0.05$).[13] 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.[14] With G1P[8], the most common viral strain, there was no evidence of homotypic protection.[14]

Vaccines

Currently, four live oral vaccines are licensed and marketed in India.

Human Monovalent Live Vaccine (RV1)

Rotarix™ is a monovalent live rotavirus vaccine, which contains a 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 10^6 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 dextran. The vaccine does not contain preservatives. 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)

RotaTeq™ is a human bovine reassortant pentavalent 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)

Rotavac™: 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, New Delhi. Follow-up of these infants indicated

that they were protected against severe rotavirus diarrhea for up to 2 years.[15] This strain was sent for vaccine development to the National Institute of Health (NIH) by Department of Biotechnology 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 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 Rotovac™ at a 0.5-mL dose volume without buffering agent was shown to be well-tolerated and immunogenic.[16]

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. Rotavac 5D, can be stored at 5°C ± 3°C till the expiry of the shelf life.

The same vaccine is also marketed by Abbott as Rotasure.

Bovine Rotavirus Pentavalent Vaccine

RotasiilTM is a pentavalent rotavirus vaccine (BRV-PV) developed from five Bovine (UK) and 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.[17]

The vaccine is supplied in a liquid, ready to use formulation, with each dose of 2.0 mL containing NLT $10^{5.6}$ FFU per serotype. ~~A liquid, ready to use formulation, is also marketed~~.

The liquid formulation is not heat-stable and needs to be stored at 5°C ± 3°C till the expiry of the shelf life.[14]

The product insert states that the 3-dose regimen, of this vaccine, can be completed by 1 year of age.

The comparative analysis of different rotavirus vaccines are given in **Table 1**.

TABLE 1: Comparative analysis of rotavirus vaccines.

	Rotavac	*Rotasiil*	*RotaTeq*	*Rotarix*
Composition	Monovalent: 116E (G9P11)	Pentavalent G1, G2, G3, G4, G9: Human P: UK bovine	• G1, G2, G3, G4: Human, P7: Bovine • G6: Bovine, P1A[8]: Human	Monovalent: G1P8
Efficacy against S-RVGE	India: 53.6%	India: 39.5%	• USA and Finland: 98% • Africa: 39.3%	• Finland: 85% • Asia: 48.3%
Efficacy against VS-RVGE	54.4%	60.5%		
Presentation	Liquid	Liquid	Liquid	Freezed dried
Volume	0.5 mL	2.0 mL	2.0 mL	1 mL
Storage	• Rotavac: – –20°C till expiry (5 years) – +2° to +8°C till expiry of VVM2 (6 m) • Rotavac 5D: – +2° to +8°C for 3 years	Liquid: +2° to +8°C till expiry date	+2° to +8°C for 24 months	+2° to +8°C for 26 months

(RVGE: rotavirus gastroenteritis; S: severe; VS: very severe)

Rotavirus Vaccines' Efficacy and Effectiveness

Although the composition of RV1 and RV5 is different, their efficacy mechanism of action is largely 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. The study showed that a rotavirus vaccine significantly reduces the episodes of SRVGE in African children during the 1st 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 anti-rotavirus neutralizing antibodies in breast milk, and interference by maternal antibody or by coadministration of the oral poliovirus vaccine, which may reduce rotavirus antibody levels.[18]

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.

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 2nd 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 2nd year.[19,20]

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

In the Indian study conducted across six centres, 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 = 3,751) at 6, 10, and 14 weeks of age along with routine vaccines.

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 intention to treat analysis over the entire follow-up period (until children reached 2 years of age). Vaccine efficacy against the very severe rotavirus cases (V-SRVGE, 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-up 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).[21]

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).[22]

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 (LMCs) and a lower VE in high-mortality countries (HMCs) for both RV1 and RV5.[23] VE tended to decline in the 2nd 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.[24] 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. The introduction of rotavirus vaccine has been shown to decrease the rotavirus prevalence by 40% as shown by the data from 69 countries participating in the Global rotavirus surveillance network. The mean proportion of hospitalization also decreased from 38 to 23% in the

postvaccination epoch.[25] Thus, introduction of the vaccine into countries is likely to have a greater effect than that predicted on the basis of the efficacy trials.

STUDIES IN INDIA

It was reported in a meta regression analysis of RCT's that in low- and medium-mortality settings, the pooled efficacy estimates against severe RVGE were high at the 2-week time point (82–98%) and provided durable protection at 12 months (77–94%) whereas, in high-mortality settings, the pooled efficacy was lower at 2 weeks (66%) and waned more rapidly to 44% by 12 months.[26]

There is no efficacy study of RV1 and RV5 conducted in India. 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 clinically significant reduction in immunogenicity against rotavirus.

Efficacy data of the Indian vaccines has been discussed above.

A multi-centric surveillance project for rotavirus VE assessment is being carried out in 32 participating sites in nine states of India over a period of 4 years. VE will be determined by a case–control evaluation.[27]

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] Although, a meta-analysis of intussusception risk following real world Rotavirus vaccination in Australia, Brazil, England, Mexico, Singapore and USA, found an increased risk of intussusception in the first 21 days following the first dose of Rotarix or Rotateq, the recent Cochrane Database of Systematic Reviews did not find any increased risk of serious adverse events (moderate- to high-certainty evidence) including intussusception.

Since the phase 3 study of Rotavac was not powered to assess the risk of intussusception. A passive surveillance for intussusception was set up in 35 sentinel health facilities covering 26.3 million populations in three states. This was a self-controlled case-series method. Intussusception was diagnosed using Brighton criteria. 151 intussusception cases were included in the analysis. The relative incidence (incidence during the risk period compared to the control period) 1–21 days after doses 1 and 2 combined was 1.56 (95% CI: 0.0–5.28) and that for three doses combined was 1.88 (95% CI: 0.76–4.30) and the attributable risk after doses 1 and 2 combined was 0.11 (95% CI: 0.0–0.25) and that for three doses combined was 0.42 (95% CI: 0.0–0.70) per 100,000 doses.

Thus, no increased risk of intussusception within 21 days of receipt of the first two doses combined or all three doses combined of Rotavac was detected.[27]

Rotasiil™: In the Indian study, adverse effects profile was similar in both groups. 13 cases of intussusception were diagnosed; six occurred in the BRV-PV arm and seven in the placebo arm. None occurred within 28 days of receiving a dose of BRV-PV or placebo.[21]

So far, no data is available about the intussusception risk after its introduction in the national immunization program (NIP).

Although the Global Advisory Committee on Vaccine Safety (GACVS) in a report in 2017 concluded that there is a definite, albeit a very small risk of acute following the use of the current rotavirus vaccines, the recent Cochrane Database of Systematic Reviews did not find any increased risk of serious adverse events (moderate- to high-certainty evidence) including intussusception.[24,28]

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 NIP 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.

The vaccine has been rolled out in the NIP, all over the India.

Initially, WHO recommended lower 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 one death caused by the vaccine).[29] WHO recommends administering rotavirus vaccine to children up

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

Schedule in Universal Immunization Programme (UIP):[30] 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.

The risk of severe RV infection, with increased hospitalization rates, increased intestinal dilatation, abdominal distension, and mucoid stools are pronounced in preterm infants. Data exists about the safety and efficacy of rotavirus vaccines in preterm infants. Hence, rotavirus vaccines should be considered for these infants, if they are clinically stable and at least 6 weeks of age.

Following the rollout of rotavirus vaccines in low- and middle-income country (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: –2–84%; $p = 0.056$), 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: –34–86%), 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 RVGE events 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.[31] 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.[32] It is ideal if immunization schedule is completed early in developing countries where natural infection might occur early.[2]

Early administration of the first dose of rotavirus vaccine as soon as possible after 6 weeks of age has been recommended by WHO recently. 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.

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 the vaccines should be completed within 8 months (32 weeks) of age. Programmatic errors have been reported with use of this vaccine including parenteral administration. ACVIP recommends to follow the manufacturers recommendation. The vaccines should not be frozen. Large vaccine volume requires full insertion of vial tip into infant's mouth. Contact with infant's mouth contaminates the vial and has always complicated the 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. Recent studies have shown the feasibility of interchangeability between Rotateq and Rotarix and between Rotavac and Rotasil.[33,34]

Delayed Doses

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

Contraindications:

- 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 intussusception in the past
- Severe (anaphylactic) allergy to latex should not receive RV1 vaccine. The RV5 dosing tube is latex-free.
- Severe combined immunodeficiency (SCID)

Precautions:

- 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.

IAP/ACVIP RECOMMENDATIONS

The first dose of all oral rotavirus vaccines should be administered before 14 completed weeks.

The last dose should be completed before 32 completed weeks.

Interval between doses should be at least 4 weeks.

Except RV1, which is to be administered in a two-dose schedule, the other vaccines are to be administered in a three-dose schedule.

Universal Immunization Programme Schedule

The first dose is to be administered at 6 weeks, with the 1st dose of the Pentavalent vaccine, anytime up to 1 year of age.

Second and third doses are to be administered at an interval of 4 weeks.

If the first dose is administered around 1 year of age, the second and third doses can be administered in the 2nd year.

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 RV1 are recommended at present with the first dose administered at 6 weeks of age and the second dose administered 4 weeks later.
- Other RV vaccines should be employed in a three-dose 6-, 10-, and 14-week schedule.
- Interchange between vaccine brands should be avoided. If unavoidable or if vaccine product is unknown for any dose in the series, a total of three 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.

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3.8 MEASLES, MUMPS, AND RUBELLA VACCINES

B Rajsekhar, Sanjay Verma

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]

Measles

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 and among the unvaccinated remain an important source of infection. While India has made significant progress in child survival, it continues to have the second-largest number of children not vaccinated against measles. Since 2001, the Measles Initiative has supported 80 countries to deliver >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 reduce 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). Indian health ministry launched a single dose measles–rubella (MR) vaccination campaign in a phased manner in January 2017 to immunize 410 million children in the age group of 9 months to 15 years, all over the country.[3] The MR campaign led to a significant reduction in measles cases in India, from 83,026 in 2015 to 10,695 in 2017.[4] India still contributes to the fourth-largest measles caseload. Studies have suggested that 47% of global measles-associated deaths were reported from India alone.[5]

Mumps

In India, there is very limited data on the burden of mumps. Mumps outbreaks have been reported from various states, at an interval of every 5–10 years.[6]

Data on the seroprevalence of mumps in India is also limited.

In a study done on 321 serum samples to detect mumps-specific antibodies in children <5 years, seropositivity for mumps was 53.3% in children aged <9 months, 20.3% in 9–12 months, and 40% in 2 years old. Mean antibody levels for mumps were low between 9 months and 2 years with a slight rise by 5 years.[7]

In a study done on Health Sciences students from Manipal University, 32% of them were susceptible to mumps.[8] Among the measles, mumps, and rubella (MMR)-vaccinated group, 34.7% were susceptible to mumps. Generally, data suggests that seropositivity for mumps among Indian population is low, and large group of the population remains susceptible.

The 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. Mumps in a pregnant woman can also give rise to fetal damage in the form of aqueductal stenosis leading to congenital hydrocephalus.[9]

Rubella

Rubella per se is a mild exanthematous illness, but if acquired in the first trimester of pregnancy, it 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, >80% coverage is achieved. Indiscriminate use of rubella vaccine (monovalent or as a constituent of MR/MMR) in young children through public health measures 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 a 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. The incidence of CRS increases when a significant proportion of women in the reproductive age group are susceptible. Susceptibility to rubella has been found to be high among adolescent girls in India. Studies conducted in Amritsar, Maharashtra, and Jammu report rubella susceptibility being 36%, 23.6%, and 32.7% in prepubertal girls, adolescent females, and girls of 11–18 years, respectively.[10-12] Although the trend is changing, as shown by a recent serosurvey conducted by Indian Council of Medical Research (ICMR) among pregnant women attending antenatal clinics in various hospitals in India, in which, 15.2% of them were seronegative for Rubella.[13] A systematic review done in India showed that 10–30% of adolescent females and 12–30% of women in the reproductive age-group are susceptible to rubella infection in India.[14]

Congenital Rubella Syndrome

Comprehensive evidence about the actual burden of CRS in India is not available.[14] 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%).[15] Other developing countries have incidence rates of 0.6–4.1 per 1,000 livebirths.[16] A sentinel surveillance done in India between 2016 and 2018, to study the epidemiology of CRS, had 645 suspected CRS patients enrolled during 2 years, of which 137 (21.2%) were classified as laboratory confirmed CRS and 8 (1.2%) as congenital rubella infection.[17] A systematic review done in India showed that 1–15% of all infants suspected to have intrauterine infection were found to have laboratory evidence of CRS.[14] About 3–10% of suspected CRS cases are ultimately proven to have confirmed CRS with the aid of laboratory tests. CRS accounts for 10–15% of pediatric cataract. About 10–50% of children with congenital anomalies have laboratory evidence of CRS. Thus, there is a significant burden of CRS in India.[14]

M/MR/R VACCINES

Globally, most developed countries use MMR vaccines. For reasons mentioned earlier, Advisory Committee on Vaccines and Immunization Practices (ACVIP) feels that the combined MMR vaccine is a better option than an MR vaccine. The burden of mumps has been reduced in developed countries following use of MMR vaccines. Like rubella, poor coverage of mumps vaccine, in early childhood, can shift epidemiology to the right and increase infection rates in adolescents and adults with greater complications.

Formulations from different manufacturers have different strains of the vaccine virus. Mumps vaccine virus strains include Leningrad–Zagreb, Leningrad-3, Jeryl Lynn, RIT 4385, Hoshini or Urabe AM9 strains and are grown in chick embryo/HDC cultures. In India, three brands of MMR vaccines are available—Tresivac (SII), Priorix (GSK), and ZyVac MMR (Zydus).

Tresivac contains live-attenuated strains of Edmonston–Zagreb measles virus propagated on human diploid cell culture, L-Zagreb mumps virus propagated on chick embryo fibroblast cells, and Wistar RA 27/3 rubella virus propagated on human diploid cell culture. The vaccine is freeze-dried and is provided with diluent. Each dose of the reconstituted vaccine contains not <1,000 cell culture infective doses ($CCID_{50}$) of Measles virus, 5000 $CCID_{50}$ of Mumps virus, and 1000 $CCID_{50}$ of rubella virus. This vaccine does not contain preservatives.[18]

Storage:

- Store between +2 and +8°C and protected from light
- The diluent should not be frozen, but should be kept cool
- The reconstituted vaccine must be kept between +2 and +8°C, away from sunlight and must be discarded 4 hours after reconstitution.

Priorix contains the Schwarz strain of live-attenuated measles virus, the RIT 4385 strain of live-attenuated mumps virus (derived from the Jeryl Lynn strain), both propagated in chick-embryo fibroblasts from embryonated eggs of specific pathogen-free flocks and the Wistar RA 27/3 strain of live-attenuated rubella virus propagated in MRC-5 human diploid cells.[19]

After reconstitution, each dose (0.5 mL) contains:

- Live attenuated measles virus (Schwarz strain) not less than 103 $CCID_{50}$
- Live attenuated mumps virus (RIT 4385 strain), derived from Jeryl Lynn strain), not less than 103.7 $CCID_{50}$
- Live attenuated rubella virus (Wistar RA 27/3 strain), not less than 103 $CCID_{50}$.

ZyVac MMR

Each 0.5 dose contains live-attenuated measles virus (Edmonston–Zagreb strain) NLT 1000 CCID (propagated on human diploid cells), live-attenuated mumps virus (Hoshino strain) NLT 5000 CCIDs (propagated on chick fibroblast cells), and live-attenuated rubella virus (RA27/13 strain) NLT 1000 CCIDs (propagated on human diploid cells).

Storage:

- Store at 2–8°C before and after reconstitution
- Keep in carton to protect from light
- The diluent should not be frozen
- Single dose vials should be used immediately after reconstitution
- The multidose vials should be used within 6 hours after reconstitution.

MR Vaccine

It is a freeze-dried vaccine, available as single-dose and multidose vials, and is to be administered subcutaneously, over the upper arm/anterolateral thigh. Each single dose of 0.5 mL, when reconstituted contains not less than 1,000 median $CCID_{50}$ of live measles virus particles and 1,000 $CCID_{50}$ of rubella virus.[20]

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 any preservative. Bacterial contamination with *Staphylococci*, which secrete several exotoxins, can cause severe shock in recipients.[21] Toxic shock syndrome (TSS) can be prevented by adhering to injection safety, and if reconstituted, the multidose MR vaccine should be used within 4–6 hours. Unused doses after this period must be discarded.

Rubella Vaccine

Rubella (R) vaccine is currently derived from RA 27/3 vaccine strain grown in human diploid/chick embryo cell cultures. The vaccine is available in a 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 vaccines. Apart from local side effects, a mild rash may develop in 5% of the vaccines. Joint symptoms such as arthralgia and arthritis may occur 1–3 weeks following vaccination, especially in susceptible post-pubertal females but are 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 4 weeks 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.

IMMUNOGENICITY

Measles Vaccine

Due to interference by preexisting maternal antibodies, immunogenicity depends on the age of administration. 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.[22] 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.[22]

Mumps Vaccine

Seroconversion rates against mumps are >90%, but clinical efficacy and long-term protection with a single dose is 60–90%; outbreaks have been noted in previously vaccinated populations.[22] Hence, two doses are needed for durable protection. When the first dose is administered before the age of 1 year, two additional doses are necessary, the second after the age of 1 year, and the third in the preschool age.

Rubella Vaccine

A single dose of vaccine provides lifelong protection in >95% of the vaccinees.[22]

ADVERSE EFFECTS

Measles Vaccine

Side effects are infrequent and usually mild.[23] 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 vaccines 7–12 days after vaccination and last for 1–2 days. The 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 a 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 vaccines. Thrombocytopenic purpura may occur at a frequency of 1/30,000 vaccines. Though depression of cell-mediated immunity may occur, it recovers within 4 weeks and is considered harmless even for those with early HIV or latent/unrecognized tuberculosis. There is no data supporting a causal relationship between the measles vaccine and encephalitis, Guillain–Barré syndrome (GBS), subacute sclerosing encephalitis, and autism. There is no transmission of the vaccine virus from the vaccines to the contacts.[23]

Mumps Vaccine

About 5% of children can get fever more than 39°C 7–12 days following vaccination, and febrile seizures may occur.[23] 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.

Rubella Vaccine

Apart from local side effects, a mild rash may develop in 5% of the vaccinees.[23] Joint symptoms such as arthralgia and arthritis may occur 1–3 weeks following vaccination, especially in susceptible postpubertal females but are usually mild. Immune thrombocytopenic purpura may occur in a frequency of 1 per 30,000 vaccinated children.

CONTRAINDICATIONS FOR MMR VACCINE[24-26]

- Severe allergic reaction to vaccine component or following a prior dose of MMR vaccine
- Severe immunocompromised state including systemic high-dose corticosteroid therapy for 14 days or more, HIV infection with severe immunosuppression, family history of congenital or heredity immunodeficiency in first-degree relatives
- Pregnancy.

PRECAUTIONS FOR MMR VACCINE[24-26]

- Moderate or severe acute illness
- Receipt of antibody-containing blood products, in the past 3–11 months
- History of thrombocytopenic purpura or thrombocytopenia
- If pregnancy is planned, then an interval of 1 month should be observed after MR vaccination.

ACVIP RECOMMENDATIONS[27]

Indian Academy of Pediatrics (IAP)/ACVIP recommends a 3-dose schedule of MMR vaccine as follows:

- *Dose 1:* Completion of 9 months
- *Dose 2:* 15–18 months
- *Dose 3:* 4–5 years of age.

UNIVERSAL IMMUNIZATION PROGRAMME RECOMMENDATIONS

The National Technical Advisory Group on Immunization (NTAGI) observed that since the "disability component" of mumps is not a serious public health problem and since the addition of mumps component to Universal Immunization Programme (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 the campaign, the MR vaccine was introduced in RI, replacing the two doses of measles vaccine—at 9–12 months and 16–24 months.

- *Dose 1:* 9–12 months
- *Dose 2:* 16–24 months.

In case of an outbreak, the vaccine can be given to infants as young as completed 6 months, but this early dose is not to be counted and the usual dose at 9 months is to be administered.

The MMR vaccine, if administered within 72 hours after exposure, to susceptible individuals, may prevent or modify measles disease and is the intervention of choice for postexposure

prophylaxis in immunocompetent hosts. Postexposure prophylaxis is not of much benefit against mumps and rubella.

The Global Measles and Rubella Strategic Plan 2012–2020 (MRSP 2012–2020) resulted in measles elimination in 82 countries and rubella elimination in 81 countries (by the end of 2018).[28] There was a sizable reduction in the measles and rubella disease burden, a steep increase in the introduction of the MCV2 and rubella-containing vaccine, and improvements in the surveillance. Now, the Measles and Rubella Strategic Framework 2021–2030 aims for a world free of measles and rubella, although the timeline and targets for eradication will be set when the necessary conditions for eradication are met. This also allows the individual WHO regions to set their regional measles and rubella elimination goals and develop strategies to achieve them.[28]

Member countries of the WHO South-East Asia region, including India, set a regional goal to eliminate measles and rubella by 2023. Measles elimination and rubella control have been a regional flagship priority since 2014. Five countries have already eliminated measles—Bhutan, DPR Korea, Maldives, Sri Lanka, Timor-Leste, and six countries have controlled rubella—Bangladesh, Bhutan, Maldives, Nepal, Sri Lanka, and Timor-Leste. Member countries adopted a "Strategic Plan for Measles and Rubella Elimination 2020–2024" that lays down the roadmap and focus areas on achieving the elimination targets in the region.[29]

Measles, mumps, and rubella (MMR) vaccine, IAP/ACVIP.

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

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
- In campaign mode, MMR vaccine can be administered irrespective of the administration of previous doses

(ACVIP: Advisory Committee on Vaccines and Immunization Practices; IAP: Indian Academy of Pediatrics)

MR vaccine.

Routine vaccination: Universal Immunization Programme:
- Dose 1 is administered at minimum age of 9 months or 270 completed days
- Dose 2 is administered at 16–24 months

Catch-up vaccination:
- Catch-up vaccination up to 5 years
- For catch-up vaccination, minimum interval between dose 1 and dose 2 should be at least 4 weeks
- 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

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3.9 VARICELLA VACCINES

Rajendra Khadke, Sanjay Srirampur

INTRODUCTION

Varicella-zoster virus (VZV) is a highly contagious 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 rarely mortality may occur 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 seen includes cerebellar ataxia and 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 peaks at a higher mean age and higher susceptibility among adults is seen, 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 prevalence 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 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 and 18 years, 18.6% between 3 and 5 years, and 15.4% between 1 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.[10]

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.[9,10] 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 and this is the time individuals become prone to develop zoster.[11]

VACCINE

A vaccine based on live-attenuated VZV (Oka strain)[12] 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 the number of passages 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)
- Nexipox (Mf. China, Mkt-NovoMedi Sciences).

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

TABLE 1: Stabilizers in varicella vaccines.

	Monosodium L-glutamate—stabilizer	*Gelatin*	*Human serum albumin*	*Trehalose as a stabilizer*	*Stability at 2–8°C*
VARIPED	Yes	Yes			24 months
VARILIX	Yes		Yes		24 months
NEXIPOX	Yes		Yes	Yes	36 months

lyophilized. They are licensed for use in persons aged >12 months. All of them employ live-attenuated VZV (Oka strain). They do differ in the number of plaque-forming units (PFUs) from 1,300 to 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.[14]

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.

IMMUNOGENICITY[11,12]

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 (VE) to be 94.4% and 98.3% respectively ($p < 0.001$). There was no breakthrough varicella till 7–10 years after two doses.

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%

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 VE appears similar across all products amounting to 80–92%.

INDIAN STUDIES

All the Indian studies are immunogenicity studies with Varilrix/Variped as comparator vaccines. There are no efficacy studies from India.

Population Impact Data

Till 2021, 49 countries have introduced varicella in National Immunization Schedule, 6 in western Pacific region, 24 in the European region, 6 in the Eastern Mediterranean region, and 13 in the Americas. The impact studies have been published from several countries, which are using either Variped, Varilrix, or both. Overall, a reduction >80% in the incidence of disease and hospitalizations has been reported in most of the studies. The second dose has conferred additional benefits as well as the induction of some herd immunity. Any increase in the incidence of HZ in older individuals has not been confirmed in most of the studies. Universal VV has been shown to be cost-effective. Most data are reported from high- and

middle-income countries, and the impact in low-income countries may not be the same.[18]

Breakthrough varicella: It is defined as varicella developing >42 days after immunization and usually occurs 2–5 years following vaccination. It occurs in about 1–4% of vaccines per year. Breakthrough varicella was observed to have the highest rate in the first 4–5 years after vaccination.[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.[19] 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/post-licensure 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 vaccines 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. There is no increased incidence of zoster after vaccination.

Contraindication for varicella vaccines:

- Known severe allergic reaction to vaccine component or following a prior dose
- Immunosuppression due to malignancies, immune deficiency disease, or immunosuppressive therapy
- Family history of congenital or heredity immunodeficiency in first-degree relatives
- Pregnancy
- Hematopoietic stem cell transplantation (HSCT)—may be given after 24 months.

Precautions for varicella vaccines:

- Moderate or severe acute illness
- Receipt of antibody-containing blood products (wait 3–11 months to vaccinate)
- Receipt of specific antiviral drugs 24 hours before vaccination
- Child on aspirin or aspirin-containing products, salicylates to be discontinued for 6 weeks after vaccination.

Risk of HZ 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 the following:

- 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 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, day-care center workers, military personnel, and healthcare professionals.

Varicella vaccine in children with acute lymphatic leukemia (ALL), with no evidence of immunity:

- Since varicella is a devastating illness in the immunocompromised especially ALL, exclusive recommendations exist for administration in ALL.

In children between 12 months and 17 years of age with a negative history of varicella in whom leukemia is in remission for at least 12 months, the peripheral blood lymphocyte count ≥700 cells/mm^3 and the platelet count is ≥100,000/mm^3, two doses of varicella vaccine may be administered. Maintenance chemotherapy should be withheld for 7 days before and after at least the first dose.

Varicella vaccine for postexposure prophylaxis in susceptible healthy nonpregnant contacts:

- Among children, protective efficacy was reported as ≥90% when vaccination occurred within 3 days of exposure.
- Protective efficacy in preventing any type of disease was 62.3% [confidence interval (CI) 95%: 47.8–74.9] and 79.4% (CI 95%: 66.4–88.9) in preventing moderate and severe disease, up to 5 days after exposure.
- Vaccination still recommended for those with no other evidence of immunity even after 5 days of exposure because it will help to provide protection against future exposures.

The following groups are at high risk for varicella complications:

- Infants born to mothers who develop varicella within 5 days before delivery to 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.
- *Exposure to varicella in*:
  - Preterms >28 weeks GA, no maternal immunity
  - Preterm <28 weeks GA or <1,000 g, irrespective of maternal immunity
  - Immunocompromised without e/o immunity. All immunocompromised children especially neoplastic disease, congenital or acquired immunodeficiency or those receiving immunosuppressive therapies. Immunosuppressed children, who received intravenous immunoglobulin (IVIg) at a dose of 400 mg/kg in the past 3 weeks are deemed protected.
  - Pregnant women without e/o immunity.

Varicella zoster immunoglobulin (VZIg) provides 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:

Management of exposure in a high-risk contact:

- VZIg: as soon after exposure, up to 10 days. *Dose*: 125 IU/10 kg BW to a maximum of 625 IU, minimum is 62.5 IU, in a neonate. 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.

If VZIg is unavailable: IVIg: 400 mg/kg, single dose.

If VZIg and IVIg is unavailable: Oral acyclovir, beginning 7 days after exposure, given for 7–10 days in a dose of 20 mg/kg/dose 6 hourly.

Administration of VZIg/IVIg is recommended as soon as possible, within 10 days, to immunocompromised children without evidence of immunity.

Following the above-mentioned postexposure prophylaxis, the child should be under observation, for a month, for development of varicella, as delayed appearance has been noted after administration of VZIg/IVIg. If clinical Varicella is noted, the high-risk contact should be treated with IV acyclovir for 10 days.

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. Some brands contain 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 2/3 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 simultaneously with all other childhood vaccines.

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 VE and a misunderstanding by physicians or parents who may lose faith in vaccination. 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 should be given 3–6 months after the first dose. 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 vaccine to the contact and even if it was to occur, the disease is likely to be very mild. If the vaccine develops a vaccine-related rash, he/she should avoid contact with a susceptible immunocompromised contact.

Two vaccines, Zostavax™ (live attenuated) and Shingrix™ (recombinant) are available in the global market, for protection against HZ. Presently, they are not available in India.

Zostavax

Zostavax zoster vaccine live (ZVL) is a lyophilized preparation of live, attenuated VZV (Oka/Merck), propagated in human diploid cell cultures. The reconstituted single dose suspension contains a minimum of 19,400 PFUs when stored at room temperature for up to 30 minutes.

The VE was 70% (95% CI = 54–81) (median follow-up time was 1.3 years), in persons aged 50–59 years, 64% (95% CI = 56–71) in persons aged 60–69 years and 38% (95% CI = 25–48) in persons aged ≥70 (median follow-up time was 3.1 years). The VE reduces substantially following the first year after receipt of ZVL, and, by 6 years postvaccination, vaccine effectiveness against HZ is <35%.

The incidence of serious adverse events were similar in vaccinated and placebo groups. Rarely, disseminated rash as well as HZ has been reported in immunocompetent recipients, and life-threatening and fatal complications in immunocompromised recipients.

Schedule: Single dose of HZ vaccine for people 50 years of age or older, irrespective of prior history of HZ, administered SC.

Contraindications: Life-threatening or severe allergic reaction to gelatin, the antibiotic neomycin or any other component of HZ vaccine, immunocompromised persons, pregnancy. Women should not become pregnant until at least 4 weeks after getting zoster vaccine.

Shingrix

Shingrix recombinant zoster vaccine (RZV) is a lyophilized preparation of sterile suspension for intramuscular injection of lyophilized recombinant VZV surface glycoprotein E (gE) antigen component, which must be reconstituted with the accompanying vial of AS01B adjuvant suspension component.

Vaccine efficacy against HZ was 96.6% [95% confidence interval (CI) = 89.6–99.3] in persons aged 50–59 years, 97.4% (95% CI = 90.1–99.7) in persons aged 60–69 years and [91.3% (95% CI = 86.8–94.5) in participants aged ≥70 years]. VE was 97.6% (95% CI = 90.9–99.8) in the first year after vaccination and was 84.7% (95% CI = 69.0–93.4) or higher for the remaining 3 years of the study in persons aged ≥70 years. Efficacy for prevention of postherpetic neuralgia was 91.2% (95% CI = 75.9–97.7) in adults aged ≥50 years and 88.8% (95% CI = 68.7–97.1) in those aged ≥70 years.

The incidence of serious adverse events were similar in vaccinated and placebo groups. The most common solicited adverse reactions (grade 1–3) were pain (78%), myalgia (45%), and fatigue (45%).

Schedule: Two doses administered IM, 2–6 months apart, in adults aged 50 years and older and for adults aged 18 years and older who are immunosuppressed.

Contraindications: History of severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine or after a previous dose of the vaccine.

This vaccine is safe in the immunocompromised.

Recommendations for use of HZ vaccines (Advisory Committee on Immunization Practices—ACIP (USA):

- Recombinant zoster vaccine is recommended for the prevention of HZ and related complications for immunocompetent adults aged ≥50 years.

- RZV is recommended for the prevention of HZ and related complications for immunocompetent adults who previously received ZVL.
- RZV is preferred over ZVL for the prevention of HZ and related complications.
- ZVL is preferred for those with a history of severe allergic reactions to any component of the RZV.[20]

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.[21] 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: PRIORIX-TETRA BY GSK VACCINES LTD.

Measles, mumps, and rubella plus varicella 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.

This vaccine is no longer marketed in India.

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3.10 HEPATITIS A VACCINES

Chandra Mohan Kumar, Sanjay Marathe

INTRODUCTION

Hepatitis A virus (HAV) is a common hepatotropic virus causing inflammation of liver. The virus primarily spreads through feco-oral route and is closely associated with unsafe water and food as well as poor sanitation and hygiene practices. It is a relatively benign infection in young children. As many as 85% of children below 2 years and 50% of those between 2 and 5 years infected with HAV are anicteric and may have no symptoms at all or just have nonspecific symptoms such as 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.

However, infection rates are low in high income countries with good sanitary and hygienic conditions.

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.[2]

Hepatitis A virus infection occurs worldwide but mostly in low/middle income group countries. Globally 1.4 million cases occur every year.[3]

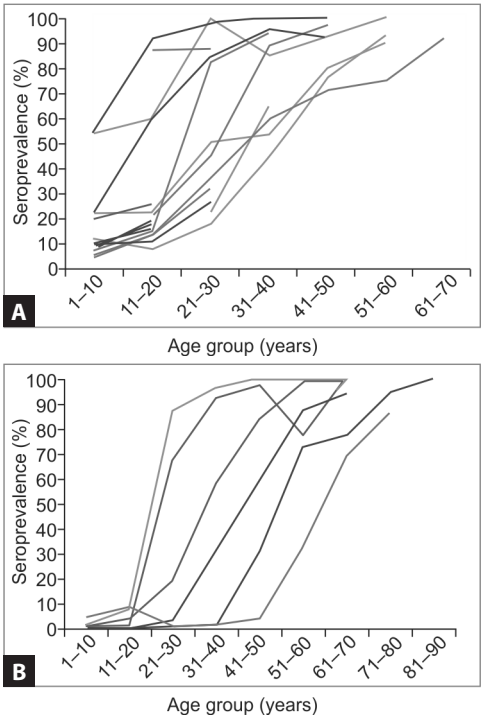
In high-income regions, the prevalence of anti-HAV antibody is very low (<50% are immune by age 30 years), there is almost no circulation of the virus and therefore the risk of acquiring HAV infection is low. In contrast, in countries with high endemicity, most individuals acquire natural infection in 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.

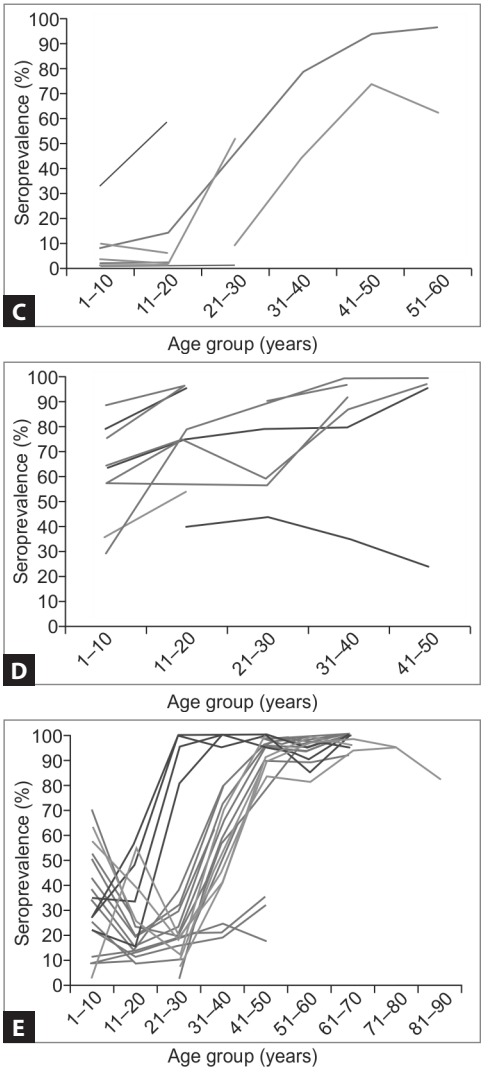
In several Asian countries, the age at first infection by hepatitis A seems to be increasing **(Figs. 1A to H)**.[4]

Indian Burden

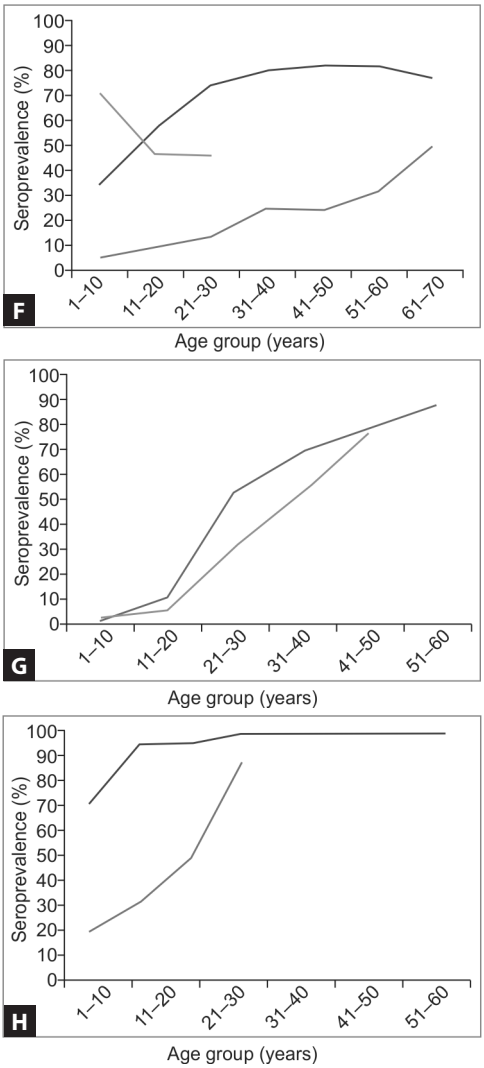
India, earlier a highly endemic country, is now shifting to intermediate endemicity in some areas in cities and in higher



Figs. 1A and B: (A) Thailand; and (B) Japan.



Figs. 1C to E: (C) Taiwan; (D) India; and (E) Korea.



Figs. 1F to H: (F) China; (G) Singapore; and (H) Indonesia. 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). 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, Marsh G, Druelles S, Nealon J. et al. Changing sero-epidemiology of hepatitis A in Asia Pacific countries: A systematic review. Int J Infect Dis. 2018;68:13-17.

socioeconomic strata of community.[5] 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. 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.[6] 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, signifying it's relatively higher burden.

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 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%).[7]

VACCINES (TABLE 1)

Inactivated Vaccines

Inactivated vaccines available in India:

- Havrix-GSK
- Avaxim-Sanofi
- HapiBEV and HAVshield.

Most of the currently available vaccines are derived from HM 175/GBM strains and grown on MRC-5 human diploid cell lines.

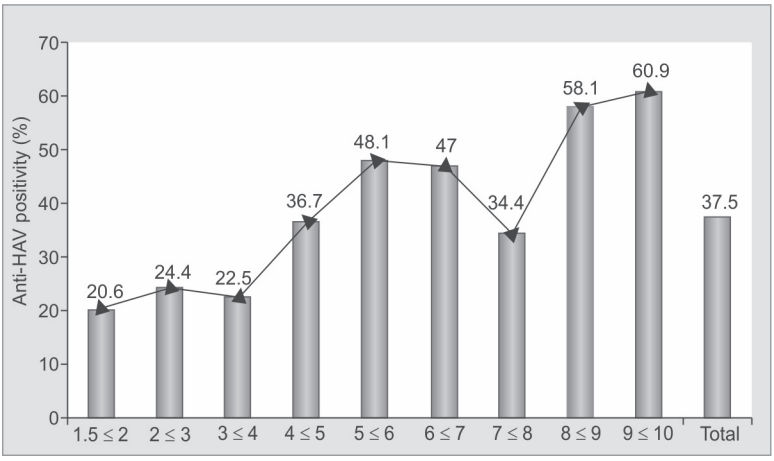


Fig. 2: Age-specific prevalence of hepatitis A in all centers in Kolkata, Pune, Chennai, and Delhi. (HAV: Hepatitis A virus)
Source: Arankalle V, Mitra M, Bhave S, Balasubramanian S, Chatterjee S, Choudhury J, et al. Changing epidemiology of hepatitis A virus in Indian children. Dovepress. 2014;4:7-13.

TABLE 1: Comparison of inactivated (two doses) and live-attenuated hepatitis A vaccines (single dose).

	Inactivated	*Live attenuated*
Source	HM-175 strain	H2 strain
Schedule and route	2 doses at 6–12 months interval, IM >12 months of age	1 dose, SC >12 months of age
SCR	100% SCR with 1 dose by 19 days postvaccination	100% SCR with 1 dose by 3–4 weeks post-vaccination
Ab response	Higher titers	Lower titers
Immuno-compromised	Can be used	Cannot be used
Long-term protection	Based on Ab titers at 15 years, expected >85% protected at 50 years	SCR of 81.3% after 15 years *Modeling:* Protection lasts at least 30 years

(IM: intramuscular; SC: subcutaneous; SCR: seroconversion rates)

Recently, BE vaccines, has introduced an inactivated vaccine derived from the TZ84 strain of Healive™. It is available in our country as Hapibev (BE) and HAVshield (Abbott). Both, Havrix (GSK) and Healive (Sinovac) are WHO prequalified. 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 immune-potentiating 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. Currently, this vaccine is not marketed in India.

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 (Both are not available in India). Similarly, combinations of hepatitis A vaccine with Vi-polysaccharide vaccines are available internationally though not in India.

Efficacy and Effectiveness

Protective antibody concentrations are elicited in >95% of healthy children, adolescents, and adults when measured 1 month after receipt of the first dose and in >99% 1 month after a second dose. The median predicted duration of protection has been estimated at 45.0 years.[8] 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 geometric mean concentration (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.[9] 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.[8]

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.[8] The vaccine may be safely given with other childhood vaccines and interchange of brands is permitted though not routinely recommended.

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, with the second dose administered 6–18 months after the first dose.[10] Minimum age for giving hepatitis A vaccine is 12 months. All the inactivated vaccines are safe and efficacious and can be used interchangeably if supply of a vaccine given earlier is not available.

Live-attenuated Vaccine

Only one brand, BioVac A is marketed in India.

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 1990s 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.[9] Studies in China have demonstrated that live-attenuated hepatitis A vaccine provide postexposure protection against HAV infection during outbreaks.[11]

Data on Immunogenicity and Safety of a Single Dose of the Live-attenuated Vaccine

A study involving 11,451 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.[12] 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 7–28 days.[13]

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 >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.[14]

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%.[15]

In a multicentric single arm study conducted in four metros of the country, children of 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 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.[16] 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 two-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 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.[17] 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.[18]

Safety

No substantial safety concerns have been identified during vaccine trials[8] and no horizontal transmission or serious adverse effects have been noted with the live vaccine.

Hepatitis A Vaccines for Postexposure Prophylaxis

Hepatitis A vaccines are preferred for PEP, as vaccines have several advantages compared with IGIM, including the induction of active immunity, longer duration of protection, ease of administration, and greater availability. A single dose of Hepatitis A should be offered, within 2 weeks of exposure, to those between 1 and 40 years of age. This is as effective as IMIg, in preventing clinical hepatitis A disease.

For those <1 year or >40 years, IMIg in a dose of 0.1 mL/kg may be offered. This offers protection for 1 month.

World Health Organization 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.[8] Immunocompromised subjects can receive only the inactivated vaccines.

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 few 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.[19] A study from Hyderabad observed that 25% of children <15 years remain susceptible to HAV infection.[20] Another study from Bijapur observed seropositivity in 54.4% children between 5 and 15 years.[21] 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 >10 years of age.

IAP/ACVIP RECOMMENDATIONS FOR INDIVIDUAL USE

The hepatitis A vaccine may be offered to all healthy children.

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.

Inactivated vaccines: For >12 months, two doses administered IM at 0 and 6–18 months.

Live vaccines: For >12 months, one dose administered SC.

PUBLIC HEALTH PERSPECTIVES

According to the 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.

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.[22] Furthermore, a single dose of this vaccine may successfully control outbreaks of hepatitis A.[8] 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%).[23]

Effectiveness of Single Dose in National Immunization Program

Argentina began a Universal Immunization Programme (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.[24] 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.[8,24] 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 ≥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 prevention.

IAP recommendations: Hepatitis A vaccine schedule.

Routine vaccination:
- Inactivated vaccines: >12 months: Two doses administered intramuscular (IM) at 0 and 6–18 months
- Live vaccines: >12 months: Single dose administered subcutaneous (SC)

Catch-up vaccination:
- Inactivated vaccines: Two doses administered IM at 0 and 6–18 months
- Live vaccines: single dose administered SC
- For catch-up vaccination, prevaccination screening for hepatitis A antibody is recommended in children >10 years, as at this age the estimated seropositive rates exceed 50%

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3.11 TYPHOID VACCINES

Kripasindhu Chatterjee, Srinivas G Kasi

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 the 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 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.

Based on the Global Burden of Disease Study 2017, it is estimated that globally, 14.3 million [95% uncertainty interval (UI) 12.5–16.3] cases of typhoid and paratyphoid fevers occurred in 2017.[2] The estimated global case fatality was 0.95% (0.54–1.53) in 2017, with an estimated 135.9 thousand (76.9–218.9) deaths from typhoid and paratyphoid fever globally in 2017. There has been a significant decline from the 1990 estimates.

Typhoid fever is one of the most common etiological sources of bacteremia in many developing countries, with most of the cases

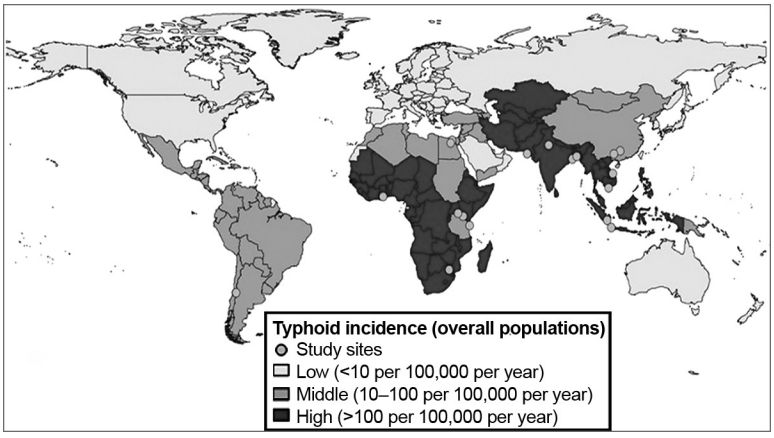

Fig. 1: Global burden with study sites.[9]

originating in the Indian subcontinent of South Asia, followed by sub-Saharan Africa **(Fig. 1)**.[3-5]

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.[6] However, it is the Indian subcontinent which has the highest incidence of the disease worldwide.[7]

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] In India, the overall incidence was 214.2/100,000.

Extensively drug-resistant typhoid fever in Pakistan 2016, resistant to five groups of antibiotics: An ongoing outbreak of XDR typhoid fever was 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, three cases of XDR typhoid fever were reported in travellers—one who returned to the United Kingdom, and two who returned to the United States. Seventy-six cases of XDR and XDR variant Typhi infections have been identified by the CDC between February 6, 2018, and March 27, 2021, in the US residents. Sixty-seven (88%) reported travel to or from Pakistan, and 9 (12%) denied having traveled internationally in the 30 days before their illness.[8]

Age Distribution

Children are disproportionately affected by typhoid fever, with peak incidence in individuals aged 5 to <15 years of age.[9] 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. In India, the incidence of Typhoid in the 0–1 year age group was 89.2/100,000, which was the highest among the countries studied. In the same study the overall incidence of Typhoid was 214.2/100,000, with the highest incidence of 493.5/100/000 in the 5–15 years age group.[7]

There is a significant burden of typhoid and paratyphoid fevers in India.[10-13] Typhoid fever in pregnancy can result in a range of maternal complications as well as miscarriage, fetal death, and neonatal infection.[14]

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%.[11]

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 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. 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%).

Infectious Disease Surveillance (IDsurv) 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.[15-17] 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.[15]

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 Programme (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.[12]

NEW GENERATION TYPHOID VACCINES

The new generation current typhoid fever vaccines include oral live-attenuated Ty21a vaccine, parenteral Vi polysaccharide and Vi-polysaccharide (Vi-PS) capsular conjugate vaccines. 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-thirds 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]

Re-vaccination with Vi-PS vaccine is advised every 3 years. With more safe and effective conjugate vaccines with long-term protection potential, the Advisory Committee on Vaccines and Immunization Practices (ACVIP) prefers the use of Vi conjugate vaccines.

Efficacy

The biological marker is anti-Vi antibodies and 1 μg/mL is proposed as the serologic correlate of protection (CoP). 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%.[18] Interestingly the herd protection of 44% was noted in unvaccinated children in the vaccinated cluster as compared to the control cluster.[17]

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), and DAVAC (Vietnam)]. Out of these vaccines, the one from Sanofi Pasteur is now prequalified by WHO.

Vi Capsular Polysaccharide Conjugate Vaccines

To overcome the limitations of polysaccharide vaccine, Vi capsular PS [derived either from *Salmonella enterica* subspecies *enterica* serovar Typhi (*S. typhi*), or from *Citrobacter freundii* sensu lato (*C. freundii* s. l.)] is conjugated to carrier proteins, TT or CRM197, converting T-independent PS to T-dependent antigen.[18]

Different TCVs, like Typbar-TCV™, Zyvac TCV™ and Typhibev™ contain 25 μg whereas PedaTyph™ contain 5 μg of Vi-PS. The dose of 25 μg was selected on the basis of the amount of PS present in the licensed Vi-PS vaccine.[18] The issue of the exact dose of Vi-PS in a TCV is still unsettled. Most of the manufacturers of TCVs have adopted a high-end dose, 25 μg of Vi-PS, in their upcoming products **(Table 1)**.

The TCVs demonstrate (i) superior efficacy and effectiveness than unconjugated Vi-PS vaccines; (ii) longer duration of protection; (iii) immunogenicity among younger children, including infants; (iv) reasonably good herd immunity; and (v) induction of immune memory.[18]

The WHO-SAGE Working Group on Typhoid Vaccines has recommended only a single dose of the TCV at any time between 6 and 23 months of age in the endemic countries.[1,12] This has been further corroborated by the published 7-year follow-up data of Typbar-TCV.[19-25]

Immune Correlate of Protection

No internationally agreed correlates or surrogates of protection have yet been identified for Vi-conjugate vaccines.[19] The study to evaluate Vi-TT in Nepal found that higher anti-Vi IgG levels are associated with greater protection against typhoid infection,

TABLE 1: 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	Robust evidence regarding safety and efficacy. Human challenge study proved efficacy, long-term efficacy and safety data up to 5 years available. DCGI approved August 2013. WHO prequalification January 2018
Zyvac TCV	Cadila Healthcare Pvt. Ltd.	25 µg purified Vi-PS of *S. typhi* (strain 2) to tetanus toxoid. 2-phenoxyethanol as preservative	1 trial. Licensed based of noninferiority to Typbar-TCV. DCGI approved
Typhibev	Biological E vaccines	25 µg purified Vi-PS conjugated to 16.7 µg to 100 µg of CRM-197	DCGI approved in February 2020. WHO prequalification December, 2020
Entero-shield	Abbott	25 µg purified Vi-PS of *S. typhi* (strain 2) to tetanus toxoid	As in Typbar-TCV above
Typbar	Bharat Biotech	25 µg purified Vi-PS of *S. typhi* (strain 2) unconjugated	Above 2 years up to adults, recommended every 3 years
Zyvac	Cadila Healthcare Pvt. Ltd.	Vi-PS unconjugated	Few studies

(DCGI: Drug Controller General of India; Vi-PS: virulence polysaccharide)

no threshold level could be identified at which the probability of infection becomes negligible within the range of antibody levels induced by vaccination. It is possible that multiple immunological parameters, including cell mediated immune responses, may be responsible for protection against *S. typhi* infection. Thus, all

second generation TCVs will be licensed on basis on noninferiority to existing licensed vaccines.

Virulence-polysaccharide 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 age. India fits in to this situation along with Southeast Asia and parts of Africa.

VI-POLYSACCHARIDE CONJUGATE VACCINE CONJUGATED WITH TETANUS TOXOID FROM BHARAT BIOTECH (TYPBAR-TCV®)

Typbar-TCV is a Vi-PS conjugate typhoid vaccine conjugated with TT, was the first licensed TCV 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).[20]

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.[21]

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).

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 anti-Vi GMTs and the proportion of individuals with titers more than fourfold over their baseline were significantly higher among recipients of the TCV. In infants 6–11 months old and toddlers 12–23 months old, a single dose of Typbar TCV elicited high titers of IgG anti-Vi antibody [1937.4 (95% CI: 1785.0, 2102.9), N = 307] that endured up to 5 years in a proportion of young children.[12,26-29]

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.

The 7-year follow-up data in **Table 2** of the 6–23 months cohort shows nonsignificant differences in the titers in the boosted and nonboosted groups at the end of 7 years.[22]

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.

No significant differences were detected among the groups at any time relevant points including days 56, 180, 360, and 720. The anti-Vi GMT and antimeasles antibodies were similar in all five groups. The anti-Vi antibodies and IgG antimeasles antibodies were similar when the vaccines were given either in combination or alone.

TABLE 2: Anti-Vi titers in the boosted and unboosted 6–23 months cohort till 7 years followup.

ELIZA method	*Boosted*	*Measure*	*Day 0*	*Day 42*	*Day 720*	*Day 762*	*Day 1095 (3 Y)*	*Day 1825 (5 Y)*	*Day 2555 (7 Y)*
Szu-NIH	Boosted (N = 86)	Persisting SCR		100% (98.8, 100)	98.8% (93.7, 99.9)	100% (98.8, 100)	100% (98.8, 100)	100% (98.8, 100)	92% (84.0, 96.7)
		GMT	0.7 (0.6, 0.8)	105.4 (90.9, 122.3)	20.7 (19.4, 22.1)	50 (47.2, 53)	40.4 (33.3, 49)	33.7 (28.8, 39.4)	13.9 (12.2, 15.9)
	Non-boosted (N = 25)	Persisting SCR	0.9	100% (98.8, 100)	96.0% (79.7, 99.9)		92.0% (74.0, 99.0)	92% (74.0, 99.0)	96% (79.7, 99.9)
		GMT		119.9 (95.2, 151.3)	22.5 (21.3, 23.8)		40.3 (31.0, 52.4)	35.6 (28.4, 44.5)	14.7 (10.1, 21.5)
Vacczyme	Boosted (N = 86)	Persisting SCR		96.5% (90.1, 99.3)	65.1% (54.1, 75.1)	97.6% (91.9, 99.7)	90.7% (82.5, 95.9)	84.8% (75.5, 91.7)	70.9% (60.1, 80.2)
		GMT	9.4″ (8.2, 10.8)	1902.7 (1670.0, 2167.8)	53.8 (44.6, 64.7)	1700.2 (1500.2, 1927.0)	319.2 (266.7, 381.9)	132.3 (109.1, 160.4)	111.0 (77.3, 159.5)

Contd…

Contd…

ELIZA method	*Boosted*	*Measure*	*Day 0*	*Day 42*	*Day 720*	*Day 762*	*Day 1095 (3 Y)*	*Day 1825 (5 Y)*	*Day 2555 (7 Y)*
	Non-boosted (N = 25)	Persisting SCR		100% (89.7, 100)	56% (34.9, 75.6)		72% (50.6, 87.9)	72% (50.6, 87.9)	44% (24.4, 65.1)
		GMT	10.9 (7.2, 16.6)	1445.7 (986.2, 2119.5)	57.9 (35.7, 94.1)		255.8 (138.5, 368.1)	79.4 (48.6, 129.7)	51.5 (22.8, 116.1)
NIBSC (IU/mL)	Boosted (N = 86)	Persisting SCR		100% (95.8, 100)	100% (95.8, 100)	100% (95.8, 100)	100% (95.8, 100)	100% (95.8, 100)	98.8% (93.7, 100)
		GMT	1.7 (0.8, 3.6)	224.9 (221.1, 228.9)	13.7 (4.20, 44.8)	326.6 (275.4, 387.2)	35.9 (26.3, 49)	33.9 (25.4, 45.2)	25.9 (19.7, 33.9)
	Non-boosted (N = 25)	Persisting SCR		100% (89.7, 100)	100% (89.7, 100)		96% (79.7, 99.9)	100% (89.7, 100)	100% (89.7, 100)
		GMT	1.2 (0.7, 2.1)	109.3 (90.3, 132.2)	9.3 (6.9, 12.3)		23.6 (20.1, 27.6)	34.2 (26.3, 44.6)	23.4 (10.1, 54.3)

Effectiveness/Efficacy Studies

In the seroefficacy study, vaccine seroefficacy was 85% (95% CI: 80–88%).[23]

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.[24]

In a phase 3 study, conducted in Lalitpur, at the end of 1 year, vaccine efficacy was 81.6% (95% CI: 58.8–91.8). The vaccine efficacy of TCV fever at 2 years was 79.0% (95% CI: 61.9–88.5; $p < 0.0001$) with no significant waning of immunity over 2 years. The adverse effects profile was similar in the vaccine and control groups, with fever developing in 5.0% of participants in the TCV group and 5.4% in the MenA vaccine group in the first week after vaccination.[25]

In a study done in Dhaka, Bangladesh, in children, between 9 months and 16 years, the overall VE was (81%; 95% CI: 39–94, $p = 0.0052$), including children vaccinated at ages under 2 years.

Fever (5.3%), a general feeling of unwellness (4.3%), diarrhea (2.1%), and pain at the injection site (1.6%) were the common adverse events reported which were similar in the two vaccine groups. The risk of serious adverse effects was similar in the vaccine and control groups. None of the reported deaths in both groups, were judged to be related to vaccination.[26]

In a phase 3, double-blind trial conducted in Blantyre, Malawi, the efficacy of Vi-TCV was 80.7% [95% confidence interval (CI), 64.2–89.6] in the intention-to-treat analysis and 83.7% (95% CI: 68.1–91.6) in the per-protocol analysis. The estimated efficacy of Vi-TCV was 84.6% (95% CI: 50.0–94.4) at 12 months, 82.9% (95% CI: 58.1–92.5) at 18 months, and 78.7% (95% CI: 52.8–91.7) at 24 months after vaccination. No serious adverse events were considered by the investigators to be related to vaccination.[27]

Navi Mumbai Municipal Corporation (NMMC) launched the world's first public sector TCV introduction aimed at vaccinating

approximately 320,000 children aged 9 months to under 15 years in two phases.

ZYVAC TCV: TYPHOID CONJUGATE VACCINE WITH TT FROM CADILA HEALTH CARE LIMITED

Single dose: 0.5 mL vial; Vi polysaccharide of *S. typhi* 25 μg, 2-phenoxyethanol 2.50 mg as preservative and buffer solution. A Phase II/III study to demonstrate the noninferiority of ZyVac-TCV to Typbar TCV in healthy individuals aged 6 months to 45 years was initiated in 2016. The seroconversion rate among ZyVac-TCV recipients was 94.8% (96.6% in adults and 93.1% in children), compared with 91.6% (91.7% in adults and 91.5% in children) for Typbar TCV recipients. The GMT of anti-Vi antibodies among ZyVac-TCV recipients was 1,121 EU/mL (adults, 1,411; children, 891.1), compared with 1,104 EU/mL (adults, 1,199; children, 1,014) among Typbar TCV recipients. ZyVac-TCV was deemed noninferior to Typbar TCV and received marketing authorization in India in 2017.[29]

TYPHIBEV: VI-PS CRM197 TCV FROM BIOLOGICAL E VACCINES

TYPHIBEV (Biological E vaccines) is a typhoid conjugate vaccine where the source of the Vi antigen is *C. frenundii*, which is in conformity with WHO specifications. Each dose of 0.5 mL contains typhoid Vi polysaccharide (produced from *C. Freundii* sensu lato 3056): 25 μg conjugated to 16.7–100 μg of CRM197. Typhibev was licensed for use in India by DCGI in February 2020 and WHO prequalified in December 2020, approved for those aged older than 6 months to 45 years, to be given in 0.5 mL single dose, intramuscular injection.[30]

A multicentric phase II/III study showed that seroconversion (anti-Vi IgG > 2 μg/mL) was obtained in 99% subjects (95% CI: 97.06, 99.79) in Typhibev compared to 99.4% in comparator group Typbar-TCV (Bharat Biotech India Limited). Noninferiority was established with comparator TCV. Anti-Vi IgG > 4.3 μg/mL (criteria defined for having sustained protection for at least 4 years) also fulfilled predefined noninferiority criteria. The side-effect profile was comparable with the comparator vaccine.[31]

RECOMMENDATIONS FOR USE

Individual Use

IAP/ACVIP Recommendation Typhoid Vaccines[32,33]

Primary schedule:

- A single dose of TCV 25 μg is recommended from the age of 6 months onward routinely.
- TCV can be administered simultaneously with 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.

The WHO position paper in 2018 has remarked that the body of evidence for the 5 μg vaccine is very limited.

Vi-polysaccharide 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.

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.

The IAP strongly urges the government to include typhoid vaccination in the UIP considering the enormous burden of the disease **(Box 1)**.

BOX 1: IAP recommendations: 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 9–12 months
- *Catch-up vaccination:*
  - Recommended throughout the adolescent period, i.e., till 18 years
  - IAP prefers the use of Vi-PS conjugate vaccine

(Vi-PS: virulence polysaccharide; TCV: typhoid conjugate vaccines)

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3.12 HUMAN PAPILLOMAVIRUS VACCINES

Srinivas Kalyani, Srinivas G Kasi

EPIDEMIOLOGY

Human papillomavirus (HPV) is a member of the family *Papillomaviridae*. They are small and nonenveloped deoxyribonucleic acid (DNA) viruses. These 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.

Over 200 serotypes of HPV have been discovered, of which 15–20 are oncogenic. 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 the oncogenic HPV infection and the invasive cervical cancer is 15–20 years.[1] Based on the association with cervical cancer, genital HPVs are further grouped into high-risk types, probable high-risk types and low-risk types.

In Indian women, the most common prevalent genotypes are HPV-16 and -18. Nononcogenic HPV serotypes-6 and -11 contribute to over 90% of benign genital infections such as genital warts. In addition, HPV has been implicated in anal, penile, vulvar, vaginal, and oropharyngeal cancers.

CERVICAL CANCER MORBIDITY AND MORTALITY IN INDIA

Globally cancer of the cervix uteri is the second most common cancer among women with an estimated 604,127 new cases and 341,831 deaths in 2020. 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 Southeast Asia, age-standardized incidence rates of cervical cancer exceed 25 per 100,000.[3]

In India, cancer of the cervix uteri is the second most important cancer in women.[2] Globally, age-standardized rate (ASR) of cervical

cancer is 13.3 per 100,000, and for Indian women it is 18 per 100,000. It is estimated that 123,907 cases of cervical cancer cases occur in India and of these 77,348 die every year[2] and this has come down from earlier very high rates even without a control program.[4] 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).[5,6]

The cumulative risk of cervical cancer at 75 years is 2%.

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.[7] It has been shown that it is possible to screen and treat cervical cancer in early stages with high success even in rural India.[8] 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%).[9] Further, to implement national screening program, large investment has to be made in terms of logistics and training of healthcare personnel.

Human papillomavirus vaccines are necessary to significantly reduce the health care burden currently required for cervical cancer prevention. In addition, cervical cancer screening is necessary due to 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.[10]

Human Papillomavirus Prevalence in Men

A multicenter clinical trial examined the baseline prevalence of penile, scrotal, and perineal/perianal HPV infection in heterosexual men. The prevalence of any HPV type was 18.7% at the penis, 13.1%

at the scrotum, 7.9% at the perineal/perianal region, and 21.0% at any site.[7]

PATHOGEN

Human papillomaviruses are nonenveloped and double-stranded 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 200 HPV genotypes are known. Certain HPV genotypes are associated with cell immortalization and transformation related to carcinogenesis. Of these, at least 14 may cause cervical cancer or are associated with other anogenital and oropharyngeal cancers.

Human papillomavirus 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.[11] 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.[12] According to data updated on 11th June 2019, in India, HPV-16 was found in 69.7% of invasive cervical cancers (ICC), HPV-18 in 13.5%, and HPV-16/18 in 83.2%.[2] HPV-16/18 was found in 62.8% (56.7–68.6) of high-grade lesions, 28.2% (22.1–35.3) of low-grade lesions and 5.0% (4.6–5.5) in women with normal cytology.[2]

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 80.3% protection against ICC in South Asia.[13]

Globally, 69.4% (69–69.8) of all ICC are caused by HPV-16/18. HPV-31 accounts for 3.5%, HPV-33 for 4.2%, HPV-45 for 5.0%, HPV-52 for 3.5%, and HPV-58 for 3.9% of cervical cancer cases.[2] Approximately 89.5% of the squamous cell carcinomas which are positive for HPV-DNA are related to HPV types-16, 18, 45, 31, 33, 52, and 58.[2,14]

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 "non-neutralizing" 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.

Human Papillomavirus Vaccines

The quadrivalent and nonavalent vaccines have been licensed globally **(Table 1)**. The bivalent vaccine has been withdrawn from the Indian market. Both vaccines are manufactured by recombinant DNA technology that produces noninfectious virus-like particles (VLPs) comprising the HPV-L1 protein. The mechanisms by which these vaccines induce protection have not been well-defined, but seem to involve both cellular immunity and neutralizing immunoglobulin G antibodies. Clinical trials with these 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 endpoints. Regulatory authorities have accepted the use of CIN grade 2 or 3 (CIN-2/3) and AIS as clinical endpoints in vaccine efficacy trials instead of invasive cervical cancer.[15]

These 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. All the three vaccines have been licensed in several countries world over.

These vaccines are equally safe and have shown nearly complete protection against precancerous and other anogenital lesions caused by the respective vaccine related HPV-types during the 10–14 years of observation so far. The consistency of these observations strongly

TABLE 1: Human papillomavirus (HPV) vaccines: A comparison.

	Gardasil 4	*Gardasil 9*	*Cervavac*
HPV types in vaccine	6, 11, 16, and 18	6, 11, 16, 18, 31, 33, 45, 52, and 58	6, 11, 16, and 18
Adjuvant	225 µg of amorphous aluminum hydroxyphosphate sulfate (AAHS)	500 µg of AAHS	$Al^{+++} \leq 1.25$ mg
Composition	• 20 µg of virus-like particle of 6, and 18 • 40 µg of VLP of 11, and 16	• 20 µg of VLP of 31, 33, 45, 52, and 58 • 30 µg of VLP of 6 • 40 µg of VLP of 11, and 18 • 60 µg of VLP of 16	• 20 µg of VLP of 6, and 18 • 40 µg of VLP of 11, and 16
Age recommendations	Females: 9–45 years	• Females: 9–26 years • Males: 9–14 years	Males and females: 9–26 years

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.[15]

Quadrivalent Vaccine

Quadrivalent vaccine (4vHPV) available in India is a mixture of L1 proteins of HPV serotypes 6, 11, 16, and 18 with aluminum 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

- 20 μg of HPV-18 L1 protein adsorbed onto 225 μg of the aluminum hydroxide.

Efficacy

The safety and efficacy of quadrivalent vaccine was assessed in a large study named FUTURE (Females United to Unilaterally Reduce Endo/Ectocervical Disease) in 17,622 women aged 15–26 years who were enrolled in one of two randomized, placebo-controlled, efficacy trials for the HPV-6/11/16/18 vaccine.

Clinical trials with three doses at 0, 2, and 6 months have shown 99% efficacy at a median follow-up of 3.9 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 endpoints.

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.[16,17] The targeted long-term follow-up studies for 14 years have been published and show sustained protection.

Nine Valent Human Papillomavirus Vaccine

Nine valent HPV (9vHPV) vaccine contains HPV-6, 11, 16, 18, 31, 33, 45, 52, and 58 VLPs. Studies have found that 9vHPV is an efficacious vaccine.

Phase III studies in ~10,000 women aged 16–26 years have demonstrated that 9vHPV is safe and highly efficacious against HPV infection and anogenital precancer lesions in both men and women with a VE of 96.7% (80.9–99.8) against high-grade cervical, vulvar, or vaginal disease as well as 6-month persistent infection caused by HPV-31, 33, 45, 52, and 58 in women not previously

infected with HPV following three doses of 9vHPV. This high efficacy (90–98%) of 9vHPV in preventing certain HPV-related precancers was sustained for >8 years.

All participants who received 9vHPV, seroconverted to the additional five HPV types (HPV-31, 33, 45, 52, and 58) 1-month following the last dose, and the levels of these five additional HPV types were significantly higher than in 4vHPV recipients. Antibody responses to HPV-6, 11, 16, and 18 were noninferior to those generated by the qHPV vaccine.[18-24]

Adverse events related to injection site were more common in the 9HPV group than in the qHPV group.[25]

In a Latin American study, GMTs for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 at month 7 were higher in girls and boys 9–15 years of age than in young women 16–26 years of age.[26]

Around 77.5–100% of individuals who received three doses of 9vHPV remained seropositive to all 9vHPV after 5 years.[27] When a fourth dose of 9vHPV was given to this group of individuals, antibody responses were 1.25–4.10- and 1.65–4.88-fold higher at 1 week and 1 month after the fourth dose, respectively, when compared to the levels at 1 month after the third dose, suggesting the induction of immunological memory to all nine HPV types following the three-dose primary series.[28]

9-valent HPV Vaccine after Quadrivalent HPV Vaccine

9-valent HPV is also immunogenic to all nine HPV types in young women previously vaccinated with three doses of 4vHPV. Women who were naïve to any HPV vaccination and received three doses of 9vHPV had higher antibody responses to HPV-31/33/45/52/58 when compared with women who previously received three doses of 4vHPV and received three doses of 9vHPV. Nevertheless, the antibody level to these types was still several-fold higher than natural infection and the study demonstrated that it was safe to give 9vHPV to individuals previously vaccinated with 4vHPV or 2vHPV after 12 months.[29] However, there is no recommendation to give a 9vHPV to females who have received a full course of 2/4vHPV vaccine.

Adverse Events Following Nonavalent Vaccine

The most common adverse event from seven Phase III clinical trials was injection-site pain, swelling, and redness, which was more common for 9vHPV than 4vHPV with increasing number of doses. It is important to note that the adjuvant content in 9vHPV is more than double that of 4vHPV (0.5 vs. 0.225 mg), and also has a higher VLP antigen content. Nevertheless, most adverse events were mild to moderate in intensity.[30]

Coadministration with Other Adolescent Vaccines

Coadministration of 9vHPV and other adolescent vaccines (i.e., *Neisseria meningitidis* serotypes A/C/Y/W-135, diphtheria/tetanus/acellular pertussis, or diphtheria/tetanus/acellular pertussis/inactivated poliomyelitis vaccine) to boys and girls aged 9–14 years was also found to be safe and immunogenic when compared with those who received the vaccines nonconcomitantly.[31,32]

4vHPV Vaccine of Serum Institute of India (Cervavac™)

Recently, the 4vHPV vaccine of Serum Institute of India (Cervavac™) has been granted market authorization.

CERVAVAC™ is a quadrivalent HPV vaccine developed by the Serum Institute of India.[33]

Each dose of 0.5 mL contains:

- HPV type 6 L1 protein ≥ 20 µg
- HPV type 11 L1 protein ≥ 40 µg
- HPV type 16 L1 protein ≥ 40 µg
- HPV type 18 L1 protein ≥ 20 µg
- Al^{+++} ≤ 1.25 mg.

It is produced from Hansenula polymorpha.

In a pivotal, phase 2/3 trial, done in 9–26 years aged population, CERVAVAC™—induced IgG geometric mean titers (GMT) were >1,000 times higher than the baseline titers against all targeted HPV types. Postvaccination, at 7-month timepoint (1 month after the last dose), a 100% seroconversion was reported across all four vaccine types (Serotypes 6, 11, 16, and 18) in initially seronegative populations.

The vaccine has demonstrated comparable immunogenicity against licensed quadrivalent vaccine when administered to female and male aged 9–26 years.

Safety Profile

The most common adverse events noted were injection site pain and headache. The majority of adverse events were mild to moderate in severity and usually resolved within a few days of vaccination. All resolved without sequelae.

Indications

In girls and women 9 through 26 years of age for the prevention of the following diseases caused by HPV types, included in the vaccine:

- Cervical, vulvar, vaginal, and anal cancer caused by HPV types 16 and 18
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11
- CIN grade 2/3 and cervical AIS, and
- CIN grade 1 caused by types 6, 11, 16, and 18
- VIN grades 2 and 3
- VaIN grades 2 and 3
- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3.

In boys and men 9 through 26 years of age for the prevention of the following diseases caused by HPV types included in the vaccine:

- Anal cancer caused by HPV types 16 and 18
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11
- AIN grades 1, 2, and 3 caused by 6, 11, 16, and 18.

Contraindications

Hypersensitivity to the active substances or to any of the excipients of the vaccine. Hypersensitivity, including severe allergic reactions to yeast (a vaccine component), or after a previous dose of the vaccine.

Schedule

Individuals 9–14 years of age (boys and girls): Two-dose schedule (0.5 mL at 0 and 6 months). The interval between the 1st and 2nd dose should not be <5 months.

Individuals 15–26 years of age (females and males): 3-dose (0.5 mL at 0, 2, and 6 months) schedule. The second dose should be administered at least 1 month after the first dose and the third dose should be administered at least 3 months after the second dose. All three doses should be given within a 1-year period.

Safety of Human Papillomavirus 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.[25] 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 the HPV vaccine safety concern. However, the 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.[34]

Analysis from the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD), published in 2019, did not reveal any unexpected safety problems with Gardasil 9. This included multiple years of data.[34]

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.[27] 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.[7]

However, introduction of vaccine in program needs 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.[7]

Efforts are being made to scale up HPV vaccination for adolescent girls in India. Since 2016, HPV vaccination was introduced in the immunization programs in Punjab, Sikkim, and Delhi. With the current thinking of the feasibility of a single dose of HPV vaccination and the availability of an affordable Indian vaccine in the near future, HPV vaccination in the national immunization program is not too far off.[35]

Individual Use

The ACVIP recommends offering HPV vaccine to all females and boys 9–14 years, 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 and warts 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.

All the available vaccines are equally efficacious and safe for protection against cervical cancer and precancerous lesions as of currently available data. The quadrivalent and nonavalent vaccine additionally protect against anogenital warts.

Currently, only the 9-valent HPV vaccine is licensed in India for use in males.

Storage: The vaccines should be stored at 2–8°C and must not be frozen.

Dose: The dose is 0.5 mL intramuscular in deltoid.

Human papillomavirus 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 is administered in a sitting/lying down position and the patient should be observed for 15 minutes postvaccination.

Human papillomavirus 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.

Breastfeeding is not a contraindication for HPV vaccination. Available evidence does not indicate an increased risk of adverse events linked to the vaccine in either the mothers or their babies after administration of HPV vaccine to lactating females.[7]

In April 2022, the WHO Strategic Advisory Group of Experts (SAGE) on immunization recommended updating the dose schedules for HPV vaccines in national immunization programs.[36,37] The new dose schedules suggested are as follows:

- One or two-dose schedule for the primary target of girls aged 9–14 years
- One or two-dose schedule for young women aged 15–20 years
- Two doses with a 6-month interval for women older than 21 years.

Immunocompromised individuals, including those with HIV, should receive three doses if feasible, and if not, at least two doses. There is limited evidence regarding the efficacy of a single dose in this group.

Till date, this recommendation is not endorsed by the Government of India or IAP.

IAP Recommendations: Human Papillomavirus Vaccines

Routine vaccination in India:

- Both, 4vHPV and 9vHPV are currently available in India.
- *Minimum age:* 9 years.
- *9–14 years girls*: 4vHPV and 9vHPV are recommended in two-dose series with a minimum gap of 6 months between the doses.
- *9–14 years boys:* 9vHPV is recommended in a 2-dose series, with a minimum interval of 6 months between the doses (0–6 months).
- *15–45 years girls and women*: Three-dose schedule:
  - 4vHPV: (0, 2, and 6 months)
  - 9vHPV: (0, 2, and 6 months) till 26 years of age
- For immunocompromised individuals, three-dose series is recommended.
- In a two-dose schedule, the minimum interval between doses should not be <5 months. 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.
- In a three-dose schedule, the minimum interval between dose 1 and 2 should not be <4 weeks, the minimum interval between dose 2 and 3 should not be <12 weeks, and the minimum interval between dose 1 and 3 should not be <5 months.
- *If a vaccine dose is administered after a shorter interval, it should be re-administered after another minimum interval has elapsed since the most recent dose.*

Catch-up Vaccination

- Administer the vaccine series to females (4vHPV) at age 13 through 45 years and 9vHPV till 26 years (in females), if not previously vaccinated.
- Use recommended routine dosing intervals (see above) for vaccine series catch-up.

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3.13 INFLUENZA VACCINES

B Rajsekhar, Sunil Kumar Agarwalla

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 are 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.[1]

Influenza vaccine is most effective when circulating viruses are well-matched with viruses contained in vaccines. Due to the constant evolving nature of influenza viruses, the WHO Global Influenza Surveillance and Response System (GISRS)—a system of 142 National Influenza Centres in 115 countries, 6 WHO Collaborating Centres around the world, 4 WHO essential regulatory laboratories, and 13 WHO H5 reference laboratories continuously monitors the influenza viruses circulating in humans and updates the composition of influenza vaccines twice a year, for the Northern (February)

and Southern (September) hemisphere influenza seasons and the hemispheric specific vaccines are generally available 4–6 months later (April–May for SH and September–October for NH vaccines).[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 co-circulate as the new seasonal virus. Thereafter, it would exhibit antigenic drift; thus, more than one drifted variant may co-circulate.

In India, the first positive case of pdmH1N1 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.[2] pdmH1N1 now circulates as a seasonal influenza strain.

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 2017, deaths attributable to influenza accounted for 0·26% (95% UI 0.2–0-32) of all deaths. 5·6% (95% UI: 4.3–7.1) of global lower respiratory tract infections (LRTI) deaths were attributable to influenza, which corresponded to 145,000 (98,000–200,000) deaths across all ages. Nearly one-third of all influenza LRTI deaths occurred in India [26,000 (95% UI: 16,000–37,000)].[3]

The incidence of influenza episodes and associated acute lower respiratory infection (ALRI) is significantly higher in developing countries as compared to developed countries.[4] A recent systemic review[5] found that 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).

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 acute respiratory infections (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.[7]

According to the GBD 2017 study,[3] the figures in India have been shown in **Table 1**.

Influenza Network in India is comprised of 10 sentinel sites strategically located to cover major areas of India. Of the 44,127 nasal swabs collected from influenza-like illness (ILI)/SARI cases between 2009 and 2013, 6,193 (14.0%) were positive for influenza virus.[8]

TABLE 1: Mortality, morbidity, and hospitalisations due to influenza lower respiratory tract infections, 2017.

	Episodes	*Hospitalizations*	*Deaths*
Numbers (95% UI)	13,966,000 (9,449,000–19,552,000)	588,000 (196,000–1,611,000)	26,000 (16,000–37,000)
Per 100,000 (95% UI)	1,011.6 (684.4–1,416)	42.6 (14.2–116.7)	1.8 (1.2–1.7)

Source: Global Burden of Disease 2017.

TABLE 2: Year-wise number of cases and deaths from 2017 to 2022 (As on 30.11.2022).

Year	*Cases*	*Deaths*
2017	38,811	2,270
2018	15,266	1,128
2019	28,798	1,218
2020	2,572	44
2021	778	12
2022	12,881	399

Source: Seasonal Influenza A (H1N1): State/UT: Yearwise number of cases and deaths from 2017 to 2022* (As on 30.11.2022). Available at https://ncdc.gov.in/showfile.php?lid=280.

SWINE FLU OR A H1N1 PANDEMIC (TABLE 2)

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.[9] A disproportionate number of deaths occurred in Southeast Asia and Africa, where access to prevention and treatment resources are more likely to be limited.[8] 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.[10] 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.[11] 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.[12]

SEASONALITY OF INFLUENZA

Influenza occurs throughout the year, but its incidence has distinct peaks in most geographical areas. Whereas, in temperate regions,

influenza epidemics occur in the winter in tropical regions, influenza occurs throughout the year with peaks in winter or monsoons.

Every season's epidemic or outbreak lasts for 6–8 weeks or longer. Reasons for seasonality may include effects of humidity and temperature on virus survival and crowding inside home in winters. The onset, peak, duration, and size of outbreak in a season may vary with the virus's antigenic variation, virulence, transmissibility and population immunity.

Globally, since September 2020, influenza activity was mostly reported from countries located in the tropics and subtropics as well as some countries present in the temperate zone of the northern hemisphere. India was among the tropical Asian countries that reported the greatest detection of influenza.

Due to the diverse climate across India, there are vast variations in the impact of influenza from the northern to southern regions. In India, influenza season differs in various parts of country. In India, the disease is observed to have two peaks: one during the winter (January to March) and the second during the post-monsoon season (August to October). However, it may vary from state to state. The month-wise trend of pan India for year 2014–2019 is described in **Figure 1**.

In northern part of India, influenza peak is in January to March which is similar to Northern hemisphere. In central India (e.g., Delhi,

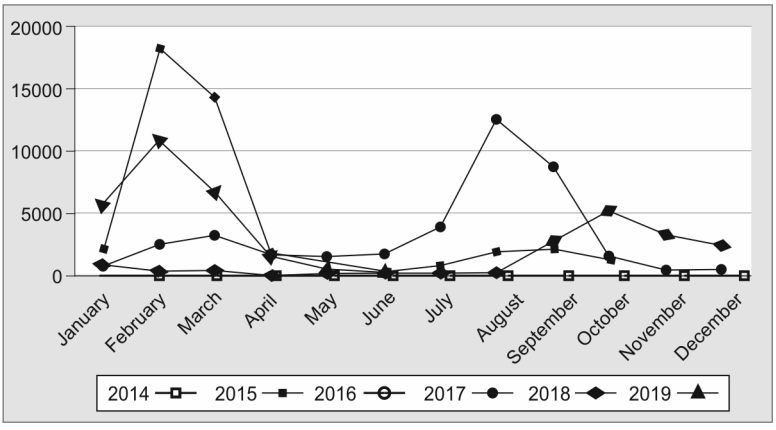

Fig. 1: Monthwise trend of cases reported in India since 2014–2019 (data up to 23rd June, 2019).

Lucknow, Nagpur, and Pune), influenza peak is in July to September and in southern part of India (e.g., Chennai and Vellore), it occurs in September to November. Thus, it is a mixture of both Northern and Southern hemisphere seasons.

Peaks of influenza were observed during July–September coinciding with monsoon in cities (north, west, southwest, central, and east) and northeast parts of India, whereas Chennai and southeast revealed peaks in October–November, coinciding with the monsoon months in these cities. In Srinagar, the northern most city at 34°N latitude influenza circulation peaked in January–March in winter months.[8]

The patterns of circulating strains also vary from year to year. In 2009 and 2010, co-circulation of A/H1N1pdm09 and type B was seen, H3N2 was the predominant circulating strain in 2011, co-circulation of A/H1N1pdm09 and influenza B in 2012 and return of A/H3N2 in 2013. In 2019, H1N1pdm09 predominated, in 2021: H3N2 followed by B-Victoria and in 2022, H1N1pdm09 predominated.[8]

INFLUENZA VACCINES

The influenza vaccine, popularly known as the "flu shot", is the first protective step against the virus. With changes in the major influenza strains year-on-year, it remains essential to take the latest influenza vaccine, comprising an updated composition to provide adequate and relevant immunity.[6]

Most of the current seasonal influenza vaccines include two influenza A strains and two influenza B strain (quadrivalent). The trivalent vaccines are not in use, in most countries. Globally, quadrivalent inactivated vaccines (QIVs3) 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, although the need for two doses remains. Quadrivalent inactivated influenza vaccine (QIIV4) formulation for seasonal influenza aims in providing more 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 in use. Most influenza vaccines are split-product vaccines, produced from detergent treated, highly-purified influenza virus, or surface antigen vaccines containing purified HA and neuraminidase. All currently available quadrivalent 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 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.

Influenza vaccine is most effective when circulating viruses are well-matched with viruses contained in vaccines. Due to the constant evolving nature of influenza viruses, the WHO Global Influenza Surveillance and Response System (GISRS)—a system of National Influenza Centres and WHO Collaborating Centres around the world—continuously monitors the influenza viruses circulating in humans and updates the composition of influenza vaccines twice a year, for the Northern Hemisphere in February and for the Southern Hemisphere in September every year.

There are occasions when the compositions of the NH and SH vaccines may be similar.

Influenza vaccination is recommended every year, for children of 6 months to 5 years of age and for the high-risk groups, beyond 5 years. IIV is administered intramuscularly.

Efficacy and Effectiveness of Inactivated 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]

Inactivated vaccines have efficacy of 59% (95% CI: 41–71%) and effectiveness at 36% (95% CI: 24–46%).[13] There is no published data on efficacy/effectiveness of influenza vaccines from India.

Quadrivalent demonstrated 63.2% efficacy against moderate-to-severe influenza and 49.8% efficacy against influenza of any severity in children 6 months through 35 months of age.

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.[14]

Safety of Inactivated 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, IIV 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.

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. Severe allergic

reaction to vaccine component or following a prior dose, is a contraindication for IIV.

Contraindication: Severe allergic reaction to vaccine component or following a prior dose.

Precaution:

- Moderate or severe acute illness
- History of GBS within 6 weeks of receipt of influenza vaccine
- History of egg-allergy.

Those who report having had reactions to egg involving symptoms other than urticaria (e.g., angioedema or swelling, respiratory distress, light-headedness, sweating, palpitations or recurrent vomiting) or who required adrenaline or another emergency medical intervention should be vaccinated in an inpatient or outpatient medical setting. The should be administered by a healthcare provider who is able to recognize and manage severe allergic reactions.

Uniform Dosing for Inactivated Influenza Vaccines

The whole virion vaccines were administered at half the standard dose (7.5 μg) to reduce reactogenicity and febrile convulsions observed with the full dose (15 μg). However, the immune response in young children was very variable, especially against the B strains in the vaccine. This was particularly significant in children younger than 3 years of age, who were vaccine-naïve.

Studies with the modern split-virus and subunit vaccines, have generally shown comparable reactogenicity and non-inferior immunogenicity with the full dose, in comparison with the half dose, in children 6–35 months of age. Superior GMTs were demonstrated against both vaccine B strains in children 6–17 months of age and unprimed children 6–35 months of age. In children 6–35 months of age, the quadrivalent vaccine in a dose of 0.5 mL, demonstrated an efficacy of 63% (97.5% CI: 52–72) against moderate-severe influenza, in a season when there was a 68% mismatch between the vaccine strains and the strains isolated in the study.[15] Several countries including USA, Finland, Australia, UK, New Zealand, Canada, have adopted a uniform dosage schedule for all age groups.

Dosage and Schedule

- 0.5 mL (15 μg) > 6 months of age
- From 6 months to 8 years for the first time, 2 doses of IIV to be given 4 weeks apart.
- *>8 years:* Single dose
- Revaccination is recommended with a single annual dose, till the age of 5 years. In those at high risk of influenza complications, annual revaccination may be continued beyond the age of 5 years.

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%).

A quadrivalent live-attenuated vaccine for intranasal application containing two influenza A strains and two influenza B strains, Nasovac S4, is marketed in India. A single intranasal dose of 0.25 mL in each nostril, is recommended above the age of 2 years.[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.

Contraindications:

- Severe allergic reaction to vaccine component or following a prior dose
- Concomitant aspirin- or salicylate-containing therapy in children and adolescents
- Children aged 2 through 5 years who have had a wheezing episode in the past 12 months
- Children who are immunosuppressed
- Close contacts and caregivers of severely immunosuppressed persons

- Pregnancy
- Receipt of influenza antiviral medication (oseltamivir and zanamivir) within the previous 48 hours.

Precautions:
- Moderate or severe acute illness with or without fever
- History of GBS within 6 weeks of receipt of influenza vaccine
- Asthma in persons aged ≥5 years
- Other underlying medical conditions that might predispose to complications after wild-type influenza infection [e.g., chronic pulmonary, cardiovascular (except isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus)].

Advisory Committee on Vaccines and Immunization Practices Recommendation

Advisory Committee on Vaccines and Immunization Practices (ACVIP) endorses the use of a uniform dosing schedule of inactivated influenza vaccines (15 μg/0.5 mL) for all children older than 6 months.

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 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.

Prioritization of target groups: (1-Highest priority, 4-Lowest priority)

1. Elderly individuals (>65 years) and nursing-home residents (the elderly or disabled)
2. Individuals with chronic medical conditions including individuals with HIV/AIDS, and pregnant women (especially to protect infants 0–6 months)
3. *Other groups:* Healthcare workers including professionals, individuals with asthma, and children from aged 6 months to 2 years.
4. Children aged 6–18 years, and healthy young adults.

Inactivated Influenza Vaccine in Pregnancy

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.

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.

When to Give?

The WHO guidelines recommend that the latest strain of influenza vaccine should be taken 2 weeks prior to the onset of the influenza season for a particular region.

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.[16]

Hence, there is a need for a staggered approach in vaccination timing, April–May for the entire country, except Tamil Nadu and southern Kerala (October–December), and northern parts (Jammu and Kashmir in October–December).

IAP recommendations.

- Risk groups for severe influenza include pregnant women, children aged <5 years, elderly and individuals with comorbids like HIV/PID, chronic lung, cardiac disease, etc.
- *Minimum age:* 6 months for IIV, 2 years for live attenuated influenza vaccination.
- *First-time vaccination: 6 months to 8 years:* Two doses 4 weeks apart, 9 years and above: single dose
- Annual revaccination with single dose
- Universal dose 0.5 mL IM
- Quadrivalent influenza vaccine is preferred over trivalent influenza vaccine
- There is no much difference in efficacy between split virion versus subunit vaccine
- Apart from known severe allergy to vaccine components or to a previous dose of IIV, there are no contraindications
- Use the most recent strains containing vaccine, in the premonsoon period

Which Hemispheric Strain should be Administered?

World Health Organization classifies India under the "South Asia" transmission zone of influenza circulation and reviews strain circulation in the country during both the meetings, i.e., February (for northern hemisphere) and September (southern hemisphere). India extends from 8° to 37° N latitudes, with climatic conditions varying from temperate to tropical types. A major part of the country has year-long circulation of influenza, with a smaller peak in winter months, whereas, northern India experiences another peak during winter just like northern hemisphere pattern. However, there is a tendency for strains to "spill" from one to another. Hence, hemispheric-specific vaccine recommendations will not be applicable, and one should use the vaccine that has the "most recent strains" irrespective of the hemisphere-specific formulations.

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3.14 JAPANESE ENCEPHALITIS VACCINES

Srinivas Kalyani, Srinivas G Kasi

BACKGROUND

Japanese encephalitis virus (JEV), a mosquito-borne flavivirus, is the most important cause of viral encephalitis in Asia based on its frequency and severity. The JEV has shown a tendency to extend to other geographic regions. Case fatality rates (CFR) averages 30% and a high percentage of the survivors are left with permanent neuropsychiatric sequelae.[1]

Currently, an estimated 3 billion people live in the 24 countries, mainly in the South-East Asia and Western Pacific Regions, considered at risk of JE.[2] JE is endemic throughout most of Asia and parts of the western Pacific. Map of JE endemic countries is shown in **Figure 1**.

For travelers to Asia, the risk of JE is very low but varies based on season, destination, duration, and activities.[3] Risk is likely to be

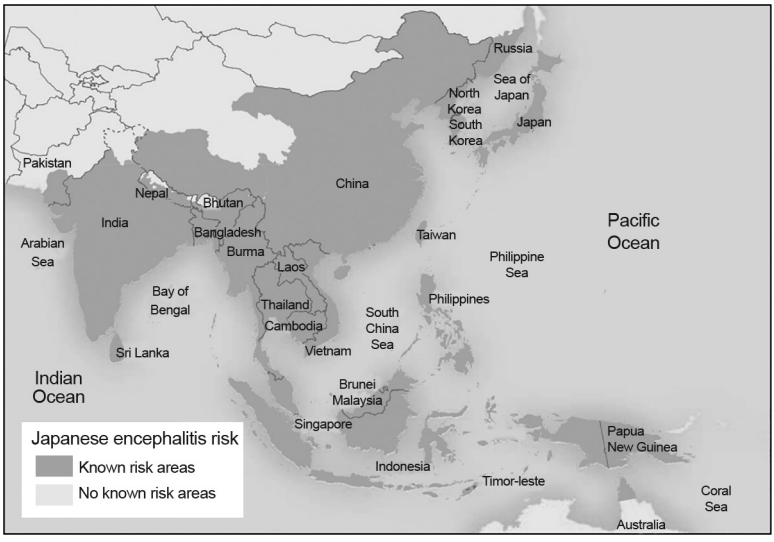

Fig. 1: Japanese encephalitis endemic countries.
Source: Hills SL, Lindsey NP, Fischer M. Japanese encephalitis. In: CDC Yellow Book 2020: health information for international travel. New York, NY: Oxford University Press. 2019:248-57.

higher for expatriates or travelers with longer duration of travel or whose plans include extensive outdoor activities in rural areas.

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).

Acute encephalitis syndrome has heterogeneous etiology and JE remains an important contributing agent (5–40%) to AES in India.[4]

GLOBAL BURDEN

Japanese encephalitis is one of the most important causes of viral encephalitis in Asia.

According to WHO, nearly 50,000 cases of JE occur worldwide per year and 15,000 of them die.[5] In endemic areas, the annual incidence of disease ranges from 10 to 100 per 100,000 population. It is postulated that the actual incidence of JE is nearly 10 times higher than reflected in recent reports to WHO.[6,7]

A recent systematic review of the literature estimates 67,900 cases of JE each year, with approximately 13,600–20,400 deaths, and an overall incidence rate of 1.8/100,000.

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

Presently, 368 districts across 22 states have been identified as JE endemic districts. 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. The risk is highest in children aged 1–15 years in rural areas and in the monsoon or postmonsoon season.

SEASONALITY

Within the JE-endemic region, there are two typical patterns of transmission:

1. In areas with temperate climates (including China, Japan, South Korea, Nepal, northern Vietnam, and northern India), most cases occur over a period of several months when the weather is warmest, usually after the monsoons begin or associated with heavy rainfall.[8,9] The peak months of transmission and the length of the season vary from place to place. There are sometimes large, explosive outbreaks.
2. In areas with tropical climates (including Cambodia, Indonesia, southern Vietnam, and southern Thailand), there is year-round transmission. An increase in cases may be observed during the rainy season.[10,11] In endemic areas, JE typically affects children, 15 years of age, and by early adulthood, the majority of the population has protective immunity following natural exposure to JEV as a result of ongoing environmental transmission.

Transmission

Japanese encephalitis virus is transmitted in an enzootic cycle involving mosquitoes and vertebrate amplifying hosts, primarily pigs and wading birds. Humans are incidental and dead-end hosts in the JEV transmission cycle as they do not develop sufficiently high viremia to infect feeding mosquitoes. Therefore, mosquitoes do not transmit the virus directly from one person to another person.

Mosquitoes of the *Culex vishnui* subgroup, particularly *Culex tritaeniorhynchus*, are the major vectors of JEV, although JEV has been isolated from over 30 mosquito species. *C. tritaeniorhynchus* commonly breeds in rice fields, marshes, and other shallow pools

of water. It is an evening and night-time biting mosquito and mainly feeds outdoors, preferentially on large animals and birds and only infrequently on humans.

Pigs and wading birds, such as herons and egrets, are the most important hosts for maintenance and amplification of JEV. Pigs are key host as they develop high levels of viremia, and in Asia, large numbers of pigs are frequently kept near human dwellings.

JE cases are more frequently in rural areas, however, Japanese encephalitis cases are occasionally reported from urban or periurban areas.[4] Transmission via infected blood products has been reported.[12]

Age Distribution

However, when the virus enters new geographic areas where there is no immunity, JE affects both adults and children.[10] In regions where childhood immunization programs have been introduced, the age distribution of disease shifts to older ages.[9,13] Among immunologically naïve travelers visiting JEV-endemic regions, the disease can affect individuals at any age.[14]

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.[15] ICMR and NIV, Pune investigated adult AES epidemic in West Bengal and Assam in 2014. The study revealed JEV as causative agent in 49.4% of AES. 70.8% were adults with case fatality ratio of 28.9%. JEV infection was detected in 134 (49.4%) among 271 AES cases tested and most of them (79.1%, 106/134) were adults.[16]

OUTBREAKS OF JAPANESE ENCEPHALITIS IN INDIA

In India, 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.[17]

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

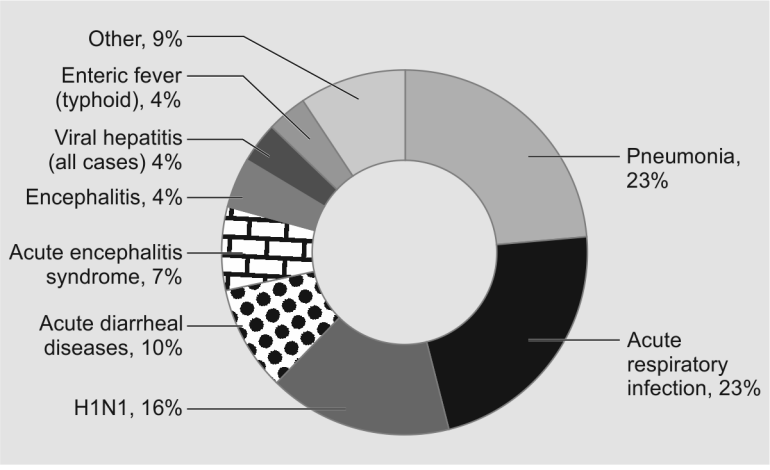

Fig. 2: Percentage distribution of mortality reported in communicable diseases in 2017.
Source: National Health Profile 2018, 13th issue, Central Bureau of Health Intelligence, DGHS, MoH and FW, GOI, p. 75.

and 528 deaths. Similarly, JE cases in Uttar Pradesh were confined predominantly in Gorakhpur during 2007 reporting 3,024 cases and 645 deaths.[18] The reported mortality rate varies between 8.5 and 72%.[19,20]

The CFR due to AES or JE in India has been around 17% with wide variations in states **(Fig. 2)**.

Acute encephalitis syndrome or encephalitis contributed to 11% of mortality due to communicable diseases in 2017 **(Fig. 3)**.[21]

Reasons for increase in JE cases while major epidemics are not reported since 2015 are presumably due to spread of JE to previously nonendemic states and spread to new districts within endemic states, increase in adult cases, and increased surveillance efforts.

VACCINES

World over, following vaccines were available for use against JE **(Fig. 4)**:

- Mouse brain-derived inactivated JE vaccine (JE-VAX): This vaccine is no longer in clinical usage.

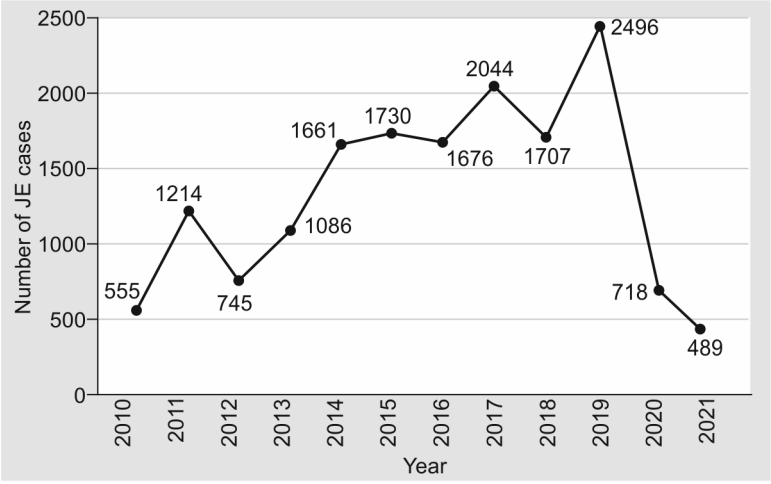

Fig. 3: Confirmed cases of Japanese encephalitis (JE) in India.
Source: Directorate of National Vector Borne Disease Control Programme, Delhi. [online] Available from http://nvbdcp.gov.in/Doc/je-aes.pdf. [Last accessed December, 2022].

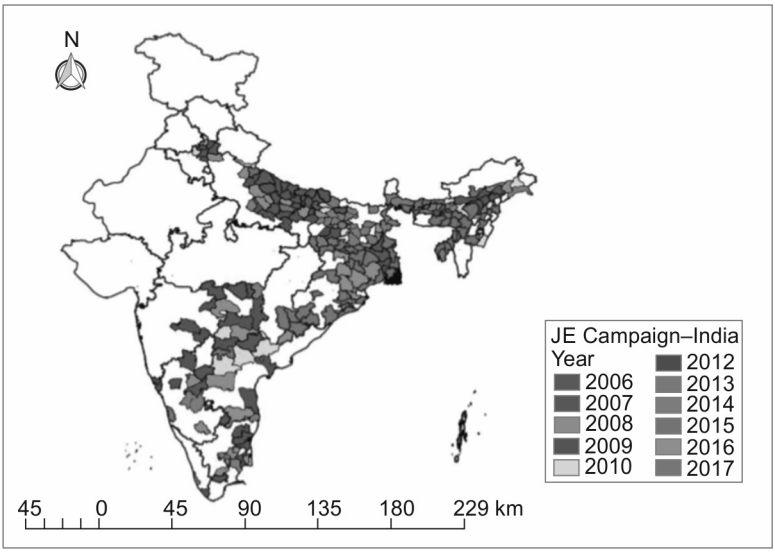

Fig. 4: Operational Guide, Japanese encephalitis (JE) vaccination in India.

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)	Lyophilized active component to be reconstituted with excipient diluent before use	Two vial set (active + excipient)	1
		Public sector only		Two vial set (active + excipient)	5
JE vaccine (inactivated)	Bharat Biotech	JENVAC	*Liquid:* Ready to use	Vial	1

- 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 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, neuro-attenuated 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.[22] 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 200 million children have been vaccinated.[17] Extensive use of this and other vaccines has significantly contributed to reducing 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.[17] The price per dose of the vaccine is comparable to the 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.[23] It can also be offered to all susceptible children up to 15 years as catch-up vaccination.[18]

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.[23]

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.[23]

Efficacy and Effectiveness

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%.[23-25] 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.[6]

Efficacy in Nepal

A field trial in Nepal in 1999 reported efficacy of a single dose of 99.3% in the same year and 98.5% 1 year later.[26,27] At 5 years, the protective efficacy was 96.2%.[28] 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, followed by integration in UIP in a 2-dose schedule, at 9 months and 16–24 months.[29,30]

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.[31] 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.[32]

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 versus single dose of SA 14-14-2 vaccine in Assam.[32]

A recent study in children, demonstrated a vaccination effectiveness of 86.7% (95% CI: 30.8–94.7).[33]

A study done in adults in Assam, demonstrated a VE of 77.0 (95% CI: 67.0-83.0) over 7 years. Vaccine effectiveness decreased from 91% (95% CI: 73.0-97.0) in first year of vaccination to 71% (95% CI: 21.0–90.0) at 6 years post-vaccination.[34]

Safety

An estimated 300 million children have been immunized with this vaccine without apparent complication.[23] 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.[35]

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.[36-38] IXIARO® has now been approved by the US-FDA and EU for use in children from the age of 2 months onward.[39] 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 RCT conducted in the Philippines,[40] and favorable interim data from a second Phase III trial in EU, US, and Australia.[40] The safety profile of the test vaccine was good, and its local tolerability profile was more favorable than that of the mouse brain vaccines.

A phase 3 uncontrolled study conducted on neutralizing antibody persistence in pediatric travelers from non-JE-endemic countries following vaccination with IXIARO®. Results showed SPRs remained high but declined from 100% 1 month after primary immunization to 91.3% at month 7 and 89.5% at month 36. GMTs declined considerably from 384.1 by day 56 to 60.8 at month 36. The decline in GMT observed in this study, together with previous data with IXIARO® support the recommendation for a booster dose in children who remain at risk of JE from 1 year after the primary series of IXIARO®, consistent with the recommendation for adults. No long-term safety concerns were identified.[40,41]

Indian Trial

A half-dose given to young children (1–3 years of age) had 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.[36] 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 (95% CI, 106–380), and 230 (95% 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.[36]

JEEV®—the Indian Variant of IC51, IXIARO by Biological E Ltd.

Biological E Ltd. has 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.[42,43]

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.

Geometric mean titers 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.[44]

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 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.

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 among 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.

Immunogenicity assessment in some subjects who withdrew after the first dose showed that the seroprotection rates were 81.82%, with GMTs of 40.90, after 12 months.

In a phase 4 study, in which participants received a single dose of the vaccine. At day 360 (postvaccination), GMTs were 33.7 (95% CI, 27.9–40.77) and SPR was 81.7% (95% CI, 74.9–87.3). GMTs at most time points in the JENVAC group were significantly higher than the comparator, SA 14-14-2 group. The results of this study led to the DCGI licensure of a single dose of Jenvac™.

Live-attenuated Recombinant SA14-14-2 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.[37] 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.[43] 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).[6] This vaccine has been licensed in Australia and is under review in Thailand.[44] The clinical development of this vaccine (IMOJEV) is currently on hold in India due to delay 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. Presently, 368 districts across 22 states have been identified as JE endemic districts. Of these, JE vaccine has been introduced in RI in 297 districts across 21 states.

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 primary schedule consists of two doses of 3 μg/0.5 mL for children aged ≥1 to ≤3 years and two doses of 6 μg/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 in endemic areas and need of boosters are still undetermined.[42] In February 2011, US ACIP approved recommendations for a booster dose of JE-VC (IXIARO®) in adults.

JENVAC® by BBIL

The primary schedule consists of 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.[42]

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.

JE vaccination via national campaign followed by national routine delivery was the most cost-effective strategy.[45]

Any of the three available JE vaccines can be used in "routine immunization", in a 2-dose schedule: the 1st dose at 9–12 months and the 2nd at the age of 16–24 months in the JE-endemic areas.

The Scientific and Technical Subcommittee recommended interchangeability on use of three JE vaccines.

A single dose of any of the three vaccines formulations (JenVaC, LAJEV or 6-μg Jeev) may be used in children (1–15 years of age) as well as adults (above 15 years) during JE vaccine campaigns in endemic areas.

IAP ACVIP supports the government's decision to include JE vaccine in its UIP 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. However, there is need to undertake periodic assessment of the effectiveness of the employed JE vaccine.

Japanese Encephalitis 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, 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. The 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.

A study was done for effectiveness of JE vaccine SA 14-14-2 and impact of immunization among adults in Assam. Vaccine effectiveness among adults was 90% in 2012; it declined to 82% in 2013. Following the second round in 2014, a marginal increase in vaccine effectiveness was noted (84%). Subsequently (2015–2018), VE stabilized at 70%. Incidence rate during the prevaccination period was 11.5 that came down and maintained at 5 (postvaccination). In

Japanese encephalitis (JE) vaccines: IAP recommendations.

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:
  1. Live-attenuated, cell culture-derived *SA 14-14-2*
  2. Inactivated JE vaccines, namely "Vero cell culture-derived SA 14-14-2 JE vaccine" (*JEEV*® by BE India)
  3. "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 MR vaccine and
  - Second dose at 16–18 months along with 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-FDA: 2 months)
  - *Primary immunization schedule:* Two doses of 3 µg 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.

Nepal, the same vaccine showed 96.2% VE among children (5 years' postvaccination) with coverage of above 70% that brought down incidence rate <1. Therefore, high vaccine coverage (at least 70%) seems to be a prerequisite for achieving the desired results.[46]

JE 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.

A severe allergic reaction after a previous dose of JE-VC, any other JE vaccine, or any component of JE-VC is a contraindication to administration of a subsequent dose. JE-VC contains protamine sulfate, which is known to cause hypersensitivity reactions in some individuals; it does not contain gelatin or murine proteins.[47-49]

Pregnancy is a precaution for the use of JE-VC. Vaccination with JE vaccine usually should be deferred because of a theoretical risk for the developing fetus. However, pregnant women who must travel to an area in which risk for JE is high should be vaccinated if the benefits outweigh the risks of vaccination to the mother and developing fetus.

Concomitant administration of JE-VC with other vaccines, inactivated hepatitis A, rabies and meningococcal vaccines has been found to be safe and immunogenic.[50]

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3.15 MENINGOCOCCAL VACCINES

Ananda Kesavan TM, Harish Kumar 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.

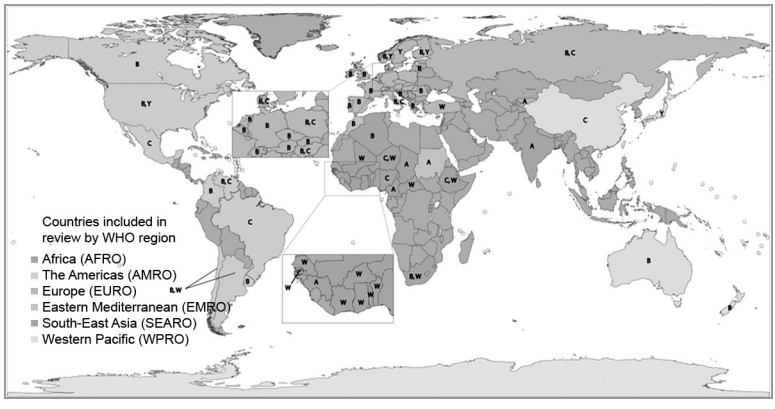

Fig. 1: Serogroups (>25% of the total cases) of *N. meningitidis* reported from various countries between 2010 and 2016.
Source: From the Reference #4.

A recent global systemic review and survey found that different serotypes are prevalent in different parts of the world.[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 <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.

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 such as Mumbai and 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 the 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).

Meningococcal Polysaccharide Vaccines

These are either bivalent (A + C) or quadrivalent (A, C, Y, and W-135) and contain 50 μg of each of the individual polysaccharides,

TABLE 1: Licensed meningococcal vaccines 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)	• Mencevax(GSK) • Quadri Meningo (BioMed) • Menomune • (Sanofi Pasteur	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
Presently, these vaccines are not marketed in India	*Bivalent* (Serogroups A and C contains individual capsular polysaccharides 50 µg each)	Bi Meningo, BioMed		0.5 mL, IM
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)	• Menactra • Sanofi Pasteur	Lyophilized, sterile distilled water	• >24 m: 0.5 mL by deep IM, revaccination after 3–5 years in high-risk children and adolescents • 9 m–23 m: 2 doses 12 weeks apart
	Meningococcal (Groups A, C, Y, and W-135) oligosaccharide diphtheria CRM197 conjugate vaccine	• Menveo • Glaxo SmithKline	MenA powder and MenCWY solution that must be combined prior to administration	• >2 years: 0.5 mL, IM • Revaccination after 3–5 years in high-risk children and adolescents
	Monovalent (Serogroup A: 10 µg of group A polysaccharide conjugated to 10–33 µg tetanus toxoid, with alum as adjuvant and thiomersal as preservative). *Licensed but not marketed in India*	Serum Institute of India Ltd.	Lyophilized vaccine	0.5 mL IM single administration for individuals 1–29 years of age

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). Presently, these vaccines are not marketed in India.

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 <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.

Quadri Meningo™ [Meningococcal polysaccharide vaccine (Group A, C, Y, and W-135) IP] by Bio-Med is available in India. Vaccination is recommended in regions of endemic infection, travelers to countries with epidemic meningococcal disease (Hajj pilgrims), household or institutional contacts, military recruits. It also

recommended for subjects living in closed communities and close contact of patients/carriers of meningococcal group A, C, Y, and W-135.

Meningococcal Conjugate Vaccines

Currently, two different types of MCVs are licensed in India. The quadrivalent conjugate vaccines include Menactra® from Sanofi Pasteur and Menveo from Glaxo SmithKline. The monovalent vaccine is MenAfriVac 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, and Y) meningococcal conjugate vaccine using diphtheria toxin as carrier protein (A, C, W-135, and 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 and the IAP/ACVIP has endorsed a similar schedule. 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 suggests 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 PCV-13 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 PCV-13 and MenACWY-D, and PCV-13 should be administered first.[11]

A safety and immunogenicity open label nonrandomized multicentric phase III trial of the MenACYW-DT vaccine among Indian children, adolescents and adults, found a robust and protective immune response 30 days postvaccination 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]

Quadrivalent Meningococcal Polysaccharide-protein Conjugate Vaccine (MenACW-135Y Menveo®, Manufactured by GlaxoSmithKline)

Menveo is meningococcal group A, C, W-135, and Y conjugate vaccine where CRM-197 is used as the conjugating protein. This vaccine contains meningococcal group A capsular oligosaccharide 10 μg in a lyophilized form, and meningococcal group C, W-135, and Y capsular oligosaccharides 5 μg each in a liquid form. All the antigens are conjugated to *Corynebacterium diphtheriae* CRM-197 protein. The volume for a single dose is 0.5 mL. This vaccine is supplied in two vials; the lyophilized MenA component which is to be dissolved in the liquid component containing MenCWY.

MenACWY-CRM-197 was studied in children and youth (2–5 years, 6–10, and 11–18 years age groups). It showed noninferiority to all serogroups in 11–18 age group. Noninferiority could not be established in other groups. However, pooled estimates in age groups 2–10 years and 11–18 years were noninferior to MenACWY-DT. Antibodies persist up to 5 years postvaccination. This can be coadministered with other vaccines.

The seroresponse rates at 1 month following vaccination were 72%, 88%, 55%, and 71% for serogroups A, C, W, and Y, respectively. No safety concerns were there and the vaccine was well tolerated. This vaccine is licensed for use as a single IM dose in >2 years of age in India. In the USA, this vaccine is licensed for use in 2 months through 55 years. The safety and efficacy of this vaccine has not yet been established below 2 years of age in India.

A quadrivalent vaccine MenACWY-TT (MenQuadfi) has also been licensed in the USA in April 2020 for age 2 years or older. This

vaccine is licensed in Europe for use in children as young as 6 weeks of age. This vaccine is not available in India.

Pentavalent Meningococcal Vaccine

A single pentavalent vaccine against meningococcal A, B, C, Y, and W is being tested in different phases. In an ongoing phase 2 randomized controlled trial in healthy adolescents and young adults, preliminary results found MenABCWY noninferior to separate administration of MenACWY and MenB vaccines. There was more than fourfold rise in serum bactericidal human complement (hSBA) against each of the 4MenB strains. The vaccine was found safe and well tolerated.[1]

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 the 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 IM 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 IM 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: (1) Memory response, (2) herd immunity, and (3) 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 <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, >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 older 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 years 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.

INDIAN ACADEMY OF PEDIATRICS 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:

- *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 MenA disease. Since majority of documented outbreaks in India are caused by MenA, monovalent MCV, like PsATT should be employed in mass vaccination.
- *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 2 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, and daycare contacts) single dose of appropriate group MCV is recommended.

- *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 >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. Single dose of polysaccharide vaccine also useful.
- *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 Serum Institute of India 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 among 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)**:

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 MenACWY-CRM197 by GSK and monovalent group A vaccine (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.

- Active case surveillance
- Early diagnosis and prompt treatment
- Chemoprophylaxis of close contacts (household members and 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.

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3.16 RABIES VACCINES

Bhaskar Shenoy, Sanjay Marathe

BACKGROUND

Rabies is a neglected zoonotic disease responsible for an estimated 59,000 human deaths annually, of which 18,000–20,000 deaths occur in India **(Fig. 1)**. Rural populations in Africa and Asia are predominantly affected, and approximately 40% of cases occur in children under the age of 15 years. As per the national multicentric rabies survey done in 2003,[1] about 17 million animal bites occur annually out of which about 35% of these are in children.[2] 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.[3] Rabies is transmitted through bites and scratches from infected animals. Human-to-human transmission occurs almost exclusively as a result of organ or tissue transplantation (including cornea). Dogs are responsible for up to 99% of human rabies cases. The incubation period for rabies is typically 2–3 months but may vary from 1 week to few years, dependent upon factors such as the location of virus entry and viral load. Although fatal once clinical signs appear, rabies is preventable

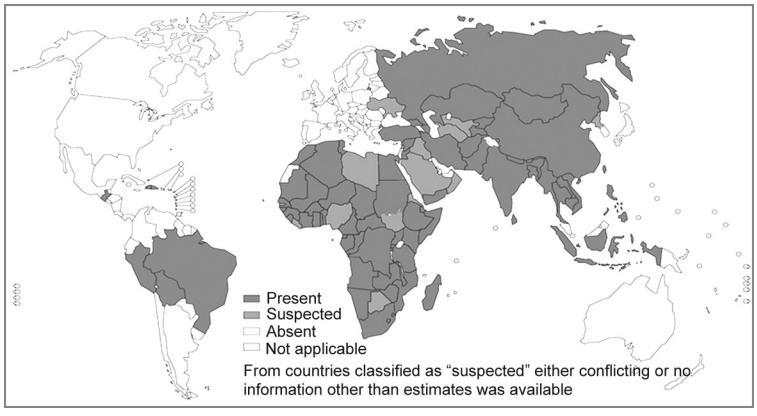

Fig. 1: Global distribution of deaths occurred due to rabies.

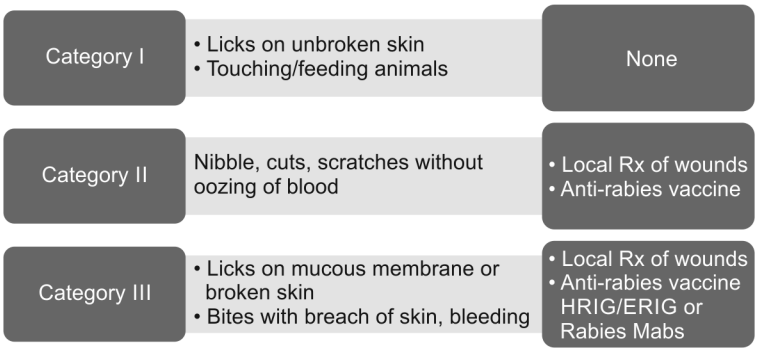

Fig. 2: category of wounds. (ERIG: equine rabies immunoglobulin; HRIG: human rabies immunoglobulin)
Source: World Health Organization (WHO) Expert Consultation on Rabies, third report: WHO Technical Series Report No. 1012, Geneva, 2018 (ISBN 978-92-4-121021-8).[4]

through (i) mass dog vaccination to control disease at its source; (ii) awareness of rabies and the need to seek treatment if exposed; (iii) timely post-exposure prophylaxis (PEP) for people potentially exposed to rabies; and (iv) preexposure prophylaxis (PrEP) for those at high risk of rabies virus exposure.

CATEGORY OF WOUNDS (FIG. 2)

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.

INITIAL CARE OF ANIMAL-BITE WOUNDS

- The first step is thorough cleansing of the wound with soap and flushing under running water for 10 minutes.
- This should be followed by application on the sites of exposure, a virucidal agent such as 70% alcohol or povidone iodine.
- Antimicrobials and tetanus toxoid should be given if indicated.
- Any suturing of wound should be avoided. When suturing is unavoidable for purpose of hemostasis, it must be ensured that rabies immunoglobulin (RIG) has been infiltrated in the wound prior to suturing.

  Proper wound care will reduce the viral load by at least 50%.

MANAGEMENT

World Health Organization recommends two main immunization strategies for the prevention of human rabies:

1. Postexposure prophylaxis which includes extensive and thorough wound washing at the RABV-exposure site, together with RIG/Mab administration if indicated, and the administration of a course of several doses of rabies vaccine.
2. Preexposure prophylaxis which is the administration of several doses of rabies vaccine before exposure to RABV.

Passive Immunization

Monoclonal Antibodies

- *Rabishield* (Serum Institute of India) is a recombinant human immunoglobulin G1 (IgG1), antirabies monoclonal antibody (SII RMab), which 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

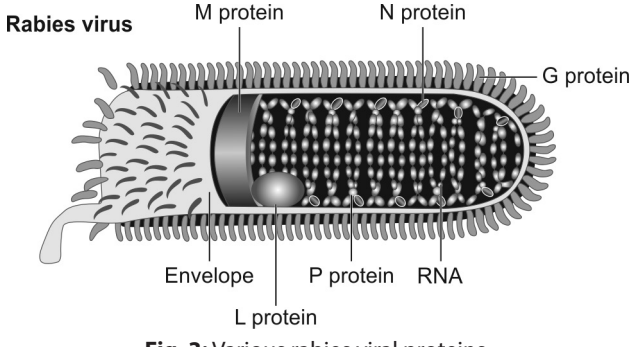

Fig. 3: Various rabies viral proteins.

a well-established in vivo model of PEP.[5] Advantages of RMab include easier to produce in bulk and adverse reactions of blood born products are avoided. Skin tests are not necessary before administration of Mabs.

Dose: 3.33 IU/kg.

Post-marketing surveillance following the use of 50,000 vials has not reported any serious adverse events. RMab can be administered till 7 days after the first dose of vaccine.

Presentation: 100 IU/2.5 mL (40 IU/mL) vial and 250 IU/2.5 mL (100 IU/mL) vial.

- *Twinrab (Zydus Cadila):* Twinrab is a combination of two murine monoclonal antibodies, docaravimab (62-71-3) and miromavimab (M777-16-3). They bind to two different epitopes on the G protein expressed on the surface of rabies virus. The two monoclonal antibodies bind to and neutralize both, rabies and rabies-like viruses, preventing their infection into the neighboring cells. The cocktail of antibodies was also found to neutralize rabies virus strains isolated from dog, canine, human, and bovine sources from southern parts of India.[6]

  Composition, dosage, and indication: Twinrab is a sterile preservative free clear colorless liquid solution for infiltration. Twinrab is available in two different strengths, viz.:

  1. 2.5 mL vial containing 1500 IU (600 IU/mL) of twinrab
  2. 1 mL vial containing 600 IU (600 IU/mL) of twinrab.

  The recommended dose of twinrab is 40 IU/kg of bodyweight. Twinrab is indicated for postexposure prophylaxis in individuals with suspected rabies exposure. Twinrab must always be used in combination with rabies vaccine as part of postexposure prophylaxis in line with the recommendation of WHO.[7]

Recommendations for monoclonal antibodies: ACVIP strongly recommends the use of MRabs over RIGs in the management of category 3 bites.

Human monoclonal rabies antibody (Rabishield) and murine cocktail, monoclonal rabies antibodies (TWINRAB), both are available in India and recommended for the postexposure management of suspected rabies exposure.

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:

1. Human rabies immunoglobulin (HRIG)—dose is 20 U/kg bodyweight, maximum dose 1,500 IU
2. 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 the 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]

Indications for RIG/Mabs: All category III bites, all wild animal bites, and class II bites in immunocompromised should be given RIG or MAbs. RIG/MAb is not necessary if the patient has received a complete course of PEP or PrEP previously. Since rabies has a long incubation period, PEP, including RIG/Mabs and vaccine, may be administered weeks, months, or even a few years after a category III exposure, if no PEP was administered earlier.

While RIG/Mabs are recommended only locally at the sites of exposure, full dose IM may be administered for aerosol exposures. Flushing of conjunctive for conjunctival exposure and rinsing of mouth with RIG/Mabs, for oral mucosal exposure, without bleeding, is recommended.

Administration: RIG/Mabs should be infiltrated thoroughly into and around the wounds. For small wounds, the maximal quantity that is anatomically feasible should be administered. It is important to avoid the compartment syndrome which occurs if large volumes of RIG are injected into a small body area with limited tissue. It is no longer recommended to give remaining part of RIG intramuscularly. Therefore, if the volume of the calculated RIG dose[1] is likely to be too large for local wound infiltration, it can be fractionated into smaller,

individual syringes and the residual unused RIG can be used that same day for other patients, if stored and handled aseptically. Unused, fractionated RIG should be discarded at the end of the day.

If the wounds are large or multiple, the maximum calculated volume of RIG can be diluted with physiological buffered saline to allow sufficient volume for complete wound infiltration. Regardless of RIG availability, all category III exposed patients should receive rabies vaccines immediately. RIG should be administered only once, preferably at initiation of PEP and not >7 days following the first rabies vaccine dose.[8]

If a limited amount of RIG is available, its allocation should be prioritized for patients with high risk, category III exposures: multiple bites; those with deep wounds, or bites to highly innervated parts of the body, such as the head, neck and hands; patients with severe immunodeficiency; and cases where the biting animal is a confirmed or probable rabies case, or where bites, scratches or exposure of a mucous membrane were caused by a bat.

It is essential that the entire body should be examined for small bites, especially in smaller children and every site should be infiltrated with RIG/Mabs.

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. Rabies vaccines are highly effective, safe, and well-tolerated.

The currently available vaccines are:

- The cell culture vaccines (CCVs) include purified chick embryo cell vaccine (PCECV), human diploid cell vaccine (HDCV), purified vero cell rabies vaccine (PVRV)
- Purified duck embryo vaccine (PDEV).

It is to be noted that all CCVs and PDEV should have potency (antigen content) >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 >99% of vaccinees following PrEP or PEP. Prompt postexposure use of CCVs combined with proper wound management and simultaneous administration of RIG/Mabs 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.

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 response 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. Intradermal vaccination may cause more local irritation as compared to the intramuscular route.[2]

Postexposure prophylaxis: Postexposure prophylaxis is a medical urgency. It should be initiated as soon as possible and should not be delayed till results of lab tests or animal observation is available.

Which exposures warrant PEP?

- All mammalian bites need PEP (dogs, cats, cows, buffaloes, sheep, goats, pigs, donkeys, horses, camels, foxes, jackals, monkeys, mongoose, bears, and others).
- Bites by small domestic rodents do not warrant PEP.
- Exposure to bats does not warrant PEP for rabies in India.
- All bites that occur in wild warrant PEP and should be managed as a category 3 exposure.
- Bites by unknown animals warrant PEP.

The comparatively long incubation period provides an opportunity for highly effective PEP. PEP consists of:

- Thorough washing and flushing of the wound
- A series of rabies vaccine administrations promptly started after an exposure, and if indicated
- RIG infiltration into and around the wound, promptly after exposure.

Thorough wound washing with soap or detergent and water and/or virucidal agents reduces the viral inoculum at the wound site. Antibodies induced by postexposure vaccination lower the risk of RABV entering peripheral nerves after a bite from a rabid animal. Additionally, timely administration of RIG neutralizes RABV at the wound site. Rabies deaths occur mainly in those who cannot access timely and effective PEP. Prompt PEP following severe exposures is 100% effective in preventing rabies. However, delay in seeking PEP, improper wound care, unnoticed wounds, direct nerve inoculation, and lack of patient compliance with vaccination schedules among other factors contribute to PEP failure and subsequent death.

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.

Schedule of Vaccination

The Essen protocol consists of five doses on days 0, 3, 7, 14, and 28, with day "0" being the day of commencement of vaccination. A regimen of five doses of HDCV or PCECV should be administered IM to previously unvaccinated persons. The first dose of the five-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 days 3, 7, 14, and 28 after the first vaccination. This schedule is recommended by the National Center for Disease Control (NCDC) of the Govt of India.[9]

If any doses are delayed, vaccination should be resumed, not restarted.

A change in the route of administration or in vaccine product during a PEP or PrEP course is acceptable if such a change is unavoidable. Vaccination should continue according to the schedule for the new route of administration.

Shortened Schedules

A shortened Essen regimen, consisting of one dose on each of days 0, 3, 7, and between 14 and 28th day, is recommended, for immune competent, exposed people provided that they receive wound care plus rabies immunoglobulin in category III and a WHO-prequalified rabies vaccine.[10]

The IAP/ACVIP has endorsed this four-dose PEP schedule and two-dose PrEP schedule recommended by the WHO in 2018.

Most interruptions in the vaccine schedule do not require re-initiation of the entire series. For most minor deviations from the schedule, vaccination can be resumed as though the patient was 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 dose would be administered between day 17 and 31st. The dose is same at all ages and is 1 mL IM for HDCV, PCEV, PDEV, and 0.5 mL for PVRV.

Re-exposure prophylaxis: If an individual has a repeat exposure <3 months after a complete PEP schedule, then *only* wound care is needed, neither ARV nor RIG is needed. For repeat exposures occurring >3 months after the last PEP, the PEP schedule for previously immunized individuals should be followed, two IM doses on days 0 and 3. RIG is not indicated. (WHO position paper 2018).

Post-vaccination serological testing: Routine estimation of serological response following the completion of preexposure or postexposure prophylaxis is not necessary.

It is necessary if:

- The person is immunosuppressed
- Significant deviations of the prophylaxis schedule have occurred
- The person's antibody status is being monitored routinely due to occupational exposure to rabies virus.

Concurrent Chloroquine and Hydroxychloroquine Use

Lower VNA titers have been reported in individuals who received ID PrEP during chloroquine treatment. The difference in observed VNA titers was small, above the 0.5 IU/mL threshold, and unlikely to be clinically significant. Based on pharmacovigilance, since 1983 there have been no additional reports of rabies cases among persons who received PEP, with or without PrEP, and who were concurrently taking chloroquine or hydroxychlorine.

There is no contraindication for individuals receiving treatment with chloroquine or hydroxychloroquine; both ID and IM route of vaccine administration can be used. However, if possible, PrEP should be completed before chloroquine or hydroxychloroquine treatment is initiated. (WHO Position Paper 2018).

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).

Intradermal Vaccination

A systematic review of vaccine potency has shown that current vaccines (>2.5 IU/IM dose), when administered by the ID route for either PEP or PrEP, have efficacy equivalent to or higher than that of the same vaccine administered by the IM route. For the ID route one dose is 0.1 mL of CCEEV (irrespective of the vaccine brand). The vaccine in one vial can therefore be fractionated to provide 5–10 doses for ID administration, depending on the vial size (0.5 mL or 1.0 mL). For the IM route, one dose is one vial of vaccine per patient. The higher concentration of antigen-presenting cells in the dermis is responsible for the strong immunologic response to vaccine administered ID, despite the lower amount of antigen injected. ID administration of rabies vaccines provides a cost-saving and dose-sparing alternative to IM vaccination. ID PEP regimens use at least 25% less vaccine vials than IM PEP regimens. As numbers of patients seen in clinics increase, ID regimens become increasingly cost-effective, using up to 85% less vaccine vials.

WHO/IAP recommended PEP by ID route: 2-sites ID on days 0, 3, and 7 for the immunologically naïve individual.

NCDC (Govt. of India) recommended PEP by ID route: Updated Thai Red Cross Schedule: 2-sites ID on days 0, 3, 7, and 28 days.

Re-exposure prophylaxis:

- *<3 months since completion of PEP:* No intervention except wound hygiene.
- *>3 months since completion of PEP:* 1-site IM on days 0–3 OR 1-site ID on days 0 and 3 or 4-site ID on day 1.

Reduced Three-dose Schedule

ThRabis: Cadila Pharmaceuticals has developed a novel three-dose recombinant nano-particle-based rabies G protein vaccine, ThRabis, based on virus-like particle (VLP) technology. The vaccine generates antibodies against rabies G protein, which leads to virus neutralization and prevents virus attachment to the cell to confer protection against rabies.

Cadila Pharmaceuticals successfully tested immunogenicity and safety of three doses, i.e., 50 μg (microgram) on days 0, 3, and 7 of the novel vaccine in Phase-I/II and Phase-III clinical trials in healthy volunteers as well as preclinical models. The safety and immunogenicity of the vaccine were established in the trials.[11]

ThRabis is an intramuscular vaccine and less painful for the recipients, and does not require reconstitution prior to use. Since it is three-dose vaccine, it will improve compliance to complete the vaccine course. This vaccine has been licensed by the Drug Controller General of India (DCGI) for use >18 years of age. However, the NCDC, WHO, and IAP have not made any statement on the use of this vaccine.

Postexposure Prophylaxis of Immunocompromised Patients (Box 1)

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

BOX 1: Rabies vaccines.

- Only modern tissue culture vaccines (MTCVs) and intramuscular (IM) routes are recommended for both "postexposure" and "preexposure" 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 human diploid cell vaccine (HDCV), 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 yet.
  - *4 dose schedule:* 0, 3, 7, and between 14- and 28th day with day "0" being the day of commencement of vaccination.
  - Monoclonal Rabies antibodies/Rabies immunoglobulin (RIG) along with rabies vaccines are recommended in all category III bites.
  - Rabishied 3.33 IU/kg, Twinrab 40 IU/kg, HRIG 20 mg/kg or equine rabies immunoglobulin (ERIG) (dose 40 U/kg) can be used. Monoclonal rabies antibodies to be preferred over RIG.
- *Preexposure prophylaxis:*
  - Two doses are given intramuscularly in deltoid/anterolateral thigh on days 0, 7, OR 2-site ID on day 0 and 7.
  - For re-exposure occurring 3 or more months after completed (and documented) pre- or postexposure prophylaxis, two doses are given on days 0 and 3.
  - Rabies immunoglobulin should not be used during re-exposure therapy.

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 14 days after the completion of course of vaccination, to assess the need for additional doses of vaccine.

Preexposure Prophylaxis (see Box 1)

Preexposure prophylaxis consists of a series of rabies vaccination administered prior to a potential exposure. PrEP is recommended for certain high-risk groups enumerated as follows:

- *Continuous exposure:* Laboratory 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.

Although PEP and PrEP can be administered intramuscularly (IM) or intradermally (ID), ID vaccination is both dose and cost-sparing. Modern purified cell-culture and embryonated egg-based rabies vaccines are highly immunogenic, effective, and safe to use in people of all ages.

Individuals with documented evidence of previous PrEP are considered previously immunized and benefit from an abridged PEP without RIG in case of exposure.

Preexposure prophylaxis eliminates the need for RIG (awareness, cost, and availability of RIG is a problem). It also reduces the number of vaccine doses.

PrEP schedules:

- *WHO/IAP:* (a) 2-site ID on days 0 and 7, or (b) 1-site IM on days 0 and 7
- *NCDC:* IM-days 0-7-21 to 28. ID-1-site ID on days 0-7-21 to 28.

Most Indian children are at risk for rabies. The Advisory Committee on Vaccines and Immunization Practices (ACVIP) recommends offering preexposure prophylaxis to children at high risk of rabies exposure after discussion with parents.

Individuals who are immunocompromised should receive a 3-visit ID or IM PrEP regimen on days 0, 7 and between days 21 and 28, and should be managed with full PEP in the case of a potential rabies exposure with particular emphasis on rigorous wound washing. (SAGE Working group on Rabies vaccine WHO 2017).

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) preexposure 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.

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3.17 CHOLERA VACCINES

Ananda Kesavan TM, Sunil Kumar Aggarwalla

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* O1 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 not marketed in India.[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 β-subunit toxoid and will therefore not protect against enterotoxigenic *E. coli*.

Shancol is the only Cholera vaccine available in India.

Shancol composition is shown in **Table 1**.

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]

TABLE 1: Composition of Shancol.

Active ingredient	*Quantity*
V. Cholerae O1 Inaba El Tor Formaldehyde killed	600 Eliza units (EU) of lipopolysaccharide (LPS)
V. Cholerae O1 Ogawa, Classical strain. Heat killed	300 EU of LPS
V. Cholerae O1 Ogawa, Classical strain, formaldehyde killed	300 EU of LPS
V. Cholerae O1 Inaba, Classical strain. Heat killed	300 EU of LPS
V. Cholerae O139, Formaldehyde killed	600 EU of LPS
Excipients	
Thiomersal	Not >0.02% w/v
Buffer	qs to 1.5 mL

TABLE 2: Shancol: Vaccine efficacy (VE) at 2 years and 5 years follow up (FU).

	VE (%)	
Age group	*2 years FU*	*5 years FU*
1–4 years	49	42
5–14 years	87	68
>15 years	63	74
Overall	67	65

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% **(Table 2)**.[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. Vaccination should not disrupt the provision of other high priority health interventions to control or prevent cholera outbreaks. 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. In a study done of a single dose of OCV in an endemic setting, in Bangladesh, the vaccine efficacy (VE) was

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.
- For continued risk of exposure, a booster may be administered after 3 years.

40% (95% CI: 11–60%); against all cholera episodes, 63% (95% CI: 24–82%) against severely dehydrating cholera episodes, and 16% (95% CI: –49–53%) in 1–4 years, 63% (95% CI: –39–90%) in the age of 5–14 years and 56% (95% CI: 16–77%) in 15 or more years, against all cholera episodes, although the differences according to age were not significant ($P = 0.25$).[10] Adverse events occurred at similar frequencies in the two groups. Thus, a single dose of the oral cholera vaccine was efficacious in older children (≥5 years of age) and in adults in a setting with a high level of cholera endemicity.[10]

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)**.

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3.18 YELLOW FEVER VACCINE

Shashi Kant Dhir, Srinivas G Kasi

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 area 50 per 100,000 and 10 per 100,000, respectively
- South America area 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 >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 0.8 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, >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**.

Recommendations for Use

The vaccine is mandatory for all travelers to YF endemic zones as per the International Health Regulations (IHR). All vaccinees receive

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

an international certificate for vaccination duly dated, stamped, and signed by the center administering the vaccine. The vaccine should be administered only at authorized centers.

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 all >9 months in any area with reported cases.

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.

From 11th 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.

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.

The current advice by the WHO for international travelers going to areas deemed to be at risk is the following:

- Vaccination against YF at least 10 days prior to the travel. 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 disinfected in accordance with the procedure recommended by WHO.
- Arrives on an aircraft that has been in an area with risk of YFV transmission and has not been disinfected in accordance with the Indian Aircraft Public Health Rules, 1954, or as recommended by the WHO **(Box 1)**.

BOX 1: Yellow fever (YF) vaccine.

- 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 YF vaccine is sufficient to confer sustained life-long 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.
- Yellow fever 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.

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.

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3.19 COVID VACCINES

Srinivas G Kasi, Arun Wadhwa

INTRODUCTION

The first human cases of coronavirus disease 2019 (COVID-19) were identified in Wuhan, People's Republic of China, in December 2019. The World Health Organization (WHO) declared the COVID-19 outbreak a Public Health Emergency of International Concern on January 30, 2020, and a pandemic on March 11, 2020.

COVID-19 IN CHILDREN

Although the brunt of the disease has been born by the elderly, immunocompromised, and the adult population, children of all ages are as susceptible to COVID-19 as adults. Surveillance data from various countries reveal that children account for up to 25% of laboratory-confirmed cases.[1] The National Center for Disease Control data of February 26, 2021 revealed that 3.9% of cases occurred in the 0–10 year age group and 7.99% in the 11–20 years age group.[2]

While ~70% of severe acute respiratory syndrome–coronavirus 2 (SARS-CoV-2) infections in children are asymptomatic, critical illness and hospitalizations are extremely rare, except in the children with risk factors. Children account for ~1.5% of all COVID hospitalizations. The morbidity and mortality of COVID-19 in children are much lower than that seen in adults and the elderly.[3] In the initial phase of the pandemic, a systematic review of fatality and intensive care unit (ICU) admission in children worldwide revealed that 91.5% of deaths were reported from low- and middle-income countries (LMIC).[4,5] The pediatric deaths/1,000,000 children, the case fatality rate (CFR), and the ICU admission/1,000,000 children were significantly higher in LMIC than in high-income countries (HIC). The highest deaths/1,000,000 children and CFR were in infants <1 years old, with the highest figures from LICs and LMICs. Severity of disease may be related to the variant.[6] In observational studies in children and adolescents, the rates of admission to the ICU and mechanical ventilation were lower with the Omicron than the

Delta variant. Deaths in children and adolescents, due to COVID-19, are rare. Children and adolescents accounted for 0.4% of all COVID-related deaths.[1]

Risk factors for severe disease and death include genetic conditions, neurologic and metabolic conditions, congenital heart disease and cardiovascular disease, obesity [body mass index (BMI)] >95th percentile for age and sex, diabetes mellitus, asthma or other chronic pulmonary diseases, sickle cell disease, immunosuppressed state, age <1 year, Down syndrome and prematurity (gestational age <37 weeks).

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

A clinical presentation in children similar to incomplete Kawasaki disease (KD) or toxic shock syndrome was first reported from South England, in April 2020. Subsequently, similar cases were reported from all over the world. Although rare, the incidence, in New York, has been reported as 2 per 100,000, when the incidence of laboratory confirmed COVID-19 was 322/100,000. Generally, it occurs in <1% of children with confirmed SARS-CoV-2 infection.[7] Several case reports and case series have appeared from India. Multisystem inflammatory syndrome in children (MIS-C) may need hospitalization and ICU care in addition to expensive medications.

LONG COVID IN CHILDREN

Post-COVID syndrome (or long COVID) by consensus is defined as signs and symptoms that develop during or after an infection consistent with COVID-19 which continue for more than 12 weeks and are not explained by alternative diagnosis. Evidence for long COVID evidence in children is limited and heterogeneous. The psychosocial consequences of lockdown are difficult to distinguish from long COVID symptoms. It can include a wide range of ongoing health problems; these conditions can last weeks, months, or years. Symptoms include involvement of the cardiovascular, gastrointestinal, respiratory, and nervous systems. A systematic review reported a prevalence varying from 1.6 to 70%. The most

frequently reported symptoms were fatigue (2–87%), headache (3.5–80%), musculoskeletal issues (5.4–66%), chest tightness or pain (1.4–51%), and dyspnea (2–57.1%). Five studies reported limitations in daily function due to long COVID.[8]

INDIRECT EFFECTS OF COVID-19 PANDEMIC

Children are not the face of this pandemic. But, they are the biggest victims of this pandemic. Children's lives have changed in profound ways. Children, of all ages, and in all countries, have been affected by the socioeconomic impacts and the mitigation measures, such as nationwide lockdown, school closures, online lectures, and quarantines, have resulted in significant adverse psychological effects on children, and adolescents and a loss of learning and developmental opportunities. Suspension of nutritional and immunization activities has aggravated nutritional deficiencies and increased susceptibility to disease outbreaks.[9,10]

CHILDREN AND COVID-19 TRANSMISSION

Studies done in the initial stages of the pandemic suggested that children do not participate significantly in the chain of transmission. Uncertainty exists in role of children in various age groups, in the transmission of COVID-19. Variable factors include socioeconomic, environmental factors and the adoption of risk mitigation strategies by the community. However, older children and adolescents transmit SARS-CoV-2 effectively in household and community settings.[9]

COVID VACCINES AVAILABLE FOR PEDIATRIC POPULATION IN INDIA

Four vaccines have received emergency use authorization (EUA) for the pediatric population in India. These are:

1. Covaxin™
2. Corbevax™
3. Covovax™
4. ZyCoV-D™

Covaxin™

This is a whole virion inactivated vaccine from the NIV-2020-770 strain developed by Bharat Biotech India and the Indian Council of Medical Research. The live virus has been inactivated by the use of beta-propiolactone. The vaccine is adjuvanted with alum and imidazoquinolinone, which is a toll-like receptor (TLR) 7/8 agonist. The vaccine received the EUA in India on January 3, 2021.[11]

Each 0.5-mL dose of the vaccine contains:

- *Whole virion inactivated antigen:* 6 μg
- *Aluminum hydroxide equivalent to aluminum:* 0.25 mg
- *TLR 7/8 agonist:* 15 μg
- *2-phenoxyethanol:* 2.5 mg.

The vaccine is to be stored at +2°C to +8°C. It should not be frozen. If frozen, the vaccine should be discarded. The vaccine is to be protected from light.

The multidose vials are eligible for the WHO Multi-Dose Vaccine Policy.

The vaccine is administered in a two-dose schedule on 0–28 days.

Known hypersensitivity to vaccine constituents is a contraindication.

In the phase 3 study, the vaccine demonstrated an efficacy of 77.8% [95% confidence interval (CI) 65.2–86.4] against symptomatic COVID-19, 93.4% (57.1–99.8) against severe symptomatic COVID-19, 79.4% (66.0–88.2) against symptomatic COVID-19 in participants aged 18–59 years and 67.8% (8.0–90.0) against symptomatic COVID-19 in participants aged >65 years. The vaccine demonstrated an efficacy of 65.2% (33.1–80.0) against the Delta variant.[12]

The vaccine demonstrated a good reactogenicity profile with similar proportions of participants reporting solicited, unsolicited, and serious adverse events (AEs) and AEs of special interest in the vaccine and placebo groups. Local injection pain was reported in >1% of participants after the first or second dose of vaccine or placebo. The most frequent solicited systemic AE overall was headache, followed by pyrexia (fever), fatigue, and myalgia, but in <1% of participants in either group.[11]

Covaxin Study in Children

A total of 526 children were enrolled into three groups: Group 1 (12–18 years, *n* = 176), Group 2 (6–12 years, *n* = 175), Group 3 (2–6 years, *n* = 175). Two 0.5-mL doses of BBV152 (Covaxin), which is the same formulation indicated in adults, were administered at an interval of 28 days.[13]

Mild injection site pain was reported by <35% after the first dose, and <25% after the second dose; there were no cases of severe pain. The most frequent systemic AE, after dose 1, was mild-to-moderate fever in 5–13% of participants. No case of severe fever was reported, and rates were all 4% or less after dose 2. This vaccine was well tolerated with no statistical difference in the incidence of adverse effects between groups.

Neutralizing antibody (Nab) responses, measured as MNT antibody titers, were similar in all three age groups. On day 56, the SCR (% age) was 100% for group 3 versus 89.8 (84.0–94.1) for Group 2 and 90.3 (84.9–94.2) for Group 3. Geometric mean titer (GMT) ratio comparing all children to adults was 0.98 (95% CI: 0.80–1.19). The GMTs by Plaque Reduction Neutralization Test (PRNT50) were higher in children as against adults with a ratio of 1.76 (1.32–2.33).

Binding IgG antibody responses against S-protein, receptor-binding domain (RBD), and N-protein were comparable in all the three age groups. Lower GMTs at day 56 were observed for N-protein in Group 3. The immunoglobulin G1 (IgG1)/IgG4 ratio at day 56 was substantially above 1 for all vaccinated groups, indicative of a Th1 bias.

Th1:Th2 index as GMT ratios of IgG1:IgG4, on day 56, were 79.6 (304–1,164) for Group 1, 49.4 (21.8–112) for Group 2, and 38.1 (7.67–188) for Group 3. These ratios indicate a Th1 bias.[13]

Corbevax™

Corbevax is a protein subunit vaccine containing RBD of S-protein produced through recombinant technology utilizing the Pichia Pastoris expression system. This vaccine contains the protein antigen adjuvanted to CpG1018 and aluminum hydroxide. CpG1018 is a short (22-mer) oligonucleotide sequence containing CpG motifs which are active in both rodents and primates, to induce

both cell-mediated and antibody-mediated immunity. CpG 1018, a potent TLR9 agonist, stimulates antibody production, stimulates helper (CD4+) and cytotoxic (CD8+) T cell populations and generates robust T- and B-cell memory responses. Additionally, CpG 1018 strongly favors development of the Th1 subset of helper T cells. CpG is in use in Heplisav™ which is a hepatitis B vaccine.[14]

Each dose of 0.5 mL contains:

- *RBD antigen:* 25 μg
- *Aluminum hydroxide:* 750 μg
- *CpG 1018:* 750 μg
- *Buffer:* qs to 0.5 mL
- The schedule is two doses administered 28 days apart through intramuscular (IM) route
- It is stored between 2 and 8°C
- The vaccine does not contain any preservatives or stabilizers.

Contraindications: Hypersensitivity to any of the components of the vaccine, pregnant and lactating women, during fever and severe infection, children <12 years of age, previous receipt of another COVID-19 vaccine, bleeding disorder or on blood thinner, immunocompromised persons or on a immunosuppressive medications.

In the phase 3 clinical study, all the adverse effects noted were mild to moderate in intensity and no severe adverse effects were reported.

Phase 1 and 2 trial assessed the immune response and safety of four different antigens and adjuvants strengthens to select the optimum dose for the phase 3 trial. At 12 months of follow-up, phase 1 and 2 trial subjects demonstrated good retention of Nabs.[15]

The phase 2/3 clinical trial (BECT069) was done in a cohort of 1,268 subjects, from 18 to 80 years of age. The immunogenicity cohort consisted of 100 individuals in subjects 18–55 years of age in the phase 2 trial and a subset of individuals >45 years of age in the phase 3 trial.[16]

The safety profile in both pediatric cohorts was comparable to the placebo-control group. Majority of reported AEs were mild in nature and all reported AEs resolved without any sequelae.

TABLE 1: CORBEVAX: Summary of anti-RBD IgG and neutralizing antibody (nAb) titers against Wuhan from phase II/III study.

	Anti-RBD IgG			*Neutralizing antibody (nAb) titers against Wuhan*		
Time point	***Parameter***	***CORBEVAX®***	***% SCR***	***Parameter***	***CORBEVAX®***	***% SCR***
Phase II:						
Baseline	N	98		N	98	
	GMC (EU/mL)	945, 95% CI: 788–1134		GMT	67, 95% CI: 52–58	
Day 42	N	98		N	98	
	GMC (EU/mL)	26,448, 95% CI: 19,858–35,223	95	GMT	1,338, 95% CI: 917–1,954	
Phase III:						
Baseline	N	65		N	65	
	GMC (EU/mL)	4,287, 95% CI: 3,137–5,857		GMT	470, 95% CI: 330–670	
Day 42	N	65		N	65	
	GMC (EU/mL)	61,138, 95% CI: 47,485–78,715	89	GMT	5,166, 95% CI: 3,830–6,967	86%

(CI: confidence interval; GMT: geometric mean titer; N: number of subjects; SCR: seroconversion rate)

Immune response in terms of increase in anti-RBD IgG concentrations and neutralizing antibody titers post-vaccination, was observed in both younger population (18–45 years) and elderly population (45–80 years). **Table 1** significant nAb titers were observed against Wuhan, Delta and Beta strains.

In the superiority phase 3 trial, wherein, Corbevax was compared to Covishield, Corbevax demonstrated superior immune response and safety with respect to the anti-RBD, i.e., G antibodies, Nabs against Wuhan strain and Delta strain.

TABLE 2: CORBEVAX: Comparison of IgG responses in pediatric age group versus adults (from other study).

Age group (in years)	*Day 0 GMC; EU/mL*	*Day 42 GMC; EU/mL*	*GMFR*	*%SCR post-vaccine*
12–18	939	18,049	19	91%
5–12	969	26,802	28	96%
18–55	945	26,448	28	94%

(GMC; geometric mean concentration; EU/mL: ELISA units/mL; GMFR: geometric mean fold rise: SCR: seroconversion rate)

The phase 2/3 clinical study (BECT072) was conducted in 624 subjects in 2 age cohorts 5–12 years and 12–18 years.[17]

The safety profile was similar to that seen with the adult cohort.

The responses in the two pediatric age groups were noninferior to that seen in the adult cohort **(Table 2)**.

Corbevax has been granted EUA initially in December 2021 for adults, for 12–18 years in February 2022 and for 5–12 years in April 2022.

Covovax

NVX-CoV2373, the COVID-19 vaccine by Novavax, will be manufactured and marketed in Europe as Nuvaxovid™ (approved by EMA) and in India as Covovax™, manufactured by Serum Institute of India (approved by the Drugs Controller General of India). This is a "recombinant nanoparticle vaccine".

The gene for the SARS-CoV-2 spike protein, which is modified by incorporating two proline amino acids in order to stabilize the prefusion form of the protein, is engineered into a baculovirus, which infects a culture of Sf9 moth cells, which then create the spike protein and display it on their cell membranes. The spike proteins are harvested and assembled onto a synthetic lipid nanoparticle about 50 nanometers across, each displaying up to 14 spike proteins. The adjuvant used is Matrix-M1 (Fraction-A42.5 micrograms and Fraction-C7.5 micrograms of *Quillaja Saponaria Molina* extract).

Each 0.5 mL dose consists of:

- 5 micrograms of SARS-CoV-2 spike protein
- *Adjuvant matrix-M1:* Fraction-A (42.5 micrograms) and Fraction-C (7.5 micrograms) of Quillaja Saponaria Molina extract.[18]
- *Schedule:* Two doses of 0.5 mL administered IM on days 0–21
- To be stored in a refrigerator (+2°C to +8°C). Should not be frozen
- *Contraindications:* Hypersensitivity to the active substance or to any of the excipients.

All opened (punctured) multidose vials of Covovax should be discarded at the end of immunization session or 6 hours after the first needle puncture, whichever comes first.[18]

In the phase 3 trial, adults between the ages of 18 and 84 years, in UK, were administered two doses of 5-µg doses of NVX-CoV2373 or placebo at an interval of 21 days. The primary efficacy endpoint was virologically confirmed mild, moderate, or severe SARS-CoV-2 infection with an onset at least 7 days after the second injection in participants who were serologically negative at baseline. The vaccine efficacy (VE) was 89.7% (95% CI: 80.2–94.6) against a symptom onset of at least 7 days after the second injection, VE against hospitalization and death was 100%. VE of 86.3% (95% CI: 71.3–93.5) was observed against the B.1.1.7 (or alpha) variant and 96.4% (95% CI: 73.8–99.5) against non-B.1.1.7 variants. There was no significant differences in VE according to age group or the presence of coexisting medical illnesses.[19]

In the phase 3 trial in USA and Mexico, VE against reverse transcription-polymerase chain reaction (RT-PCR) confirmed COVID-19 occurring at least 7 days after the second dose was 90.4% (95% CI: 82.9–94.6). VE against moderate-to-severe disease was 100% (95% CI: 87.0–100). There were no significant differences in the VE as regard to age, sex, presence or absence of co-existing illnesses or those who were at high risk for complications of COVID-19. VE against the alpha variant was 93.6% (95% CI: 81.7–97.8), and against any variant of concern or interest was 92.6% (95% CI: 83.6–96.7).

The most common solicited systemic AEs were headache, myalgia, fatigue, and malaise, which were slightly more frequent among NVX-CoV2373 recipients than among placebo recipients.[20]

The Technical Advisory Group for Emergency Use Listing (of WHO) listed Nuvaxovid (NVX-CoV2373) vaccine against COVID-19 and Covovax (NVX-CoV2373) vaccine against COVID-19 for emergency use on December 20, 2021 and December 17, 2021, respectively.

The pediatric expansion of phase 3 study in USA of NVX-CoV2373 was conducted in 2,247 adolescent participants 12 to <18 years of age who received two IM injections of Nuvaxovid or placebo (normal saline) 21 days apart. The observed VE of Nuvaxovid against PCR-confirmed, symptomatic mild, moderate, or severe COVID-19 in the per-protocol efficacy population was 79.54% (95% CI: 46.83–92.13). VE against the delta variant was 82.0% (95% CI: 32.4–95.2). IgG responses against spike proteins of several variants (including alpha, beta, delta, gamma, Mu, and Omicron) were twofold to threefold higher than in adults, with 100% seroconversion against all variants following a two-dose series of vaccinations. Nab responses in adolescents functional against these variants were 2.4–4-fold higher than in adults against all evaluated variants.[21]

The pediatric trial of Covovax was conducted in Indian children, 2–17 years of age, to evaluate the safety and immunogenicity of Covovax. 460 children received at least one dose of the study vaccine. None of the participants had any comorbid condition.

The anti-S IgG antibody titers measured as the geometric mean Eliza units (GMEUs) were comparable between the groups at baseline—day 1. They increased substantially after each dose of the vaccine in the Covovax group with no response seen in the placebo group.

More than 98% seroconversion was seen in the Covovax group on day 36 (14 days after the second dose). The immunogenicity data indicates that Covovax is highly immunogenic in the children of 12–17 years of age[18] **(Table 3)**.

Seroconversion was 95.5% (92.7, 97.4) 28 (21+7) days after dose 1 and 98.8% (96.9, 99.7) 21 (14+7) days after dose 2. No significant seroconversion was seen in the placebo group.[21]

In December 2021, the Drugs Controller General of India (DCGI) granted EUA for Covovax in those >18 years and in March 2022 for the 12–17 years age group.

TABLE 3: Immunogenicity of Covovax: anti-S IgG.

Timepoint	*Statistic*	*Covovax N = 333*	*Placebo N = 108*
Baseline	N	333	108
	GMEU	1664.2	1366.6
	95% CI	413.7, 1959.1	1033.1, 1807.8
28 (21+7) days after dose 1	N	332	108
	GMEU	72660.4	1614.6
	95% CI	(63586.3, 83029.4)	(1174.7, 2219.3)
21 (14+7) days after dose 1	N	330	107
	GMEU	170193.6	1480.4
	95% CI	(157429.7, 183992.4)	(1110.1, 1974.3)

(CI: confidence interval; N: number of subjects; GMEU: geometric mean ELISA units)

ZyCoV-D®

This is a DNA-based vaccine for prevention of COVID-19. It comprises a DNA plasmid vector carrying full-length spike (S) gene region expressing SARS-CoV-2 spike (S) protein along with gene coding for signal peptide. The spike gene region was selected from submitted Wuhan Hu-1 isolate sequence. The S protein of the virus includes the RBD, responsible for binding to the human angiotensin-converting enzyme-2 (ACE-2) receptor, which mediates the entry of virus inside the cell. The DNA plasmid construct was transformed into *Escherichia coli* cells for large-scale production.

Each 0.1 mL contains:

- *DNA plasmid construct with spike protein gene region from SARS-CoV-2 virus produced in E. coli*: 1.0 mg
- *Phosphate-buffered saline:* qs
- *Mode of administration:* This vaccine has to be injected intradermally using the needle-free injector (Pharmajet Tropis

device) only. It should preferably be administered in the deltoid region of both the arms

- *Schedule:* 0.1 mL ID, two doses on days 0–28–56
- *Contraindications:* In individuals known to have hypersensitivity to the active substance or to any of the excipients.

Administration should be postponed in individuals suffering from an acute severe febrile illness.[22]

Interchangeability

There is no data on the use of *ZyCoV-D*® in persons who have previously received partial/complete vaccine series with another COVID-19 vaccine.

The phase 3 study was done on 27,703 participants aged >12 years, of whom 3.23% were 12–17 years, 89.26% in the 18–60 years age group, and 7.5% in >60 years age group. The VE of ZyCoV-D was found to be 66.6% (95% CI: 47.6–80.7) against the first occurrence of symptomatic RT-PCR-positive COVID-19, 28 days after the third dose. The efficacy against mild cases was 64.9% (95% CI: 44.9–79.8). The efficacy against moderate and severe cases was 100%, after 2 doses.[23]

The occurrence of solicited AEs was similar between the treatment groups [623 (4.49%) in the ZyCoV-D group vs. 620 (4.47%) in the placebo group].

The seroconversion rates, the IgG, geometric mean concentrations (GMCs), and geometric mean fold rise (GMFR) at day 84 were higher in the ZyCoV-D group compared with the placebo group **(Table 4)**. The immunogenicity response at day 84 in the group aged 12–17 years was higher than the overall participant population **(Table 5)**.

The proportion of participants who achieved seroconversion of Nabs at day 84, the Nabs GMTs, and GMFR was significantly higher in the ZyCoV-D group than the placebo group **(Table 6)**.[23]

Robust cellular response (IFN-γ) to ZyCoV-D was seen.[23]

In August 2021, ZyCoV-D was granted EUA, in a three-dose schedule for subjects >12 years of age.

TABLE 4: ZyCoV D: Immunogenicity antibody titers.

		ZyCoV D	*Placebo*
Day 0	GMT (95% CI)	7 (7.00–7.00)	7 (7.00–7.00)
Day 56	GMT (95% CI)	407.58 (266.73–622.83)	57.97 (36.10–93.07)
	GMFR (95% CI)	58.23 (38.10–88.98)	8.28 (5.16–13.30)
Day 84	GMT (95% CI)	952.67 (707.94–1282.00)	154.82 (91.25–262.70)
	GMFR (95% CI)	136.10 (101.13–183.14)	22.12 (13.04–37.53)

(GMT: geometric mean titer; GMFR: geometric mean fold rise)

TABLE 5: Immunogenicity response in 12–17 years vs overall cohort.

	Adolescents 12–17 years	*Overall*
SCR %	100	93.3
GMT	2083	952.67
GMFR	297.65	136.1

TABLE 6: Neutralizing antibody response on day 84.

	ZyCoV D	*Placebo*
SCR%	88	42.55
GMT (95% CI)	133.39 $PRNT_{50}$, (86.88–204.81)	30.40 $PRNT_{50}$, (16.35–56.53)
GMFR (95% CI)	26.68, (17.38–40.96)	5.74, (3.14–10.48)

In April 2022, ZyCoV-D received EUA from the DCGI as a two-dose vaccine, be administered on day 0 and day 28.[22,24]

BNT162b2 (Pfizer) Vaccine

In a phase 3 trial involving 2,260 adolescents 12–15 years of age, BNT162b2 was found to have a favorable safety and side effect profile. The GMT geometric ratios of Nabs after dose 2, in 12–15-year-old participants relative to 16–25-year-old participants were 1.76 (95% CI: 1.47–2.10), which satisfied the noninferiority criterion, indicating

a greater response in the 12–15-year-old cohort. The observed VE was 100% (95% CI: 75.3–100).[25]

The EUA was granted by the US Food and Drug Administration (FDA), on May 10, 2020, for use in children 12–15 years of age and is now being used in this age group in many countries.

In the 5–11 years cohort, with a dose of 10 μg, the Nab GMT was 1,197.6 (95% CI: 1,106.1–1,296.6), as compared to [1,146.5 (95% CI: 1,045.5–1,257.2)] the 16–25 years cohort.[26] This proved noninferiority. On October 29, 2021, EUA was granted by the US FDA for use in children 5–11 years.

mRNA-1273 (Moderna) Vaccine

Following two doses of 100 μg/dose of Moderna vaccines, at 0–28 days, in adolescents aged 12–17 years, the GMTs of Nabs were 1,401.7 (1,276.3–1,539.4) compared to levels of 1,301.3 (1,177.0–1,438.8) in young adults, thus proving noninferiority. The VE against COVID-19, 14 days after second dose, was 100% (28.9 to NE—not estimated). On September 4, 2021, this vaccine was granted EUA by the US FDA for adolescent 12–17 years and subsequently from >6 months of age.[27,28]

Bivalent Vaccines

The US FDA has granted EUA for the bivalent mRNA COVID-19 vaccines. The BNT162b2 (Pfizer) vaccine contains 30 μg of mRNA (15 μg original strain, 15 μg Omicron BA.4/BA.5).

The Moderna mRNA bivalent vaccine contains 50 μg of mRNA (25 μg original strain and 25 μg Omicron BA.4/BA.5).

Both formulations are recommended only for the booster dose and not for the primary series **(Table 7)**.[29]

POSTIMMUNIZATION MYOCARDITIS

In April 2021, increased cases of myocarditis and pericarditis were reported in the United States after mRNA COVID-19 vaccination (Pfizer-BioNTech and Moderna). Myocarditis and/or pericarditis occurs most frequently in adolescent and young adult males, ages 16 years and older, within 7 days after receiving the second dose

TABLE 7: mRNA vaccines recommendations in the United States.

Age indication	*Vaccine composition*	*Dose: Primary*	*Dose: Booster*
Pfizer:			
6 m–4 y	Monovalent	3 mcg	NA
5–11 y	Monovalent	10 mcg	10 mcg
>12 y	Monovalent	30 mcg	NA
>12 y	Bivalent	NA	30 mcg
Moderna:			
6 m–5 y	Monovalent	25 mcg	NA
6–11 y	Monovalent	50 mcg	NA
12–17 y	Monovalent	100 mcg	NA
>18 y	Monovalent	100 mcg	NA
>18 y	Bivalent	NA	50 mcg

of an mRNA COVID-19 vaccine. Postimmunization myocarditis is relatively straightforward to diagnose and treat, and the clinical course tends to be mild in most patients. In USA, the reporting rates of myocarditis were 40.6/100,000 cases after second doses of mRNA COVID-19 vaccines in males aged 12–29 years and 2.4/100,000 second doses administered to males aged ≥30 years. In females, the reporting rates were much lower, at 4.2 and 1.0 per million second doses, respectively, in the same age groups. The highest reporting rates were among males aged 12–17 years (62.5/100,000) and those aged 18–24 years (50.5/100,000) after second doses of mRNA COVID-19 vaccine administered, respectively.[30]

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Chapter 4

Vaccination of Special Groups

4.1 ADOLESCENT VACCINATION

Kripasindhu Chatterjee, Srinivas G Kasi

INTRODUCTION

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 (VPDs) in adolescents and young adults. Adolescents need vaccinations for the following reasons:

- To protect against diseases that have higher morbidity in adolescence (hepatitis A, varicella)
- To boost the waning immune responses of certain vaccines administered during infancy/early childhood (measles, pertussis, tetanus, diphtheria, etc.)
- Adolescents also need vaccines to prevent diseases that appear later in adult life (cervical cancer)
- As a part of control or elimination projects of some VPDs such as measles elimination, and rubella and congenital rubella syndrome (CRS) control program
- For travel and study abroad
- As a catch-up who missed the previous opportunities.

The adolescent-specific vaccines are Tdap/Td and human papillomavirus (HPV) vaccines.

Indian Academy of Pediatrics (IAP)-recommended vaccines for adolescents are given in **Table 1**.

TABLE 1: Indian Academy of Pediatrics, Advisory Committee on Vaccines and Immunization Practices-recommended vaccines in adolescents (11–18 years).

Vaccine	*Schedule*
Tdap/Td*	10 years
HPV†	9 years
Covid vaccines	12 years onwards

*Tdap preferred to Td, followed by repeat Td every 10 years.
†Two doses at 0 and 6 months (ages 9–14 years) or 0, 2, and 6 months (15 years or above).
[HPV: human papillomavirus; Td: tetanus and diphtheria (low dose); Tdap: tetanus diphtheria (low dose) toxoid and acellular pertussis]

PERTUSSIS VACCINATION

Pertussis vaccination in adolescents is of particular interest, as it is known that the humoral and cellular immunities evoked by vaccines tend to wane after some years, and this has been confirmed by immunological and clinical studies in recent years.[3,4] Many factors determine the speed at which the immunity wanes such as vaccination schedule and the type of vaccine. Acellular pertussis vaccines have shown to provide shorter-lasting protection than whole-cell pertussis (wP) vaccines.[5] 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.[6] 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.[7] 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.[8] 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.[9] A detailed account on pertussis immunization through all ages is available in a recent publication.[10] In India, the incidence of pertussis in adolescents is unknown. In a recently published article titled "prospective multinational serosurveillance study of B. pertussis infection among 10-18 years subjects from 8 Asian countries", with 200 subjects from India, high titers of anti-PT immunoglobulin G (IgG) >62.5 IU/mL (indicative of B. pertussis infection within 12 months prior) was found in 18% of subjects.[11]

In a study done in Vellore on 281 subjects, of whom all had received three primary vaccines and one booster, 42.7% had received the second booster and 5.3% had received the adolescent booster of pertussis containing vaccines, around 7% of adolescents had evidence of recent infection and 54% of the adolescents tested had no detectable antibodies, suggesting waning immunity and susceptibility to pertussis, which can lead to periodic epidemics.[12]

Safety and Immunogenicity in Adolescents and Adults

Studies comparing the adverse effect profile of subjects who received Tdap followed by another dose of Tdap or Td, after varying intervals, revealed that the adverse effects profile was similar in both groups. The seroprotective levels of antibodies to tetanus and diphtheria were similar in both groups.[13-17]

Anti-pertussis antibodies decline rapidly after the first year following a Tdap vaccination and protection begins to wane within 2–4 years after receipt of a single Tdap dose. Moreover, Tdap vaccines have an uncertain role in prevention of transmission and in herd protection. Thus, a second dose of Tdap is unlikely to have significant public health impact.[18]

There are no published data comparing rates of adverse events among pregnant women who received multiple doses of Tdap during a single pregnancy with those who received a single Tdap dose and additional Td doses for catch-up vaccination.

A cohort study examining reactogenicity of Tdap in pregnant women included only eight study participants who received more than one Tdap dose within a 12-month period; none experienced severe reactions or fever.[19] A study on safety of Tdap in 633,542 singleton pregnancies identified 187 women who had received more than one Tdap dose during a single pregnancy found similar rates of adverse birth outcomes (i.e., small for gestational age, preterm delivery, and low birthweight) in those women receiving multiple Tdap compared with women who had received a single Tdap dose in pregnancy.[20]

Conclusion

Advisory Committee on Immunization Practices (ACIP) in 2018 concluded that due to higher cost of Tdap relative to Td and uncertainty about the impact of multiple Tdap doses on pertussis control and transmission, evidence appeared to be insufficient to preferentially recommend Tdap to replace Td.[21] There is no advantage in replacing Td with Tdap for the decennial Td booster, tetanus prophylaxis for wound management, and for additional required doses in the catch-up immunization schedule if a person has received at least one Tdap dose.[18]

Routine Immunization Recommendations

- *Adolescents:* 11–18 years: Single dose of Tdap at age 11–12 years followed by booster dose of either Td or Tdap every 10 years throughout life.
- *Adults above 19 years:* Adults above 19 years who have never received Tdap should get one dose of Tdap regardless of the interval since their last tetanus or diphtheria toxoid containing vaccine followed by booster doses of either Td or Tdap every 10 years throughout life.
- *Pregnant women:* Pregnant women should receive one dose of Tdap during each pregnancy, irrespective of their history of receiving the vaccine, at 27–36 weeks' gestation, preferably during the earlier part of this period, although it may be administered at any time during pregnancy.[21,22]
- *Wound management:* A tetanus toxoid containing vaccine is indicated if >5 years have passed since the last tetanus toxoid containing vaccine, in case of contaminated wounds and 10 years in

case of clean wounds. In adolescent of age >11 years who have not previously received Tdap or whose Tdap history is unknown, Tdap is preferred. For a pregnant woman if a tetanus toxoid containing vaccine is indicated, Tdap should be used. Nonpregnant persons with documented previous Tdap if a tetanus toxoid containing vaccine is indicated, either Td or Tdap may be used.[21]

Catch-up Immunization Recommendations

- *Children and adolescents:* 7–18 years: Children and adolescents aged 7 years and older, and adults who have never received tetanus containing vaccines, or whose vaccination history is unknown, should receive the three-dose series. In this situation, Tdap for dose one, followed 4 weeks later by Td or Tdap for dose two, followed at least 6 months later by Td or Tdap for dose three. Following the primary series, booster doses of Td or Tdap should be given every 10 years thereafter. The vaccination series does not need to be restarted for those with incomplete DTaP/DTwP history, regardless of the time that has elapsed between doses.
- *Children aged 7–9 years:* Children aged 7–9 years who receive a dose of Tdap as part of the catch-up series, an adolescent Tdap dose should be administered at age 11–12 years. If a Tdap dose is administered in children 10 years or older, it may count as the adolescent Tdap dose.
- DTaP/DTwP is not indicated for children aged older than 7 years. If DTaP/DTwP is administered inadvertently to an incompletely vaccinated child aged 7–9 years, this dose should count as the Tdap dose of the catch-up series, and the child should receive an adolescent Tdap dose at age 11–12 years. If DTaP/DTwP is administered inadvertently to a person aged 10 years or older, this dose should count as the adolescent Tdap dose routinely administered at age 11–12 years.
- *Pregnant women:* To prevent neonatal tetanus, pregnant women who have completed the childhood schedule should receive a dose of Tdap. Incompletely vaccinated or unvaccinated woman should receive at least two doses, of which one should be Tdap. If more than one dose is needed, either Td or Tdap may be used. The three-dose primary series should be completed at the recommended intervals of 0–1–6 months in unvaccinated.[21]

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; most infections are acquired early during adolescence, at the time of initial sexual activities,[23] HPV-related diseases are mainly caused by a few types of oncogenic HPV strains, against which three vaccines have been developed, the bivalent HPV vaccine (types 16 and 18), the quadrivalent HPV vaccine (HPV types 6, 11, 16, and 18), and the nonavalent vaccine (types 6, 11, 16, 18, 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.[24]

Regarding the time of administration, HPV vaccines should be administered to adolescents before they start to engage in sexual activity.[25] 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.

Recommendations

- *4vHPV:* Indicated in females aged 9–45 years
- *9–14 years:* Two doses in a 0–6 months schedule
- *15 years and above:* Three dose 0–2–6 months
- *9vHPV:*
  - *9–14 years females and males:* Two doses 0–6 months
  - *15–26 years females:* Three doses 0–2–6 months.

  For more details, please refer to chapter on HPV vaccines.

CURRENT STATUS OF ADOLESCENT'S IMMUNIZATION

In India, routine immunization given to young children is dismally low. National Family Health Survey 4 (2015–2016) 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.[26] 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 VPDs as they are more exposed to infection due to greater mobility.

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 such as pertussis. IAP recommendations for catch-up immunization in adolescents are given in **Table 2**. There are also special circumstances for adolescents and vaccination schedule for these situations which 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 the following link: http://wwwnc.cdc.gov/travel/.

TABLE 2: Indian Academy of Pediatrics, Advisory Committee on Vaccines and Immunization Practices-recommended vaccines in adolescents for catch-up.

Vaccine	*Schedule*
MMR*	Two doses at 4–8 weeks' interval
Hepatitis B†	Three doses 0, 1, and 6 months
Hepatitis A	Two doses at 0 and 6 months (prior check for anti-HAV IgG may be cost-effective in children of age >10 years)
Typhoid TCV‡	Single dose
Varicella	Two doses at 4–8 weeks of interval
HPV	• *9–14 years (boys and girls):* Two dose 6 months apart • *15 years or older (girls and women):* 4vHPV: 0–2–6 months • *9vHPV (females):* 15–26 years 0–2–6 months

*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.
‡Up to 45 years.
[HAV: hepatitis A vaccine; HPV: human papillomavirus; IgG: immunoglobulin G; MMR: measles, mumps, and rubella; TCV: typhoid conjugate vaccine; Td: tetanus and diphtheria (low dose); Tdap: tetanus diphtheria (low dose) toxoid and acellular pertussis]

TABLE 3: Indian Academy of Pediatrics, Advisory Committee on Vaccines and Immunization Practices-recommended vaccines in adolescents in special circumstances.

Vaccine	*Schedule*
Influenza	One dose every year
Japanese encephalitis vaccine	Catch-up. Up to 15 years*
PPSV23 (pneumococcal)	Maximum two doses 5 years apart†
Rabies vaccine	0, 3, 7, 14, and 28 days

*Only in endemic area as catch-up.
†Maximum number of doses—two.
(PPSV: pneumococcal polysaccharide vaccine)

WHAT IS NEEDED?

Universally, the uptake of vaccines in adolescents is inadequate. Reasons for low vaccine uptake among adolescents include:

- Lack of knowledge about the vaccines necessary for adolescents, among providers, parents, and adolescents
- Lack of specific adolescent immunization programs
- Behavioral attitude of adolescents toward vaccinations
- Lack of routine "well-adolescent clinics" and thus fewer encounters with the healthcare system
- Missed opportunities for vaccination as visits for minor illnesses are not utilized for promoting vaccinations.

Successful strategies for improving adolescent vaccination rates involve communication of benefits of vaccination to the general public, presentation of information in an evidence-based and youth-friendly way, sensitizing the providers with information regarding adolescent vaccinations, creating adolescent-specific immunization programs, having adolescent-friendly immunization clinics, and utilizing all missed opportunities.

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.[27]

TABLE 4: Indian Academy of Pediatrics, Advisory Committee on Vaccines and Immunization Practices-recommended vaccines in adolescents with range.

Vaccine	*Age*		
	7–10 years	*11–12 years*	*13–18 years*
Tdap	One dose (if indicated)	One dose	One dose (if indicated)
HPV-1 (see Footnote 1)	Two doses 0–6 months	Two doses 0–6 months	Two doses 0–6 months till 14 completed years. Above 15 years, three-dose series—0–2–6 months
MMR	Complete two-dose series, at least 4 weeks apart		
Hepatitis B	Complete three-dose series, 0–1–6 months		
Hepatitis A	Complete two doses 6–12 months apart, series of inactivated or single dose live		
Varicella	Two doses at 4–8 weeks' interval		
Typhoid conjugate vaccine	Single dose		
Influenza	Single annual dose		
Japanese encephalitis	Two doses at 4 weeks' interval		
Pneumococcal polysaccharide PPSV23	See Footnote 2		
Meningococcal • MenACWY-D • MenACWY-CRM	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.

(HPV: human papillomavirus; MMR: measles, mumps, and rubella; PPSV: pneumococcal polysaccharide vaccine)

FOOTNOTES

HPV Vaccines

Routine vaccination:

- *Minimum age:* 9 years
- HPV4 and HPV9 are recommended in a two-dose series (0 and 6 months) for females and males aged 9–14 years of age.

- HPV4 is recommended in a three-dose series (0, 2, and 6 months) for females aged 15–45 years.
- HPV9 is recommended in females aged 15–26 years in a three-dose schedule 0–2–6 months.
- The vaccine series can be started beginning at age 9 years.

Catch-up vaccination:

- Administer the vaccine series to females (HPV 4) at age 13 years through 45 years if not previously vaccinated.
- Administer the second dose 2 months after the first dose and the third dose 6 months after the first dose (at least 24 weeks after the first dose).

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 years 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.

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.
- Meningococcal conjugate vaccines (quadrivalent MenACWY-D, Menactra® Sanofi Pasteur, Menveo and monovalent group A, PsA-TT, MenAfriVac® by Serum Institute of India) and polysaccharide vaccines (bi- and quadrivalent) are licensed in India.
- These vaccines are not recommended for routine use.

Special situations: Anatomic or functional asplenia (including sickle cell disease), human immunodeficiency virus (HIV) infection, persistent complement component deficiency, complement inhibitor (e.g., eculizumab, ravulizumab), use:

- After primary immunization, one booster every 5 years in cases of persistent risk such as asplenia.
- *Children for whom boosters are recommended* because of an ongoing increased risk of meningococcal disease (e.g., those with complement deficiency, HIV, or asplenia): Follow the booster schedule for persons at increased risk.
- *Children for whom boosters are not recommended* (e.g., a healthy child who received a single dose for travel to a country where meningococcal disease is endemic): Administer MenACWY according to the recommended adolescent schedule with dose one at age 11–12 years and dose two at age 16 years.

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4.2 IMMUNIZATION IN SPECIAL SITUATIONS

Srinivas G Kasi, Sanjay Srirampur

IMMUNIZATION IN THE IMMUNOCOMPROMISED

The immunocompromised are in greater need for vaccines as they are more susceptible to infections. But at the same time, the immunogenicity or efficacy is lower and risk of adverse effects with live vaccines is higher. However, vaccination in an immunocompromised child is safer than often perceived. 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).
- 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, rubella (MMR) and varicella. All household contacts should be fully immunized, including varicella and influenza, to reduce risk of transmission to the immunocompromised. After administration of oral rotavirus vaccines, strict hand hygiene should be observed by all caregivers for a week after administration.

- Some vaccines including pneumococcal, varicella (depending on degree of immunocompromise), hepatitis A, and inactivated influenza vaccines (IIVs) should be given. Although, there are no guidelines regarding rotavirus vaccines in the immunocompromised (except in severe combined immunodeficiency), there have been no safety concerns when administered to HIV infected subjects.

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 depend on the degree of immunodeficiency. Generally, cluster of differentiation 4+ (CD4+) counts <200 cells/mm^3 or < 15% 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 such as 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: Indian Academy of Pediatrics recommendations for immunization of human immunodeficiency virus (HIV)-infected children.

Vaccine	*Asymptomatic*	*Symptomatic*
BCG	Yes (at birth)	No
DTwP/DTaP/TT/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 • If IPV is not affordable, OPV should be given in asymptomatic subjects	
MMR	Yes, at 9 months, 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, and 14 weeks and 12–18 months	
Pneumococcal vaccines (PCV and PPSV23)	• *PCV:* Yes, as per routine schedule at 6, 10, and 14 weeks and 12–15 months • *PPSV23:* One dose 8 weeks after PCV, second 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	

Contd…

Contd…

Vaccine	*Asymptomatic*	*Symptomatic*
Rotavirus vaccine	Insufficient data to recommend, to be given as per ACIP/WHO recommendations in asymptomatic	
Hepatitis A vaccine (inactivated only)	Yes	Yes, check for seroconversion, boosters if needed
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, as per routine schedule of three doses at 0–2 and 6 months starting at 9 years of age. For details see chapter on HPV vaccines	

*Hepatitis B virus surface antigen (HBsAg) positive mothers, infant to be given hepatitis immunoglobulin (HBIg) within 12 hours of birth as per birth weight, if status unknown <2,000 g infant to be given both HBV vaccine and HBIg. If >2,000 g to check the status and give HBIg accordingly (not later than 1 week).
**As per Advisory Committee on Immunization Practices/Centers for Disease Control and Prevention and World Health Organization. If varicella vaccine was given before initiation of combination antiretroviral therapy (c-ART), repeat the doses of varicella vaccine after start of c-ART.
(BCG: bacillus Calmette-Guérin; CD: cluster of differentiation; DTP: diphtheria, tetanus, and pertussis; Hib: *Haemophilus influenzae* type b; HIV: human immunodeficiency virus; HPV: human papillomavirus; 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

Corticosteroids

Children receiving oral corticosteroids in high doses (prednisolone 2 mg/kg/day for those weighing <10 kg or for those weighing >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 receiving oral corticosteroids in high doses (prednisolone 2 mg/kg/day for those weighing <10 kg or for those weighing >10 kg, 20 mg/day or its equivalent) for <2 weeks can receive live-virus vaccines after discontinuation of treatment.

Children receiving oral corticosteroids in lower doses (prednisolone <2 mg/kg/day for those weighing <10 kg or for those weighing >10 kg, <20 mg/day or its equivalent) can receive live vaccines, while on therapy. These doses are not immunosuppressive.

Children who are receiving only maintenance physiologic doses of corticosteroids can receive live-virus vaccines.

Children on alternate day therapy, 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 should not receive live-virus vaccines during therapy, except in special circumstances during which the potential benefit of protection and the risk of adverse reaction are weighed.[6]

Other Immunosuppressive Medications

Children receiving methotrexate at a dosage of ≤0.4 mg/kg/week, azathioprine at a dosage of ≤3 mg/kg/day, or 6-mercaptopurine at a dosage of ≤1.5 mg/kg/day are not immunosuppressed and can receive all vaccines.[6]

Biologic Response-modifying Drugs

The biologic response-modifying drugs (BRMs) target different components of the immune system causing various degrees of immunosuppression that can last for weeks to several months after discontinuation. Inactivated vaccines should be preferably administered at least 2 weeks before the initiation of biologics. Live-attenuated vaccines are generally contraindicated during and for weeks to months following discontinuation of the BRMs. They should be administered at least 4 weeks before the initiation of therapy.

Biologic response-modifying drugs are considered highly immunosuppressive and live-virus vaccines are contraindicated during therapy; inactivated vaccines, including IIV, should be administered as per the immunization schedule and should not be withheld.

The interval between cessation of BRM therapy and safe administration of live vaccines has not been established and is likely to vary by agent. Generally, live vaccines may be administered 3 months after cessation of BRM therapy. However, the recommendations following rituximab therapy is different. Any vaccine history prior to rituximab therapy should be disregarded and complete re-immunization should be done. Once B-cell and Ig levels have recovered, immunization should be recommenced, which is generally 6 months after cessation of rituximab therapy.[7]

In-utero exposure to BRMs: Concerns exist regarding immunosuppression in infants exposed in utero to maternally administered BRMs as detectable drug concentrations may be present for many months following delivery. For such infants, live vaccines should be avoided for 12 months after the last maternal dose during pregnancy. BCG, OPV, and MMR/MR should be avoided in the first year of life. The safety of rotavirus vaccines in such infants is debatable and hence may be avoided.

All inactivated vaccines should be administered according to routine schedule, immune response during the first few months may be suboptimal, depending on the monoclonal used and the gestational period during which it was administered.[8]

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.[9] 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.[6,10]

Specific recommendations for children with cancer and their family members:

- Live vaccines are contraindicated during and for 6 months after the end of chemotherapy. Nonlive vaccines are also best given after 6 months from the end of treatment for durable immunity.
- Annual IIV is the only vaccine recommended for all children during chemotherapy, whereas hepatitis B vaccine is recommended only for previously unimmunized children with risk of transfusion-associated transmission.
- Post-treatment reimmunization or catch-up schedule largely depends on the prechemotherapy immunization status.
- In general, a booster dose of all age-appropriate vaccines should be administered.
- Sibling immunization should continue uninterrupted except for OPV which needs to be substituted by the injectable vaccine. IIV 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.

The vaccine recommendations in a child who has received chemotherapy are shown in **Table 2**.

Special Situations in Cancer Patients

- *Postexposure prophylaxis for rabies:*[11] Children with cancer undergoing treatment, may mount a significantly lower 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.

TABLE 2: Vaccine recommendations in child who has received chemotherapy.

Vaccine	*During chemotherapy**	*After end of chemotherapy**	
		Previously unimmunized children	*Children with completed immunization*
BCG	Not recommended, contact vaccination not discouraged	Single dose BCG at 6 months after completion of chemotherapy	Not recommended in previously immunized children with visible BCG scar
OPV	Not recommended, contact vaccination not recommended	IPV preferred, when unavailable three doses of bOPV 1 month apart (maximum age 5 years)	IPV preferred, when unavailable two doses of bOPV 1 month apart (maximum age 5 years)
MMR	Not recommended, contact vaccination not discouraged	Two doses of MMR (1–3 months apart) should be given to all children after at least 6 months of completion of chemotherapy	One dose of MMR should be given to all children after at least 6 months of completion of chemotherapy
Varicella	Not recommended, contact vaccination encouraged	Two doses of vaccine 1–3 months apart (after 6 months of completing chemotherapy)	One dose of vaccine (after 6 months of completing chemotherapy)
Live-attenuated hepatitis A	Not recommended	Single dose after 6 months of completing chemotherapy	Single dose after 6 months of completing chemotherapy
Rotavirus	Not recommended, contact vaccination not discouraged	Generally, child outgrows the maximum permissible age, therefore not indicated	Generally, child outgrows the maximum permissible age, therefore not indicated

Contd…

Contd…

Vaccine	*During chemotherapy**	*After end of chemotherapy**	
		Previously unimmunized children	*Children with completed immunization*
DPT	Not recommended during ongoing chemotherapy	• Three doses at 0, 1, and 6 months (6 months after stopping chemotherapy) • If <7 years: DTaP/DTwP • If >7 years: Tdap-Td-Td	• Single booster dose (6 months after stopping chemotherapy) • *If <7 years:* DtaP/DTwP • *If >7 years:* Tdap
Hib	Not recommended during ongoing chemotherapy	*6–12 months:* Two doses 8 weeks apart, followed by booster at 12 months; 12–15 months single dose followed by booster at 18 months; 15–60 months single dose (6 months after stopping chemotherapy)	Single booster dose (6 months after stopping chemotherapy)
IPV	Not recommended during ongoing chemotherapy	Two doses of IPV 2 months apart and third dose after 6 months (6 months after stopping chemotherapy)	Single booster dose (6 months after stopping chemotherapy). Two doses for children who received OPV as primary immunization
HBV**	Four doses of vaccine (0, 1, 2, and 12 months) at double dosage is recommended for previously unimmunized children, no further doses for children who completed primary schedule prior to diagnosis	Three doses at 0, 1, and 6 months (6 months after stopping chemotherapy)	Single booster dose (6 months after stopping chemotherapy)

Contd…

Contd…

Vaccine	*During chemotherapy**	*After end of chemotherapy**	
		Previously unimmunized children	*Children with completed immunization*
HAV (inactivated)	Not recommended during ongoing chemotherapy	Two doses 6 months apart (6 months after stopping chemotherapy)	Single booster dose (6 months after stopping chemotherapy)
IIV***	Recommended single dose annually during chemotherapy	Not recommended routinely beyond 1 year from the end of chemotherapy****	Not recommended routinely beyond 1 year from the end of chemotherapy****
Pneumococcal	Not recommended during ongoing chemotherapy	*Age <1 year:* Two doses of PCV-13 at 4–8 weeks interval followed by a booster dose at 12–15 months age *Age 1–2 years:* Two doses of PCV-13, 4–8 weeks apart; age >2 years: 1 dose of PCV-13. PPV-23 booster is not recommended for this group of children (6 months after stopping chemotherapy)	Single booster dose (6 months after stopping chemotherapy)
TCV	Not recommended during ongoing chemotherapy	Single-dose typhoid conjugate vaccine 6 months after stopping chemotherapy	Single dose typhoid conjugate vaccine 6 months after stopping chemotherapy

Contd…

Contd…

Vaccine	*During chemotherapy**	*After end of chemotherapy**	
		Previously unimmunized children	*Children with completed immunization*
HPV	Not recommended during ongoing chemotherapy	3-dose series of 0–2–6 months for all above 9 years of age	No recommendation for booster. Single dose may be considered in females

Notes:
BCG: 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)

- *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 varicella zoster immunoglobulin (VZIg)/ intravenous immunoglobulin (IVIg) and/or oral acyclovir. Under ideal circumstances, VZV IgG levels should be assessed at the time of exposure and for children with less than protective levels, VZIg should be offered (dose: 125 u/10 kg, 62.5 U if <2 kg, to a maximum of 625 U) by the intramuscular (IM) route. If VZIg is unavailable, IVIg at 400 mg/kg can be administered intravenously. In case both the above are unaffordable/unavailable, acyclovir (20 mg/kg per dose, administered orally four times per day, with a maximum daily dose of 3,200 mg) or valacyclovir (20 mg/kg per dose, administered orally three times per day, with a maximum daily dose of 3,000 mg) beginning 7 days after exposure and continuing for 7 days can be used.[12]
- *Other vaccines*: Other nonlive vaccines such as 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.

TRANSPLANT RECIPIENTS

Hematopoietic Stem Cell Transplants

Patients for whom hematopoietic stem cell transplant (HSCT) is planned should receive all routinely recommended inactivated

vaccines (including IIV) at least 2 weeks before the start of the conditioning period, when possible. Routinely recommended live-virus vaccines should be administered if the patient is not already immunosuppressed and the interval to the start of the conditioning period is at least 4 weeks. By vaccinating the nonimmune patient before HSCT, some protection likely will persist in the months after transplant.

However, 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 vaccine for the first time, two doses should be administered. Influenza vaccine is recommended annually lifelong in post-transplant recipient **(Tables 3 to 5)**.
- Two doses of meningococcal conjugate vaccine (MCV4) should be administered 6–12 months after HSCT, if the risk of meningococcal disease is high.

TABLE 3: Schedule for post-HSCT vaccinations.[14]

Vaccine	*Months post-HSCT*	*Schedule*	*Comments*
BCG			Contraindicated
DPT/Tdap	6–12 months	Three doses at 0–1–6 months interval	*<7 years:* DTaP/DTwP *>7 years:* Tdap-Td-Td
Hib	6–12 months	Three doses at 4 weeks interval	
IPV	6–12 months	Three doses at 4 weeks interval	
HBV	6–12 months	Three doses at 4 weeks interval	Postvaccination, check anti-HBs. If <10 u/mL, repeat schedule with standard or double dose
PCV13	3–6 months	Three doses at 4 weeks interval	Give regardless of age
PPSV23	12–18 months, if no GVHD (6–12 months after the last dose of PCV13). If GVHD, give fourth dose of Pneu-C-13 and delay polysaccharide until GVHD resolved	One dose	Consider reimmunization after 1 year
Rotavirus	Contraindicated		

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Vaccine	*Months post-HSCT*	*Schedule*	*Comments*
IIV	4–6 months	Two doses, 4 weeks apart, the first year post-transplant, if <9 years old	Repeat annually
MMR	24 months	Two doses, 4 weeks apart	Serology recommended after second dose
TCV	6–12 months	One dose	
Hep A Inactivated	6–12 months	Two doses at 6–12 months interval	Serology recommended after second dose
Varicella	24 months	Two doses, 4 weeks apart	Serology recommended after second dose
HPV	6–12 months	Three doses	Recommended if indicated by age
Meningococcal conjugate vaccine	6–12 months If the risk of meningococcal disease is high	*(Menactra) <24 months:* 2 doses, 3 months apart (Menactra and Menveo) *>24 months:* One dose	For people with ongoing increased risk of invasive meningococcal disease who completed the primary series at: ≤6 years of age—3 years after completing the primary schedule, then every 5 years after that ≥7 years of age—every 5 years after completing the primary schedule
JE vaccines	6–12 months	Two doses, 4 weeks apart	Use if indicated

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Vaccine	*Months post-HSCT*	*Schedule*	*Comments*
Rabies	6 months (PrEP)		Use if indicated ID not recommended five-dose PEP recommended post-immunization serology recommended RIG/Mabs for cat two bites
MMRV			Contraindicated
Yellow fever	24 months		May be given if indicated

(BCG: bacille Calmette-Guérin; DPT: diphtheria, pertussis, and tetanus; DTaP: diphtheria, tetanus, and pertussis; DTwP: diphtheria toxoid, tetanus toxoid, whole cell pertussis; GVHD: graft-versus-host disease; HB: hepatitis B; HBV: hepatitis B virus; Hib: *Haemophilus influenzae* type b; HPV: human papillomavirus; IIV: inactivated influenza vaccine; IPV: inactivated poliovirus vaccine; JE: Japanese encephalitis; MMR: measles, mumps, rubella; MMRV: measles, mumps, rubella, varicella; PCV: pneumococcal conjugate vaccine; PEP: postexposure prophylaxis; PPSV: pneumococcal polysaccharide vaccine; PrEP: pre-exposure prophylaxis; RIG: rabies immunoglobulin; TCV: typhoid conjugate vaccine; Td: tetanus and diphtheria; Tdap: tetanus, diphtheria, and pertussis)

TABLE 4: Immunization of children with primary immunodeficiency.

	Clinical syndrome	*Vaccines that are contraindicated*	*Comments*
B-lymphocyte defects	X-linked agammaglobulinemia	All live vaccines	Annual IIV is the only vaccine administered routinely to patients receiving IVIG replacement therapy
	Common variable immunodeficiency	All live vaccines	
	Selective IgA deficiency	OPV	All inactivated and live-virus vaccines on the standard annual schedule are safe, likely are effective (although responses may be attenuated), and should be administered. PPSV23 should be administered beginning at 2 years of age
	IgG subclass deficiency	None	
T-lymphocytes defects	Severe combined immunodeficiency (SCID)	All live viral and bacterial vaccines	All inactivated vaccines are ineffective. Annual IIV is the only vaccine administered routinely to patients receiving IG replacement therapy, if there is some residual antibody-producing capacity
	Complete Di George syndrome		
	• Partial Di George syndrome • Wiskott–Aldrich syndrome • Hyper IgM syndrome, ataxia telangiectasia	All live viral and bacterial vaccines	• All inactivated vaccines are safe and may be effective depending on the degree of the immune defect. Age-appropriate vaccines should be administered. • MMR and varicella vaccine (not MMRV) can be considered for those with ≥500 CD3+ T lymphocytes/mm^3, ≥200 CD8+ T lymphocytes/mm^3, and normal mitogen response

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	Clinical syndrome	*Vaccines that are contraindicated*	*Comments*
	Interferon-alpha; interferon-gamma; interleukin 12 axis deficiencies; STAT1 deficiencies	All live-bacteria vaccines and YF vaccine; other live-virus vaccines if severely lymphopenic	• All age-appropriate inactivated vaccines are safe and should be administered • MMR and Varicella vaccines may be safe
Complement deficiencies	Deficiency of components C1-C9, properdin, factor B	None	• All age-appropriate inactivated and live-virus vaccines are safe and should be administered • Hib, meningococcal, pneumococcal, typhoid
Phagocytic defects	Chronic granulomatous disease	All live bacterial vaccines	All inactivated and live-virus vaccines are safe, effective, and should be administered
	• Ill-defined phagocytic defects+/– defects in T-lymphocyte and NK cell dysfunction • Leukocyte adhesion defects, Chediak-Higashi syndrome, MPO deficiency	All live viral and bacterial vaccines	• All age-appropriate inactivated vaccines are safe, effective, and should be given • PPSV23 should be administered >2 years • Consider MenACWY-CRM series beginning in infancy

(IgA: immunoglobulin A; IgG: immunoglobulin G; IgM: immunoglobulin M; IVIG: intravenous immunoglobulin; MMR: measles, mumps, rubella; MMRV: measles, mumps, rubella, varicella; MPO: myeloperoxidase; NK: natural killer; OPV: oral polio vaccine; PPSV: pneumococcal polysaccharide vaccine; YF: yellow fever)

TABLE 5: Vaccination prior to and after solid organ transplant.

Vaccine	*Type*	*Pre-transplant*	*Post-transplant*	*Evaluation of serologic response*
BCG	LAV	Yes	No	No
Diphtheria	I	Yes	Yes	No
Pertussis	I	Yes	Yes	No
Tetanus	I	Yes	Yes	Yes
Hepatitis B	I	Yes	Yes	Yes
Hib	I	Yes	Yes	No
IPV	I	Yes	Yes	No
Rotavirus	LA	Yes	No	No
PCV	I	Yes	Yes	No
PPSV23	I	Yes	Yes	No
MMR	LA	Yes	No	Yes
Varicella	LA	Yes	No	Yes
TCV	I	Yes	Yes	No
Hepatitis A	I	Yes	Yes	Yes
Influenza	I	Yes	Yes	No
HPV	I	Yes	Yes	No
Rabies	I	Yes	Yes	Yes
JE	I	Yes	Yes	No
MCV4	I	Yes	Yes	No

(HPV: human papilloma virus; IPV: injectable polio vaccine; LAV: live attenuated vaccines; MCV4: meningococcal conjugate vaccine; MMR: measles, mumps and rubella; PCV: pneumococcal conjugate vaccine; PPSV23: pneumococcal polysaccharide vaccine; TCV: typhoid conjugate vaccine)

- *Pre-transplant:* Inactivated (I) vaccines: complete schedule at least 2 weeks prior to date of transplant, LAV: Complete schedule at least 4 weeks prior to date of transplant
- *Post-transplant:* 6 months post-transplant, when immunosuppression is at baseline levels. Inactivated influenza vaccine can be administered as early as 1–2 months post-transplant.
- Serological response should be assesses at least 4 weeks after the final dose.

- 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.[11,13]

Solid Organ Transplants

The need for immunization in solid organ transplant (SOT) recipients can arise from three factors, each causing 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 less likely to be significantly suppressed and the patient is more likely to respond, to the vaccine.[15] 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. Solid organ recipients generally receive lifelong immunosuppression. The degree of immune suppression is greatest in the first 3–6 months post-transplant.

Pre-solid Organ Transplantation

Generally, standard vaccine series should be given to children awaiting SOT. Recipients of SOTs should complete all age-appropriate immunizations prior to transplant, in accelerated schedules if needed. HPV vaccine should be given using a three-dose schedule regardless of age. Transplant candidates should receive PCV regardless of age, PPSV if 2 years of age or older, and one dose of Hib vaccine after age 5 years regardless of prior Hib vaccination history. Quadrivalent conjugate meningococcal vaccine is recommended if there are risk factors for meningococcal infection (e.g., hyposplenia, complement deficiency, or increased

risk of exposure from travel or occupation). Vaccination schedules with inactivated vaccines should be completed at least 2 weeks before the scheduled transplant. Vaccination with live vaccines should be completed at least 4 weeks prior to transplant.[15] MMR and varicella vaccine may be given to infants 6–11 months of age if transplantation is expected to occur before age 12 months. If transplantation is delayed, repeat doses should be given starting at 1 year of age. It is desirable that seroconversion be documented.[15]

Post-solid Organ Transplantation

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. Inactivated vaccines are safe in the post-transplant period, however, they are best administered at least 6 months post-transplant, to elicit an optimal immune response. 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 healthcare workers (HCWs) contacts should be immunized against influenza, measles, rotavirus, and varicella. Generally, all live vaccines are contraindicated in the post-transplant period. However, recent studies show that live vaccines may be administered at least 1 year after transplant and when the degree of immunosuppression is very low.[15]

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 conjugate vaccine, meningococcal conjugate vaccine, and typhoid conjugate vaccines is indicated in addition

to all routine vaccines. In patients with planned splenectomy, vaccination schedules should be completed 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. However, vaccination can be initiated at the time of discharge. All live vaccines may be safely given.[16,17]

CONGENITAL IMMUNODEFICIENCY (PRIMARY IMMUNODEFICIENCY DISORDERS) (see TABLE 4)

Primary immunodeficiency diseases (PIDs) are a heterogenous group of inherited disorders that may involve one or multiple components of the immune system. PIDs are classified according to the compartment of the immune system that is primarily involved. Vaccine recommendation vary according to the type and severity of the immune deficiency.[18]

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 indicated higher antigen content or more doses (hepatitis B). Assessment for 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 cystic fibrosis or celiac disease may mount a suboptimal immune response and hence assessment of antibody response is recommended. Children with severe cardiac and pulmonary diseases should receive pneumococcal and annual influenza vaccines.[19]

IMMUNIZATION IN CHILDREN WITH HISTORY OF ALLERGY

It is essential that parents should be asked whether their children experienced any allergic symptoms following previous vaccinations. 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. All vaccinating units need to have adrenaline, antihistamine, parenteral steroids, and oxygen available at the site of vaccination. Children with history of serious egg allergy should not receive yellow fever vaccines but can safely receive other vaccines including measles and MMR vaccines. Children 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). Children with previous anaphylaxis to egg can receive the IIV, in a center wherein staff experienced in recognizing and treating anaphylactic reactions are available and the child should be under observation for a minimum of 1 hour. 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.[19] Children sensitized to a vaccine or its components with previous anaphylaxis to this vaccine should be revaccinated only if absolutely necessary (rabies vaccine). In this situation, rapid desensitization with increasing vaccine doses are administered every 15–30 minutes provided that there are no signs of allergic reaction (0.05 mL of 1:10 dilution, then 0.05 mL, 0.1 mL, 0.15 mL, 0.2 mL, of a 0.5 mL full-strength vaccine). This results in transient desensitization and such children must still be considered allergic to the vaccine. This protocol should be done in a setting where prompt treatment of anaphylaxis by experienced staff is available.[20]

IMMUNIZATIONS FOR HEALTHCARE PERSONNEL

Healthcare personnel (HCPs) need to be immunized for two reasons. First, susceptible HCPs are at increased risk for occupational acquisition of VPDs. Elderly HCPs and HCPs who have underlying diseases (e.g., immunosuppression, chronic diseases) or specific conditions (pregnancy, elderly) should be protected.

Second, HCPs may transmit VPDs to their patients, many of whom are at high risk for a serious disease course, complications, or even death because of their age (e.g., neonates, young infants, elderly) and/or underlying conditions (e.g., pregnant women, immunocompromised patients, patients with underlying diseases).

In many outbreaks of VPDs including influenza, pertussis, measles, rubella, varicella, hepatitis A, and hepatitis B, HCPs have been traced as the primary source of infection.[21]

Moreover, HCPs may have significant immunity gaps against some of the common VPDs.[21]

Vaccine Recommendations for Healthcare Personnel

- *Hepatitis B:* HCPs without documented evidence of a complete HepB vaccine series or no serologic evidence of immunity should receive three doses of HepB vaccine in a 0–1–6 months schedule. Anti-HBs serologic test should be done 1–2 months after the final dose. A vaccinee whose anti-HBs remains <10 mIU/mL after two complete series is considered a "non-responder."
- *Influenza:* HCPs should receive annual influenza vaccination. Live-attenuated influenza vaccine (LAIV) may only be given to nonpregnant healthy HCP age 49 years and younger and such HCPs should avoid close contact with severely immunosuppressed patients who require protective isolation for at least 7 days after vaccine administration.
- *MMR:* HCPs without documented evidence of MMR vaccine series or no serologic evidence of immunity to MMR should receive two doses of MMR at an interval of at least 28 days. During outbreaks of measles or mumps, HCPs without documentation of vaccination or serologic evidence of immunity to measles or

mumps should receive two doses of MMR vaccine. One dose of MMR vaccine should be considered for HCP with no laboratory evidence of disease or immunity to rubella.

- *Varicella:* HCPs without documented evidence of varicella vaccine series or no serologic evidence of immunity to varicella should receive two doses of Varicella vaccine, at an interval of at least 28 days.
- *Tdap:* HCPs without documentation of receipt of Tdap should receive a dose of Tdap, followed by decennial Td doses. Pregnant HCPs should be revaccinated during each pregnancy.[22]

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 IVIg) can inhibit the immune response to live vaccines such as measles and rubella vaccines for 3 months or longer. 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 such as Ty21a typhoid, rotavirus, yellow fever, LAIV, and zoster vaccines may be administered at any time before, concurrent with, or after administration of any Ig, hyperimmunoglobulin, or IVIg.[19] 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 **(***see* **Table 6)**, the vaccine dose should be repeated unless serologic testing is feasible

TABLE 6: Guidelines for administering antibody-containing products* and vaccines.[23]

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†

Notes:

*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 IgG/kg) maximum 625 units	IM	5
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

Contd…

Contd…

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

Notes:

*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.

Contd…

Contd…

¶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)

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 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.[19]

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 **(***see* **Tables 6 and 7)** unless serologic testing indicates a protective antibody response.[19]

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.[19]

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 such as upper respiratory tract infections, mild diarrhea, and otitis media.[19]

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 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, and PPSV.[19]

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 first trimester).[24] 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.[13,25] IIV 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 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.[24]

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.[26,27] 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.[28] The birth dose of hepatitis B vaccine can be administered at any time after birth in babies weighing 2 kg. However, in babies <2 kg that immunogenicity of the birth dose of the vaccine has been shown to be suboptimal in some studies.[26] 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 <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. Since most developing countries employ the UPI schedule of 6–10–14 weeks, with a pentavalent or hexavalent vaccine, containing the Hepatitis B antigen, in 2017, the WHO recommended that a birth dose of hepatitis B vaccine can be given to low birth weight and premature infants. For these infants, the birth dose should not count as part of the primary three-dose series; the three doses of the standard primary series should be given according to the national vaccination schedule.[23]

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 HCPs 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.[19]

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 2.5 cm between different vaccination sites. 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 catchup immunization, doses should preferably be given at the minimum possible interval to entail early protection.[19]

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4.3 VACCINATION STRATEGIES FOR TRAVELERS

Srinivas G Kasi, Harish Kumar Pemde

INTRODUCTION

The importance of protecting the health of individual travelers, as well as safeguarding the health of the communities to which they return, cannot be overstated. In the past 10 years, e.g., travelers have faced newly emerging threats, including Ebola, chikungunya, Zika, multidrug-resistant typhoid, and tuberculosis (TB). For travelers, vaccination offers the possibility of avoiding a number of diseases that may be encountered during 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 the 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 given simultaneously at multiple sites, as otherwise inoculation of two live virus vaccines should be separated by at least 4 weeks. All schedules should be completed at least 2 weeks before the day of travel.

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 be up-to-date in age-recommended vaccinations or have a change in the routine immunization schedule as it applies to travelers.[3,4]

Bacillus Calmette–Guérin Vaccine

Bacillus Calmette–Guérin (BCG) immunization may be considered for travelers planning extended stays in areas of high tuberculosis

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 • 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

prevalence and where tuberculin skin testing and appropriate chemoprophylaxis may not be feasible or where primary isoniazid resistance of *Mycobacterium tuberculosis* is high. This may not be relevant to Indian travelers, who have all received BCG during the neonatal period.

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 be

started at 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 a measles containing vaccine (MR/MMR) is 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 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 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: (1) Travelers to areas with current outbreaks; (2) travelers particularly <30 years of age who are traveling to the sub-Saharan meningitis belt during the dry season (December–June); (3) all pilgrims arriving to Saudi Arabia for purposes of Umrah and Hajj;[7] (4) refugee settings with overcrowding, and persons who travel to work in these settings; (5) 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. The period of validity of the International Vaccination Certificate for yellow fever is life time beginning 10 days after vaccination.[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, preexposure 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: (1) travelers intending to live or work in areas where rabies is enzootic and rabies control programs for domestic animals are inadequate; (2) travel to area where adequate and safe postexposure management is not available; (3) travelers with extensive outdoor exposure in rural areas—such as might occur while running, bicycling, hiking, and camping, irrespective of the travel duration; (4) individuals traveling to countries or areas where modern rabies vaccines are in short supply.

A course of one-site intramuscular (or two sites intradermal) injection of modern vaccines should be administered on day 0 and

7 (total of two doses). The national guidelines on rabies prophylaxis (National Center for Disease Control, India; 2019) recommends one full dose of the rabies vaccine intramuscularly or 0.1 mL intradermally on one site on days 0, 7, and booster on either day 21 or 28 (total three doses).

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 are for: (1) Travelers who plan to spend ≥1 month in endemic areas during the Japanese encephalitis virus (JEV) transmission season; (2) 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; (3) short-term (<1 month) travelers to endemic areas during the JEV transmission season for travelers with extensive outdoor exposure (camping, hiking, working, etc.); (4) 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. Two doses of the inactivated JE vaccines should be administered at an interval of 4 weeks and the schedule should be completed at least 1 week before potential exposure to JEV.

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. For the unimmunized, a single dose of the typhoid-conjugated vaccine can be administered at any age beyond 6 months. The polysaccharide typhoid vaccine can be used above 2 years of age.

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 (Shancol™) is available. Two doses are given 14 days apart for individuals aged ≥1 year. One booster dose is recommended after 3 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 and Pakistan) and those traveling to countries where poliovirus is in circulation following importation 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 (OPVs) 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 need to take a single dose of OPV 4 weeks before the travel date.

Recently, it has been recommended to give one dose of OPV and one fractional dose of inactivated polio vaccine (IPV) to all the immigrants/returnees from Afghanistan and stool samples of the immigrants up to 15 years of age, to be collected, to detect polio virus.

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 have been on corticosteroid therapy for >2 weeks at a dose equivalent to >20 mg/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. 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.

COVID VACCINATION FOR TRAVELER

Most countries insist on a fully vaccinated certificate for entry into the country. According to the Centers for Disease Control and Prevention (CDC), "Fully vaccinated" implies:

- 2 weeks (14 days) after a dose of an accepted single-dose vaccine
- 2 weeks (14 days) after the second dose of an accepted two-dose series
- 2 weeks (14 days) after receipt of the full series of an accepted COVID-19 vaccine (not placebo) in a clinical trial
- 2 weeks (14 days) after receipt of two doses of any "mix-and-match" combination of accepted COVID-19 vaccines administered at least 17 days apart.

Generally, all WHO listed COVID-19 vaccines are accepted in most countries. Some countries require traveler to get tested for COVID virus 3–5 days after arrival and some have mandatory quarantine period (7–14 days).

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 the 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. Yellow fever vaccines should be administered only in authorized vaccination centers. Receipt of vaccine with date of

administration should be mentioned in the International Certificate of Vaccination and signed by the administering authority. As a proof of yellow fever vaccination, traveler must carry the original International Certificate of Vaccination.

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Chapter 5

Future Vaccines and Vaccine Hesitancy

5.1 FUTURE VACCINES

Srinivas G Kasi, S Balasubramanium

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 TECHNOLOGIES

In the early stages of modern vaccinology, vaccines were produced by the "empirical approach," which consisted of isolate, inactivate, and inject the microorganism which causes the disease. Many of the highly successful vaccines, such as the diphtheria and tetanus toxoids, pertussis, rabies, influenza, smallpox, polio, and the bacillus Calmette-Guérin (BCG) vaccines, were produced utilizing this technology. This was followed by the period of recombinant DNA vaccines and the glycol-conjugated vaccines. Reverse vaccinology,

which was the first successful platform in the genomic area, resulted in successful vaccines against the Group B meningococcus.[2]

Next-generation technologies are playing a very important role in the development of vaccines against some of the diseases for which vaccines are presently unavailable. These new technologies have been made possible by the integration of developments in biology, computer science, engineering, bioinformatics, physics, and many other physical sciences. Structural vaccinology, wherein protective B-cell epitopes are optimized in terms of stability epitope, presentation, ease of production, and safety, has enabled design of rationally engineered vaccines. The systems biology approach to vaccines development enables prediction of immune response on the basis of molecular signatures, which are identified within a few days of vaccine administration.[3,4]

Several new platforms are in development and some are in use. These include DNA vaccines, mRNA vaccines, viral-vectored vaccines, and chimeric vaccines. The rapid development and deployment of COVID-19 vaccines has resulted in some of these platforms entering clinical usage.

With vaccines utilizing hidden epitopes, which are generally less immunogenic, there is a need for potent adjuvants which are also capable of skewing the immune response to a Th1 type. Some of the novel adjuvants include MF59, liposomes, saponins, toll-like receptor (TLR) agonists, and oligodendronucleotides.[5]

Needle-free vaccine delivery devices are being actively investigated. These devices increase the ease and speed of delivery vaccines, offer improved safety and compliance, decrease costs, and reduce the pain associated with vaccinations, thereby making vaccinations more acceptable. Transcutaneous immunization using patches with microneedles coated with vaccine and antigen is proving to be successful and is found to initiate robust humoral and cell mediated immune responses.[6]

Vaccines in development are targeting pathogens with multiple stages of development (malaria), unstable genomes [human immunodeficiency virus (HIV)], or chronic infections [hepatitis B virus (HBV) and human papillomavirus (HPV)]. Therapeutic cancer vaccines, vaccines against autoimmune diseases, diabetes mellitus,

hypertension, allergies, addictions, obesity, and pregnancy are being actively investigated.

NEWER VIRAL VACCINES

Dengue Virus Vaccine

Dengvaxia™ (also referred to as CYD-TDV) is a live recombinant tetravalent dengue vaccine developed by Sanofi Pasteur and administered in a three-dose schedule (0/6/12 months). Dengvaxia was first licensed in December 2015. Due to the occurrence of vaccine-induced antibody-dependent enhancement, in 2018, the World Health Organization (WHO) issued fresh recommendations for its use. The WHO recommended that only persons with evidence of a past dengue infection should be vaccinated (based on an antibody test, or on a documented laboratory confirmed dengue infection in the past). Where pre-vaccination screening is not feasible, the vaccine should be administered only in those areas vaccination wherein recent serosurveys have documented seroprevalence rates of at least 80% by age 9 years.[7]

Vaccines in phase III trials:

- The Takeda vaccine (TAK-003) is a tetravalent vaccine in which wild DEN2 is attenuated and the *Env* and *PrM* genes of DEN 1, 3, and 4 are inserted into the genome of the attenuated DENV2 backbone. The primary efficacy data from part 1 of an ongoing phase 3 randomized trial was recently published.[8] Vaccine efficacy was 80.2% [95% confidence interval (CI), 73.3–85.3] against virologically confirmed dengue and 95.4% (95% CI, 88.4–98.2) against dengue leading to hospitalization. In those who were seronegative at baseline (27.7%), the vaccine efficacy was 74.9% (95% CI, 57.0–85). VE against DEN 1 was 73.7% (74.5–87.6), DEN 2: 97.7% (92.7–99.3), DEN 3: 62.6% (43.3–75.4), and DEN 4: 63.2% (–64.6 to 91.8).

  The incidence of serious adverse events was similar in the vaccine group and placebo group (3.1% and 3.8%, respectively).

In August 2022, Takeda's QDENGA® [Dengue Tetravalent Vaccine (live, attenuated)] received approval in Indonesia, for use regardless of prior dengue exposure.

- TetraVax-DV (NIH) is a combination of four monovalent attenuated DENVs, which have been attenuated by a targeted 30-nucleotide (nt) deletion (D30) in the 30 non-translated region (NTR).[9,10] Approximately 17,000 subjects including children, adolescents, and adults have been included in a multicenter trial in Brazil.[9] Additional phase II trials of TetraVax-DV are also ongoing in Thailand, Taiwan, and Bangladesh.[10,11] This vaccine has been licensed for further development to Instituto Butantan in Brazil; VaBiotech in Vietnam; Panacea Biotec, Serum Institute of India and Indian Immunologicals in India, and Medigen Biotech in Taiwan.[12]

Vaccines in phase II trials:

- *TDENV-PIV*: This is a purified inactivated vaccine (TDENV-PIV), which consists of all four dengue serotypes. The encouraging results in phase 1 trials in USA and Puerto Rico have resulted in progress to phase 2 trials.[13,14]

Vaccines in phase I trials:

- Merck's V180, a recombinant subunit dengue vaccine, adjuvanted with ISCOMATRIX, is in phase 1 studies.[12]

A DNA vaccine by the US Naval Medical Research Center (NMRC) is being evaluated in a phase 1 trial.[12]

The Serum Institute of India is currently recruiting in Australia for its phase I trial of its Dengusiil™ dengue vaccine candidate.[15]

Human Immunodeficiency Virus Vaccine

The extraordinary genetic diversity and high mutability rate of the virus and its capacity to "evade and escape" inside lymphoid and macrophage cells, and the tropism of the virus for T helper cells facilitating infection, spread, and persistence are some of the obstacles researchers face in the development of vaccines against HIV infections. Nevertheless, the possibility of T cell-based or broadly neutralizing antibody-based vaccines hold promise and are the cornerstone of future research.[16]

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 was tested in the RV144 trial in 16,000 Thai subjects. A vaccine efficacy of 31.2% (74 seroconversions versus 51) was seen in this trial. There was, however, no effect on viral load at the set point. This was the first time that a HIV vaccine trial showed a positive efficacy. Immunogenicity analysis suggested that IgG specific for the V1V2 region of gp120 was associated with reduced risk of HIV-1 infection and that plasma Env IgA was directly correlated with infection risk.[17]

Two HIV vaccines are in phase 3 trials. The Imbokodo trial (HVTN 705/HPX2008) is evaluating a prime-boost regimen consisting of priming immunizations with adenovirus serotype 26 (Ad26) vectors encoding four different HIV "mosaic" antigens that combine elements from multiple virus clades, followed by a boost containing the HIV gp140 envelope protein in alum adjuvant. The gp140 boost is derived from a clade C virus.[18]

The Mosaico trial is also evaluating a prime-boost strategy with priming similar to the Imbokodo trial, while the boosting is done with a bivalent clade C and mosaic gp140 protein construct.[18]

HVTN 704/HPTN 085 and HVTN 703/HPTN 081 trials investigated the efficacy of intravenous infusions of the broadly neutralizing antibody (bNAb) VRC01, administered every 8 weeks. Unfortunately, both trials did not demonstrate any significant efficacy.[19]

ALVAC-HIV (vCP2438) Bivalent clade C gp120/MF59, which is a Canarypox vector encoding HIV-1 clade C gp120, clade B gp41, Gag, and protease + protein boost comprising two clade C Env proteins (TV1.C gp120 and 1086.C gp120), is in phase IIb/III trials (HVTN 702).[20]

HIV DNA-rTV: DNA prime and replication-competent Tiantan vaccinia virus vector boost encoding Gag, Pol, and Env proteins from HIV-1 CN54 is in phase IIb trials.[20]

ALVAC-HIV vCP1521 AIDSVAX B/E: Canarypox vector encoding HIV-1 CRF01_AE Env, clade B Gag, the protease-encoding portion of the Pol protein, and a synthetic polypeptide encompassing several known CD8+ T-cell epitopes from the Nef and Pol proteins. AIDSVAX B/E recombinant protein vaccine containing gp120 from HIV-1 clades B and CRF01_AE is in phase II trials.[20]

Respiratory Syncytial Virus Vaccine

Currently, there are at least 17 investigational RSV vaccines in clinical development, including live-attenuated, vector-based, particle-based, nucleic acid, and subunit vaccines. Target groups include pediatrics, elderly, and maternal immunization to protect the infant.[21]

An effective antiviral response following an RSV vaccine must include a prolonged neutralizing antibody response, Th-1 polarized immunity that promotes both CD8+ and CD4+ T cells, type I interferon (IFN) secretion and an efficient mucosa immune response.

Figure 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.[22]

The only vaccine to complete phase 3 trials, ResVax, an aluminum adjuvanted, fusion (F) protein recombinant nanoparticle vaccine, showed a vaccine efficacy of 39% against medically significant RSV LRTI (97.5% CI, –1 to 64%) 44% against RSV LRTI hospitalizations (95% CI, 20–62%), and 48% against RSV LRTI with severe hypoxemia (95% CI, –8 to 75%). This study did not meet the prespecified success criterion for the primary clinical endpoint of this trial.[23]

It is estimated that it will be at least 5–10 years until a safe and effective vaccine is approved for clinical use.

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 cure HCV infection are quite promising but concerns loom over therapy accessibility and potential drug resistance. Evolution of viral infections has 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

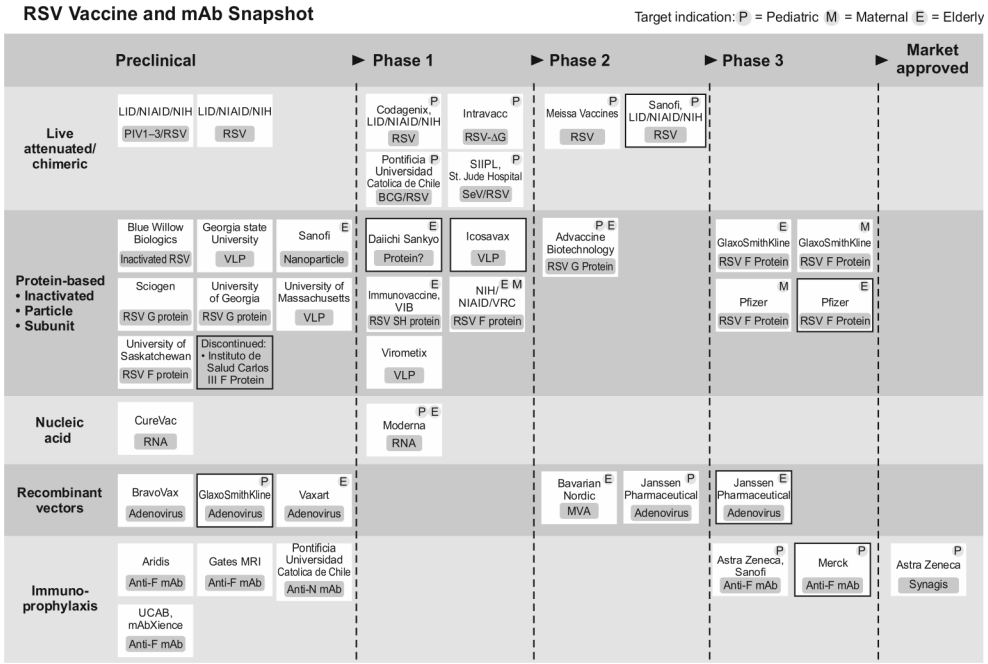

Fig. 1: RSV vaccines in development.

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 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.[24]

A recombinant E1E2 protein (rE1E2) derived from a Gt1a isolate, adjuvanted with MF59, has completed phase 1 trials. It was found to be safe. The vaccine elicited polyfunctional CD4+ T cell responses and humoral responses. Some participants also elicited cross reactive nAbs.[24]

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.[24]

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.[25] ERVEB is a replication-competent, live, attenuated recombinant vesicular stomatitis virus (rVSV) vaccine manufactured by Merck. It is approved by the US Food and Drug Administration (FDA) for the prevention of disease caused by *Zaire ebolavirus* in individuals 18 years of age and older as a single-dose administration.[26] 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.

Malaria Vaccine

Vaccine development efforts have focused on preventing illness from *Plasmodium falciparum* and to a lesser extent, on *Plasmodium 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

The RTS,S/AS01 vaccine is the only malaria vaccine to be recommended for use by the WHO. The WHO has recommended this vaccine for the prevention of *P. falciparum* malaria in children living in regions with moderate-to-high malaria transmission, as defined by WHO.[27]

Schedule: Three primary doses at a minimum interval of 4 weeks between doses, beginning at 5 months of age, with a fourth dose provided approximately 12–18 months after the third dose.

In the pivotal phase 3 studies done in 11 countries, over 12 months of follow-up after the third dose, the vaccine efficacy against clinical malaria (uncomplicated and severe) was 51% (95% CI 47–55) and against severe malaria was 45% (95% CI 22–60). Over 46 months' follow-up after the third dose, children who received a fourth dose 18 months after the third dose showed vaccine efficacy against clinical malaria was 39% (95% CI 34–43) and against severe malaria 29% (95% CI 6–46).[27]

In addition, a reduction of 61% (95% CI 27–81) was seen in malarial anemia, 29% (95% CI 4–47) reduction in blood transfusions and 37% (95% CI 24–49) in malarial hospitalization, over a follow-up of 4 years.[27]

PfSPZ, an attenuated whole sporozoite vaccine, which is given intravenously, has shown a vaccine efficacy of 100% against Controlled Human Malarial Infection model up to 79 days of follow-up. It is now being studied in a cohort of 2,100 subjects.[28]

The R21/Matrix-M vaccine has shown an efficacy of 71–76% against at least one malaria episode over 12 months (depending on adjuvant dosage).[28]

RH5.1, which is a vaccine targeting blood stages, has completed phase 2 trials and Pfs230D1M, which is a transmission blocking agent, has completed phase 2 trials. [28]

In addition, over 30 candidate vaccines are in various stages of clinical trials.[28]

BACTERIAL VACCINES

Tuberculosis Vaccine

As on date, there are 14 tuberculosis (TB) vaccine candidates in clinical trials **(Fig. 2)**. These include vaccines based on subunits, whole-cell mycobacteria, mycobacterial fusion protein(s) in new adjuvant formulations (ID93: GLA-SE, H56.IC31, M72:ASO1E, GamTBVac), and recombinant live-attenuated or replication-deficient virus-vectored expressing one or more *Mtb* proteins (Ad5Ag85, ChadOx1.85/MVA85A, TB/FLU-04L).[29,30]

Three vaccines are in phase 3 trials. These include the recombinant BCG (VPM1002), which is being assessed in newborns as a BCG replacement, in adolescents and adults as a BCG booster and as a therapeutic vaccine. *Mycobacterium indicus pranii* (MIP) vaccine by Cadilla and Indian Council of Medical Research (ICMR) is a heat-killed *MIP* vaccine, approved by the Drug Controller General of INDIA and FDA as an immune-therapeutic and immunoprophylactic adjunct therapy in multibacillary leprosy patients and for preventing the development of leprosy among close contacts of leprosy patients. The phase 3 trial, in India, is investigating the efficacy and safety for the prevention of pulmonary TB among healthy household contacts of sputum smear-positive TB patients. *M. vaccae*™ vaccine, which is inactivated *Mycobacterium vaccae,* is licensed in China as a therapeutic vaccine to shorten TB treatment for patients with drug-susceptible TB.[29,30]

Shigella Vaccine

Shigellosis is an important cause of morbidity and mortality, particularly in children <5 years old in developing countries. Several vaccines are in various phases of clinical development.[31]

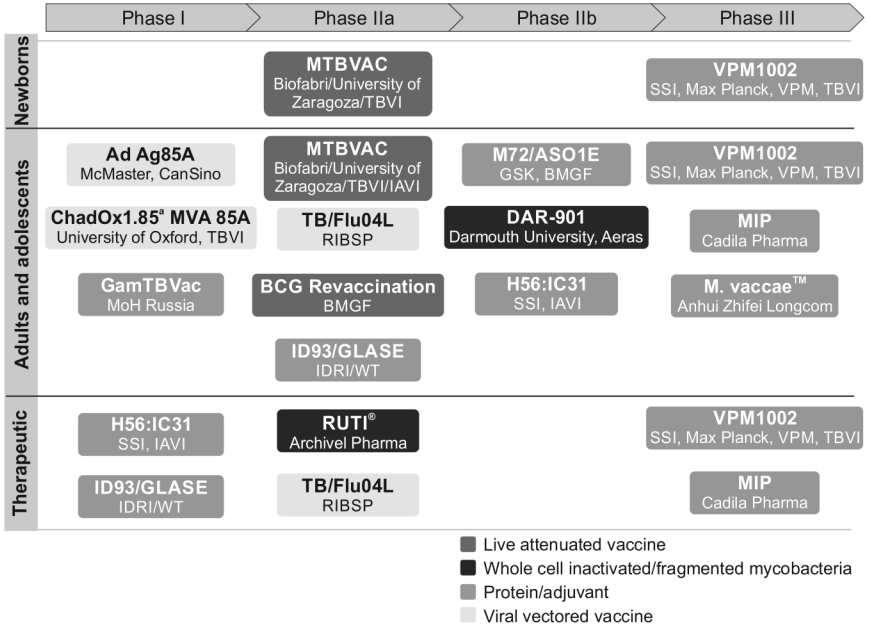

Fig. 2: Tuberculosis vaccines in clinical trials.

The chemically prepared glycoconjugate (O polysaccharide covalently linked to carrier protein) of National Institutes of Health (NIH) is in phase 3 trials.

The virG-based live-attenuated (WRSS1, WRSs3, WRSf3) of WRAIR, Silver Spring, Maryland, USA, and the Recombinant glycoconjugate O polysaccharide specific biconjugate vaccine of LimmaTech Biologics AG Schlieren, Switzerland, are in phase 2 trials.

Inactivated trivalent *Shigella* whole cell formalin inactivated vaccine of PATH and WRAIR, guaBA-based live-attenuated (CVD 1208, CVD 1208S) University of Maryland School of Medicine, Baltimore, and the GMMA vaccine of Sclavo Behring Vaccines Institute for Global Health are in phase 1 trials.

Nine vaccines are in the preclinical phase of development.[31]

Escherichia coli Vaccine

The majority of enterotoxigenic *Escherichia coli* (ETEC) vaccine candidates currently under development use various platforms to induce anti-labile toxin (LT) and anti-colonization factor/coli surface (CF/CS) antibodies. This will result in thereby blockage of adherence to the intestinal lining and pathogenicity. Two cellular candidate vaccines have completed phase ½ studies. ACE527 is a vaccine consisting of three ETEC strains expressing major colonizing factor (CF) and coli surface (CS) antigens, combined with the B subunit of labile toxin, was demonstrated a significant efficacy, when combined with a mucosal adjuvant, nontoxic double mutant of LT, dmLT. This candidate is not currently under active development.[31] ETVAX, consists of four *E. coli* preparations engineered to express large quantities of colonization factors (CFA/I) and coli surface proteins designated CS3, CS5, or CS6, formulated with B subunit of the cholera toxin and coadministered with dmLT as a mucosal adjuvant. This vaccine has successfully completed a phase 1/2 trial in Bangladeshi children in three age groups between 6 and 23 months.[32] It was found to be safe and elicited mucosal IgA antibody responses in most participants in the two older age groups, whereas such responses to four of the five antigens were less frequent and of lower magnitude in infants aged 6–11 months than in older children.

This vaccine was successful in a protection trial in Finnish travelers to Benin.[33]

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.[34]

Other vaccines in development include vaccines targeting hepatitis E,[35] *Staphylococcus* aureus,[36] cytomegalovirus,[37] Epstein–Barr virus,[38] Group A streptococci,[39] and vaccines targeting the neglected tropical diseases.[40]

While vaccines have long been considered to be prophylactic interventions, therapeutic vaccines against cancers,[41] autoimmune diseases,[42] and chronic infections, e.g., hepatitis B, HPV, and HCV are being investigated. In addition, vaccines targeting hypertension, obesity, allergies, and addictions are also being investigated.

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.[43]

Single-peptide vaccines continue to be tested extensively, especially in "immunogenic" cancers such as melanoma.[41] 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.

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5.2 VACCINE HESITANCY

M Indra Shekhar Rao, Srinivas Kalyani

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 (VPDs). Vaccine hesitancy has been recognized as an important emerging risk factor for nonvaccination and was listed as one of the World Health Organization (WHO)'s Ten Threats to Global Health in 2019.[1]

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 anti-vaccinationists or the anti-vaccine lobby with its global existence.

Vaccine hesitancy is a behavior influenced by a number of factors. The WHO's 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) **(Fig. 1)**.[2]

A 2018 Wellcome Trust study[3] on vaccine hesitancy found that over 95% of Indian parents surveyed believed vaccines to be safe, effective, and important. In a study done in Chandigarh in 2021, it was found that those with a high school education had 0.10 times the odds of vaccine hesitancy compared to those with less education. Those having more antenatal care visits were less vaccine hesitant.[4]

In a cross-sectional study conducted in the pediatric outpatient department of a tertiary care hospital in Chennai, among mothers of children between 1 and 5 years of age attending the pediatrics outpatient department of the tertiary care hospital, it was noted that >99% of mothers felt that childhood vaccines are important and effective, ~61% felt that the newer vaccines carried a greater risk of adverse effects, >90% had concerns about serious adverse effects, and surprisingly ~85% felt that there was no need for vaccines against diseases that were uncommon.

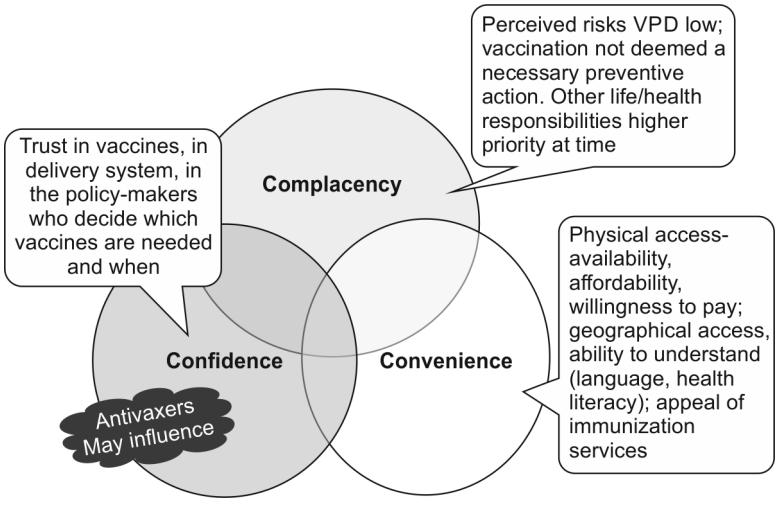

Fig. 1: Vaccine hesitancy determinants. (VPD: vaccine-preventable disease)
Source: SAGE Working Group on Vaccine Hesitancy Final Report www.who.int/immunization/sage/meetings/2014/october/SAGE_working_group_revised_report_vaccine_hesitancy.pdf?ug=1.

The reasons for missing vaccination sessions, during the Mission Indradhanush program, obtained by routine monitoring interviews with caregivers of undervaccinated children between October 2017 and February 2018 are shown in **Figure 2**. It is to be noted that awareness gap was responsible for 48% of missed vaccine sessions, fear of adverse event following immunization (AEFI) was noted in 24%, and vaccine resistance in 11%.

During the Covid pandemic, inadequate primary healthcare services, disruption of immunization services, fear of getting infected with Covid, social distancing norms, and other infection prevention control practices have adversely affected health-seeking behavior and routine visits to healthcare facilities.

Vaccine-hesitant individuals hold varying degrees of indecision regarding certain vaccines or vaccination in general. 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

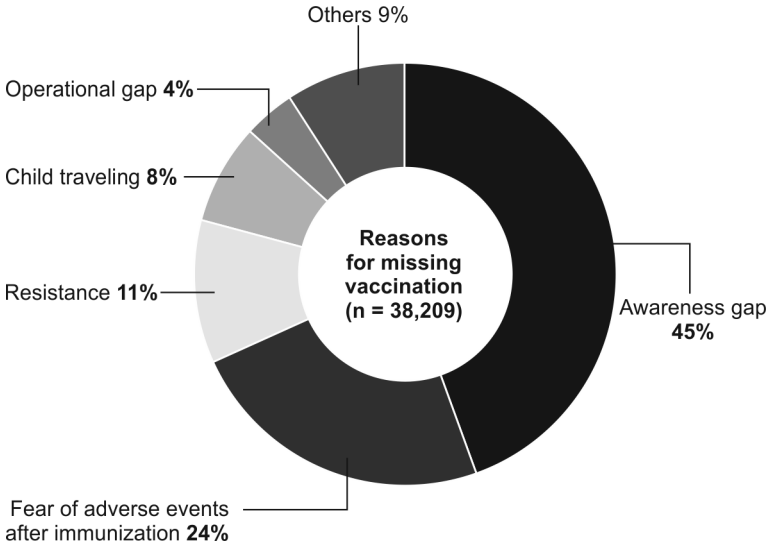

Fig. 2: Reasons for missing vaccination sessions.

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.

As vaccine uptake peaks, the disease incidence declines, and the total number of adverse events after vaccination increases, but these adverse events may lead to loss of confidence in the vaccine as the public perceives the risk of vaccination to outweigh the risk of disease ("loss of confidence" phase). This, in turn, may increase vaccine refusal and ultimately lead to disease resurgence. After disease resurgence or an outbreak, as the public again appreciates the increasing burden of disease, vaccine acceptance is restored and vaccination rates increase ("resumption of confidence" phase). In the rare incidents in which disease is eradicated by vaccine, as occurred with smallpox, vaccination can stop ("eradication" phase). This conceptual framework is more applicable to diseases for which the time between exposure and infection is short, such as measles, pertussis, or polio, and less relevant to vaccines against human papillomavirus (HPV), for which the benefits of

immunization in preventing cancer may take years or decades to become apparent.

PRE-EMPTING VACCINE HESITANCY

Discussions and dissemination of information about vaccines should be initiated with the prospective parents before the delivery and during the first few postnatal appointments. At these visits, parents can be provided with the "IAP Q & A on vaccines" leaflets, information about credible web sources for information about vaccines, and opportunities should be provided to ask questions.

It is necessary to have a presumptive approach to discussions about vaccinations and restating the recommendation after addressing parents' concerns. Tell the parents that "Today we are going to give your child the recommended vaccines to keep your child healthy and your child needs three vaccines today" instead of saying "What do you want to do about the shots?"

The vaccine provider should initiate a conversation about the role of vaccines in saving lives, hospitalization, and improving child survival. Emphasis should be placed on the safety aspects, which are investigated at every stage of vaccine development and are continued even after licensure and usage in the population. It is to be emphasized that minor adverse effects are common but serious adverse effects are very uncommon and the benefit–risk ratio is heavily tilted toward benefit.

VACCINE FEARS AND MISUNDERSTANDINGS

The three main factors affecting the acceptance of vaccines are concerns about vaccine safety, doubts about the necessity of vaccines, and a lack of trust in the authorities recommending the vaccines **(Fig. 3)**.

APPROACH TO MANAGEMENT OF VACCINE HESITANCY

Vaccine hesitancy is a continuum, from a parent who accepts all vaccines to a parent who refuses all vaccines **(Fig. 4)**. The aim of any vaccine hesitancy intervention is to move the caregiver from a state of hesitancy to acceptance of vaccinations.

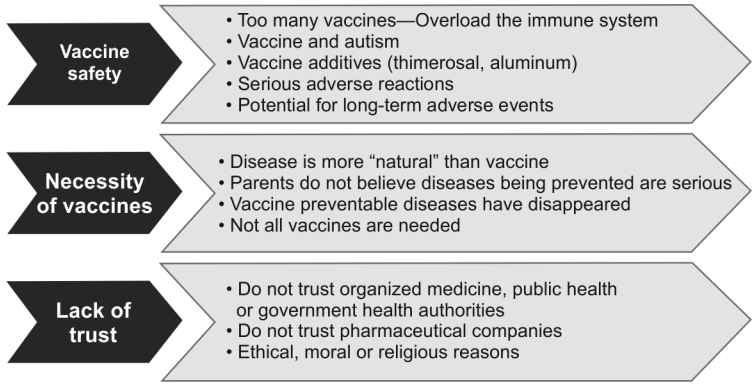

Fig. 3: Factors affecting the acceptance of vaccines.

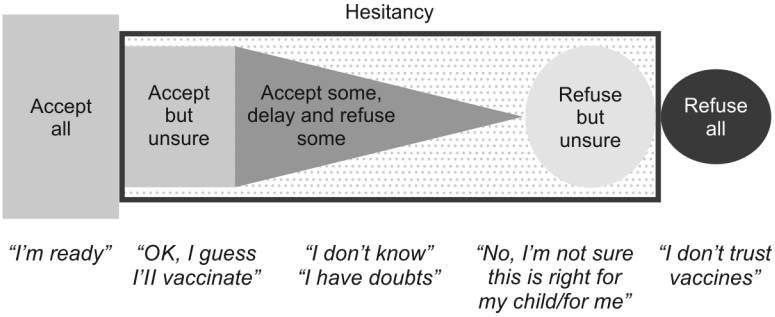

Fig. 4: The vaccine hesitancy continuum.

The first step is to establish a positive dialog. Listen to the caregiver's concerns and ask for the sources of information on the basis of which hesitancy has occurred and summarizes the concerns.

At this stage, the vaccine provider should initiate a conversation about the role of vaccines in saving lives, hospitalization, and improving child survival. Emphasis should be placed on the safety aspects that are investigated at every stage of vaccine development and even after licensure and usage in the population.

As the conversation evolves, explore the concerns further. Provide information, obtained from authentic sources, and explain

using simple language. Verify what they have understood and what they will do with this information. Discuss specific concerns. Some of these concerns include pain during vaccination, adjuvants, preservatives, formaldehyde, mercury, and overload of immune system.

Motivational Interviewing[8]

Motivational interviewing (MI) is an effective counseling method that enhances motivation through the resolution of ambivalence. MI emphasizes a collaborative therapeutic relationship in which the autonomy of the patient is respected and the patient's intrinsic resources for change are elicited by the therapist. Adoption of a nonconfrontational approach to guide the patient toward change is the essence of MI. The process of MI includes the following:

- *Ask open-ended questions*: Do you think MMR vaccines cause autism? is a close-ended question. The response could be yes or no. If the answer is yes, the conversation ends. On the other hand "What is your opinion about the link between MMR vaccine and autism?" is an open-ended question. There is scope for discussion.
- Reflective listening is a special type of listening that involves paying respectful attention to the content and feeling expressed in another persons' communication. Reflective listening is hearing and understanding, and then letting the other know that he or she is being heard and understood.
- *Eliciting pros and cons of change*: Risk of disease versus the risk of vaccination. Discuss the indirect benefits of vaccination.
- Inquiring about the importance and confidence of making a change.

If the end result is reversal of hesitancy, vaccinate and offer praise to affirm the positive decision.

IF FOR FOLLOW-UP (if possible): Schedule a new discussion:

"Let's revisit this once you have had a chance to think more about vaccination. When could you come back?"

IF REFUSAL: Do not debate. Leave the door open:

"I understand. Please know that if you change your mind and want to talk about vaccinating, we are always available."

COMMUNICATION STRATEGIES[5,9]

At the public health level, 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 the benefits of vaccination, as well as restore confidence in the National Immunization Programme (NIP), should an 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.

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.[7]

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.

Maintain relationship with parents:[6] Providers to make continuous and strident efforts toward educating parents who are vaccine hesitant, with every visit, child comes to the center for any ailment.

ROLE OF MEDIA

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.

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. Applications 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.

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. 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.

CONCLUSION

Vaccine hesitancy is a complex issue. In addition to the need for more educational materials for healthcare workers, vaccination strategies need to be contextualized. The social sciences have an important role in future vaccination strategies. One-on-one discussion with a trusted pediatrician is the most likely avenue for changing a parent's stance on vaccines. An observational study found that 47% of parents eventually consented to vaccines after initial refusal when their physicians continued to engage with them on the issue.

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Annexures

Annexure I: Immunization Schedule 2022
Annexure II: Internet Resources on Immunization Information
Annexure III: Ready Reckoner for Vaccines Currently Available in India
Annexure IV: AEFI Reporting Form

Annexure I

Immunization Schedule 2022

TABLE 1: National Immunization Schedule (NIS) for pregnant women, infants, and children (Vaccine-wise).

Vaccine	*When to give*	*Dose*	*Route*	*Site*
For pregnant women:				
Tetanus and adult diphtheria (Td)	Early in pregnancy	0.5 mL	Intramuscular	Upper arm
Td-2	4 weeks after Td-1	0.5 mL	Intramuscular	Upper arm
Td-booster	If received 2 TT/Td doses in a pregnancy within the last 3 years*	0.5 mL	Intramuscular	Upper arm
For infants:				
Bacillus-Calmette Guérin (BCG)	At birth or as early as possible till 1 year of age	0.1 mL (0.05 mL until 1 month age)	Intradermal	Left upper arm
Hepatitis B-birth dose	At birth or as early as possible within 24 hours	0.5 mL	Intramuscular	Antero-lateral side of mid-thigh
Oral polio vaccine (OPV)-0	At birth or as early as possible within the first 15 days	2 drops	Oral	Oral
OPV-1, 2, and 3	At 6 weeks, 10 weeks and 14 weeks (OPV can be given till 5 years of age)	2 drops	Oral	Oral

Contd...

Contd...

Vaccine	*When to give*	*Dose*	*Route*	*Site*
Pentavalent 1, 2, and 3	At 6 weeks, 10 weeks, and 14 weeks (can be given till 1 year of age)	0.5 mL	Intramuscular	Antero-lateral side of mid-thigh
Pneumococcal conjugate vaccine (PCV)	Two primary doses at 6 and 14 weeks followed by booster dose at 9–12 months	0.5 mL	Intramuscular	Antero-lateral side of mid-thigh
Rotavirus vaccine (RV)	At 6 weeks, 10 weeks, and 14 weeks (can be given till 1 year of age)	5 drops (liquid vaccine) 2.5 mL (lyophilized vaccine)	Oral	Oral
Inactivated polio vaccine (IPV)	Three fractional doses at 6–14 weeks and 9 months	0.1 mL	Intradermal two fractional dose	*Intradermal:* Right upper arm (UA) at 6–14 weeks Left UA at 9 months
Measles-rubella (MR) 1-dose	9 completed months–12 months. (Measles can be given till 5 years of age)	0.5 mL	Subcutaneous	Right UA
Japanese encephalitis (JE)-1	9 completed months–12 months	0.5 mL	• Subcutaneous (Live-attenuated vaccine) • Intramuscular (Killed vaccine)	• Left upper arm (Live-attenuated vaccine) • Anterolateral aspect of mid-thigh (Killed vaccine)
Vitamin A (1-dose)	At 9 completed months with measles-rubella	1 mL (1 lakh IU)	Oral	Oral

Contd...

Contd...

Vaccine	*When to give*	*Dose*	*Route*	*Site*
For children:				
Diphtheria, pertussis, and tetanus (DPT) booster-1	16–24 months	0.5 mL	Intramuscular	Antero-lateral side of mid-thigh
MR-2-dose	16–24 months	0.5 mL	Subcutaneous	Right upper arm
OPV booster	16–24 months	2 drops	Oral	Oral
JE-2	16–24 months	0.5 mL	• Subcutaneous (Live-attenuated vaccine) • Intramuscular (Killed vaccine)	• Left upper arm (Live-attenuated vaccine) • Anterolateral aspect of mid-thigh (Killed vaccine)
Vitamin A (2nd to 9th dose)	16–18 months. Then one dose every 6 months up to the age of 5 years	2 mL (2 lakh IU)	Oral	Oral
DPT booster-2	5–6 years	0.5 mL	Intramuscular	Upper arm
Td	10 years and 16 years	0.5 mL	Intramuscular	Upper arm

*One dose if previously vaccinated within 3 years.

Note:

- Japanese encephalitis vaccine is introduced in select endemic districts after the campaign.
- The 2nd to 9th doses of vitamin A can be administered to children 1–5 years old during biannual rounds, in collaboration with ICDS.

TABLE 2: Indian Academy of Pediatrics (IAP) immunization timetable: IAP recommended vaccines for routine use.

Age	*Vaccine*	*Comments*
Birth	BCG	BCG: Before discharge
	OPV	OPV: As soon as possible after birth
	Hepatitis B-I (BD)	Hep B should be administered within 24 hours of birth
6 weeks	DTwP, DTaP-1	• DTwP or DTaP may be administered in primary immunization • IPV: 6–10–14 weeks is the recommended schedule. If IPV, as part of a hexavalent combination vaccine is unaffordable, the infant should be sent to a government facility for primary immunization as per UIP schedule
	IPV-1	
	Hib-1	
	Hep B-2	
	Rotavirus-1	
	PCV-1	
10 weeks	DTwP, DTaP-2	RV1: 2-dose schedule: All other rotavirus brands: 3-dose schedule
	IPV-2	
	Hib-2	
	Hep B-3	
	Rotavirus-2	
	PCV-2	
14 weeks	DTwP, DTaP-3	An additional 4th dose of Hep B vaccine is safe and is permitted as a component of a combination vaccine
	IPV-3	
	Hib-3	
	Hep B-4	
	Rotavirus-3	
	PCV-3	
6 months	Influenza (IIV)-1	Uniform dose of 0.5 mL for DCGI approved brands

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Age	*Vaccine*	*Comments*
7 months	Influenza (IIV)-2	To be repeated every year in premonsoon period till 5 years of age
6–9 months	Typhoid conjugate vaccine	As of available data, there is no recommendation for a booster dose
9 months	MMR-1	
12 months	Hepatitis A	Single dose for live-attenuated vaccine
15 months	MMR-2, varicella-1, PCV booster	
16–18 months	DTwP/DTaP-B1, Hib-B1, IPV-B1	
18–19 months	Hep A-2, varicella-2	Only for inactivated Hep A vaccine
4–6 years	DTwP/DTaP-B2, IPV-B2, MMR-3	
10–12 years	Tdap, HPV	Tdap is to be administered even if it has been administered earlier (as DTP-B2)
		• HPV: 9–14-year-old girls: 9vHPV and 4vHPV are recommended in a 2-dose series (0–6 m) • 9–14 years boys: HPV9 is recommended in a 2-dose schedule of 0-6 months • 15–45 years: 4vHPV (0–2–6 m) is recommended in a 3-dose series • 15–26 years: 9vHPV is recommended in a 3-dose schedule of 0–2–6 months

(BCG: bacille Calmette-Guérin; DCGI: Drugs Controller General of India; DPT: diphtheria, pertussis and tetanus; DTaP: diphtheria, tetanus, and pertussis; DTwP: diphtheria, tetanus, and whole cell pertussis; HPV: human papilloma virus; IPV: injectable polio vaccine; MMR: measles, mumps, and rubella; OPV: oral poliovirus vaccines; PCV: pneumococcal conjugate vaccine; Tdap: tetanus, diphtheria toxoids, and acellular pertussis; UIP: Universal Immunization Programme)

TABLE 3: Age in completed weeks/month/years.

Vaccine	*Birth*	*6 w*	*10 w*	*14 w*	*6 m*	*7 m*	*9 m*	*12 m*	*13 m*	*15 m*	*16–18 m*	*18–24 m*	*2–3 y*	*4–6 y*	*9–14 y*	*15–18 y*
BCG																
Hepatitis B	HB 1[a]	HB 2	HB 3	HB 4[b]												
Polio	OPV	IPV 1[c]	IPV 2[c]	IPV 3[c]							IPV[c] B1			IPV[c] B2		
DTwP/DTaP		DPT 1	DPT 2	DPT 3							DPT B1			DPT B2		
Hib		Hib 1	Hib 2	Hib 3							Hib B1					
PCV		PCV 1	PCV 2	PCV 3				PCV B								
Rotavirus		RV 1	RV 2	RV 3[d]												
Influenza					Dose 1[e]	Dose 2	Annual vaccination									
MMR							Dose 1			Dose 2				Dose 3		
TCV																
Hepatitis A								Dose 1				Dose 2[f]				
Varicella										Dose 1		Dose 2[g]				
Tdap[h]/Td																
HPV															1 and 2[i]	1, 2, and 3[i]
Meningo-coccal[k]							Dose 1	Dose 2								
JE								Dose 1	Dose 2							
Cholera								Dose 1	Dose 2							

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Vaccine	*Birth*	*6 w*	*10 w*	*14 w*	*6 m*	*7 m*	*9 m*	*12 m*	*13 m*	*15 m*	*16–18 m*	*18–24 m*	*2–3 y*	*4–6 y*	*9–14 y*	*15–18 y*
PPSV-23																
Rabies																
Yellow fever																

Recommended age | *Catch up age range* | *Vaccines in special situations*

(BCG: bacille Calmette-Guérin; DTaP: diphtheria, tetanus, and pertussis; DTwP: diphtheria, tetanus, and whole cell pertussis; DPT: diphtheria, pertussis and tetanus; HPV: human papilloma virus; IPV: injectable polio vaccine; JE: Japanese encephalitis; MMR: measles, mumps, and rubella; OPV: oral poliovirus vaccines; PCV: pneumococcal conjugate vaccine; PPSV: pneumococcal polysaccharide vaccine; Tdap: tetanus, diphtheria toxoids, and acellular pertussis; TCV: typhoid conjugate vaccine)

Notes:

[a]To be given within 24 hours after birth. When this is missed, it can be administered at first contact with health facility; [b]An extra dose of Hepatitis B vaccine is permitted as part of a combination vaccine when use of this combination vaccine is necessary; [c]IPV can be given as part of a combination vaccine; [d]3rd dose of Rota vaccine is not necessary for RV1; [e]Influenza vaccine should be started after 6 months of age, 2 doses 4 weeks apart, usually in the pre-monsoon period. At other times of the year, the most recent available strain should be used. Annual influenza vaccination should be continued, for all, till 5 years of age; after the age of 5 years, this vaccine is recommended in the high-risk group only; [f]Single dose is to be given for the live attenuated Hepatitis A vaccine. The inactivated vaccine needs two doses; [g]2nd dose of varicella vaccine should be given 3–6 months of age after dose 1. However, it can be administered anytime 3 months after dose 1 or at 4–6 years; [h]Tdap should not be administered as the second booster of DPT at 4–6 years. For delayed 2nd booster, Tdap can be given after 7 years of age. A dose of Tdap is necessary at 10–12 years, irrespective of previous Tdap administration. If Tdap is unavailable/unaffordable, it can be substituted with Td; [i]Before 14 completed years, HPV vaccines are recommended as a 2-dose schedule, 6 months apart; [j]From 15th year onwards and the immunocompromised subjects at all ages, HPV vaccines are recommended as a 3-dose schedule, 0-1-6 (HPV2) or 0-2-6 (HPV4); [k]Menactra is approved in a 2-dose schedule between 9 and 23 months. Minimum interval between two doses should be 3 months. Menveo is recommended as a single dose schedule after 2 years of age.

Japanese encephalitis (JE) 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 (Only Menactra)
- 2 years through 55 years: Single dose. (Menactra and Menveo)

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 traveling 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 (for rabies PrEP)
- Children perceived with higher threat of being bitten by dogs such as hostellers, risk of stray dog menace while going outdoor (for rabies PrEP).
- Influenza vaccination annually is recommended yearly for high-risk children from 5 years of age onward.

II

Annexure

Internet Resources on Immunization Information

Organization/ Sponsor	*Web address*	*Salient contents*
National Center for Biotechnology Information	www.pubmed.com	Abstracts and full texts of vaccine-related articles published in indexed journals
Indian Academy of Pediatrics Advisory Committee on Vaccines and Immunization Practices	www.acvip.org	Electronic copy of guidebook, Q&A facility
World Health Organization (WHO)	https://www.who.int/immunization/en/ https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers https://www.who.int/health-topics/vaccines-and-immunization	WHO position papers, WHO policy recommendations, national programs and systems, monitoring and surveillance, pre-qualification status of vaccines

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Organization/ Sponsor	*Web address*	*Salient contents*
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
Immunization Action Coalition	https://www.immunize.org/askexperts/	Answers to >1000 questions about vaccines and administration
National Network for Immunization Information	http://www.nnii.org/	Information on VPD, background on vaccine development and vaccine safety, resource kit to help healthcare providers discuss immunization with their patients
Children's Hospital Philadelphia	www.vaccine.chop.edu/	Information for parents, vaccine safety, vaccine ingredients
Global Alliance for Vaccines and Immunization	www.gavialliance.org	Information on GAVI programmatic policies and funding
PATH	www.path.org/vaccineresources/index.php	Vaccine resource library

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Organization/ Sponsor	*Web address*	*Salient contents*
Vaccine manufacturers (in alphabetical order) (Not all-inclusive)	https://www.abbott.in/products/therapy-areas.vaccine.html www.bharatbiotech.com www.biologicale.com www.gskvaccines.com www.indimmune.com www.msdindia.in www.novomedi.com www.panacea-biotec.com www.pfizer.com www.sanofipasteur.com www.seruminstitute.com https://zyduslife.com/research https://www.indimmune.com/business-unit/human-health/vaccines/ www. drreddys.com	Prescribing information for various vaccines
Miscellaneous	*Indian Pediatrics*: www.indianpediatrics.net/ *Vaccines*: www.sciencedirect.com/journal/vaccine *Expert Review of Vaccines*: www.tandfonline.com/loi/ierv20 https://www.medscape.com/resource/vaccines https://www.health.gov.au/committees-and-groups/Australian-technical-advisory-group-on-immunisation-atagi https://www.canada.ca/en/public-health/services/canadianimmunization-guide.html https://vaccine.icmr.org.in	Information, presentations, and journal articles on vaccines and immunization practices

(GAVI: Global Alliance for Vaccines and Immunization)

ANNEXURE III

Ready Reckoner for Vaccines Currently Available in India

This List is not Exhaustive. Details as per Product Inserts

Vaccine/type/ brand name/s	*Content/Dose*	*Nature and diluent*	*Storage*	*Dose, route, and site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
BCG-LAV Tubervac	Each 1 mL contains 2×10^6 to 8×10^6 CFU of viable mycobacteria	Normal saline	Freezer/ 2–8°C, protect from light	0.05 mL/ 0.1 mL 0.1 mL ID, left deltoid	Single dose at birth or first contact below 5 years	0–80%	Axillary lymphadenitis	Defects of cell mediated-immunity
bOPV-LAV BioPolio	Sabin strain: • *Type 1*: 10^6 $CCID_{50}$ • *Type 3*: 10^6 $CCID_{50}$	Liquid vaccine	Freezer/ 2–8°C	Two drops orally	Birth, 6–10–14 weeks, 15–18 months, NIDs, and SNIDs	• *HIG countries*: 100% after three doses • *LIG countries*: 73/90/70% to type 1, 2, 3	VAPP, VDPV	Immunodeficient patients and household contacts of such patients
IPV (inact) Poliovac	Salk strain: • *Type 1:* 40 µ • *Type 2:* 8 µ • *Type 3:* 32 µ	Liquid vaccine	2–8°C Not to freeze	0.5 mL IM or SC, thigh/ deltoid	Birth, 6–10–14 weeks, boosters at 15–18 months and 4–6 years	95–100%	None	Serious hypersensitivity
DTwP-Inact Triple antigen SII	Diphtheria toxoid 20–30 Lf, tetanus toxoid 5–25 Lf, wP 4 IU	Liquid vaccine	2–8°C Not to freeze	0.5 mL IM thigh/ deltoid	• Birth, 6–10–14 weeks, boosters at 15–18 months and 4–6 years • Not to be used above 7 years	95–100% for diphtheria/ tetanus and 70–90% for pertussis	Excessive crying, seizures, HHE	Serious hypersensitivity, encephalopathy following previous dose

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Vaccine/type/ brand name/s	*Content/Dose*	*Nature and diluent*	*Storage*	*Dose, route, and site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
DTaP-Inact Tripacel	• *Diphtheria toxoid:* ≥30 IU (15 Lf) • *Tetanus toxoid:* ≥40 IU (5 Lf) • *Pertussis toxoid:* 10 µg • *FHA:* 5 µg • *Fimbriae:* 5 µg • *Pertactin:* 3 µg • *$AlPO_4$:* 1.5 mg	Liquid vaccine	2–8°C Not to freeze	0.5 mL IM or SC, thigh/ deltoid	Birth, 6–10–14 weeks, boosters at 15–18 months and 4–6 years Not to be used above 7 years	95–100% for diphtheria/ tetanus and 70–90% for pertussis	As for DTwP but much less in intensity and frequency	Serious hypersensitivity, encephalopathy following previous dose
Tetanus toxoid: Inact BE-TT	Tetanus toxoid 5 Lf	Liquid vaccine	2–8°C Not to freeze	0.5 mL IM or SC, thigh/ deltoid	As routine at 10 years and every 10 years thereafter, pregnancy and wound management (Td/TdaP preferred to TT)			
Td: Inact. Tdvac, BE: Td	Tetanus toxoid 5 Lf, diphtheria 2 Lf	Liquid vaccine	2–8°C Not to freeze	0.5 mL IM or SC, 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: Inact Boostrix	• *DT:* Not <2.5 Lf, *TT*: Not <5 Lf • *PT:* 8 µg • *FHA:* 8 µg, *Pertactin*: 2.5 µg • *$Al(OH)_3$:* 0.3 mg • *$AlPO_4$:* 0.2 mg of	Liquid vaccine	2–8°C Not to freeze	0.5 mL IM or SC, thigh/ deltoid	Single dose at 10–12 years and beyond	90%	As for DTwP but much less in intensity and frequency	Serious hypersensitivity, encephalopathy following previous dose
Tdap: Inact Adacel	*TT:* 5 Lf, DT: 2 Lf, PT: 2.5 µg, *FHA:* 5 µg, *PRN:* 3 µg, *FIM 2 and 3*: 5 µg, *$AlPO_4$:* (adjuvant) 1.5 mg, 2-phenoxyethanol 0.6% v/v	Liquid vaccine	2–8°C Not to freeze	0.5 mL IM or SC, thigh/ deltoid	Single dose at 11–54 years	90%	As for DTwP but much less in intensity and frequency	Serious hypersensitivity, encephalopathy following previous dose

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Vaccine/type/ brand name/s	*Content/Dose*	*Nature and diluent*	*Storage*	*Dose, route, and site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
Rubella-LAV R-Vac	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	Given combined with measles and mumps 9 months to 15 months to 5 years	95%	Mild rubella-like illness in <5%, rarely arthritis, ITP	Severely immunocompromised, pregnancy. Avoid pregnancy for 1 month
MMR-LAV Tresivac Priorix ZyVac-MMR	• *Tresivac*: Edmonston-Zagreb, Measles virus not <1,000, $CCID_{50}$, L-Zagreb, Mumps virus 5,000, $CCID_{50}$ and Wistar RA 27/3 Rubella virus 1,000, $CCID_{50}$ • *ZyVac MMR:* (Edmonston-Zagreb Strain) NLT 1,000 CCID, live-attenuated mumps virus (Hoshino Strain) NLT 5,000 CCIDs and live-attenuated rubella virus (RA27/13 strain) NLT 1,000 CCIDs • *Priorix*: Measles Schwarz strain not <103 $CCID_{50}$, mumps virus RIT 4385 strain, derived from Jeryl Lynn strain, not <103.7 $CCID_{50}$ and rubella virus Wistar RA 27/3 strain not <103 $CCID_{50}$	Lyophilized, diluent sterile water	Freezer/ 2–8°C	0.5 mL SC thigh/ deltoid	9 months to 15 months to 5 years	86–95%	• *Measles*: Mild measles-like illness in <5%, rarely ITP • *Mumps:* Rarely, fever, transient parotitis, aseptic meningitis, ITP • *Rubella:* Mild rubella-like illness in <5%, rarely arthritis, ITP	Severely immunocompromised, pregnancy

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Vaccine/type/ brand name/s	*Content/Dose*	*Nature and diluent*	*Storage*	*Dose, route, and site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
• Hepatitis B-Inact • Bevac 0.5 mL • Bevac 1 mL • Revac B MCF Thiomersal free • Genevac 0.5 mL • Genevac B 1.0 mL • Genevac B 10 mL multidose	*Ped:* • HBsAg: 10 µg • $Al(OH)_3$: 0.25 mg • Thiomersal: 0.025 mg *Adult:* • HBsAg: 20 µg • $Al(OH)_3$: 0.5 mg • Thiomersal: 0.05 mg	Liquid vaccine	2–8°C Not to freeze	*Ped. dose:* 10 µg/0.5 mL *Adult dose:* 20 µg in 1 mL <18 years 0.5 mL, >18 years 1 m IM deltoid/ thigh	*Primary:* Birth: 6–10–14 weeks *Catchup:* 0–1–6 months	>90%	Nil	Known serious hypersensitivity to vaccine components or following a previous dose
DTwP/Hib Quadrovax	As for DTwP and Hib	Liquid vaccine	2–8°C Not to freeze	0.5 mL IM thigh/ deltoid	6–10–14 weeks booster at 15–18 months	As for DTwP and Hib		
DTwP/Hib/HBV Pentavac Easyfive-TT Combivac5	As for DTwP, HBV, and Hib	Liquid vaccine	2–8°C Not to freeze	0.5 mL IM thigh/ deltoid	6–10–14 weeks booster at 15–18 months	As for DTwP, Hib, and Hib		
DTaP/HepB/Hib Pentaxim	As per DTaP HBV and Hib	DTaP/IPV component is a turbid white suspension. Hib component is a white powder	2–8° C Not to freeze	0.5 mL IM Thigh/ deltoid	16–18 months booster	As for DTaP, Hib, and HBV		
DTwP/Hib/HBV/ IPV EasySix	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 Not to freeze	0.5 mL IM thigh/ deltoid	6–10–14 weeks Can be given up to 2 years	As for DTwP, Hib, Hib, and IPV		

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Vaccine/type/ brand name/s	*Content/Dose*	*Nature and diluent*	*Storage*	*Dose, route, and site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
DTaP/Hib/HBV/ IPV Infanrix Hexa	• *DT:* Not <30 IU, *TT:* Not <40 IU • *Acellular PT:* 25 µg, *FHA:* 25 µg, *Pertactin:* 8 µg • *HbsAg:* 10 µg • *IPV:* Type 1: 40 D-Ag U, type 2: 8 D-Ag U, type 3: 32 D-Ag U • *Hib-PRP:* 10 µg, conjugated to tetanus toxoid: 25 µg	DTaP/HBV/IPV component is a turbid white suspension. Hib component is a white powder	2–8°C Not to freeze	0.5 mL IM thigh/ deltoid	6–10–14 weeks Can be given up to 2 years	As for DTaP, Hib, Hib, and IPV		
DTaP/Hib/HBV/ IPV Hexaxim	• *DT:* 30 Lf, *TT:* 10 Lf, *HepB:* 10 µg, *Hib:* 12 µg (*TT:* 22–36 µg) • *Acellular PT and FHA:* 25 µg each • *IPV:* Type 1: 40 D-Ag U, type 2: 8 D-Ag U, type 3: 32 D-Ag U hydroxide: 0.6 mg	Liquid vaccine	2–8°C Not to freeze	0.5 mL IM thigh/ deltoid	6–10–14 weeks Can be given up to 2 years	As for DTaP, Hib, HBV, and IPV		
DTaP/Hib/ IPV Tetraxim	(DT ≥30 IU), (TT ≥40 IU), acellular PT 25 µg, *FHA:* 25 µg, *IPV:* type 1: 40 DU, type 2: 8 DU, type 3; 32 DU. Adsorbed on hydroxide, hydrated 0.3 mg Al3+	Liquid vaccine	2–8°C Not to freeze	0.5 mL IM thigh/ deltoid	4–6 years booster	As for DTaP and IPV		

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Vaccine/type/ brand name/s	*Content/Dose*	*Nature and diluent*	*Storage*	*Dose, route, and site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
• Vi Typhoid polysaccharide-Inact • Typbar, VacTyph	25–30 mg of Vi-polysaccharide	Liquid vaccine	2–8°C Not to freeze	0.5 mL IM thigh/ deltoid	Above 2 years, single dose, revaccination every 3 years	60%	None	Known serious hypersensitivity to vaccine components or following a previous dose
• Vi-CPS conjugate vaccine-Inact. • Typbar TCV, Enteroshield, Zyvac TCV, TyphiBev, Biovac TCV	25 µg of Vi-CPS conjugated to tetanus toxoid per 0.5 mL *Enteroshield:* Conjugated to CRM197	Liquid vaccine	2–8°C Not to freeze	0.5 mL IM thigh/ deltoid	Single dose at ≥6 months	>90% seroconversion in >6 months to 45 years *Efficacy:* 80–87% over 2 years	None, only minor systemic and local side effects	Known serious hypersensitivity to vaccine components or following a previous dose
HPV-Inact. Gardasil	Each 0.5-mL dose contains 20 µg of HPV 6 L1 protein, 40 µg of HPV 11 L1 protein, 40 µg of HPV 16 L1 protein, 20 µg of HPV 18 L1 protein and 225 µg of aluminum	Liquid vaccine	2–8°C Not to freeze	0.5 mL IM thigh/ deltoid	*In females:* 9–14 years, 0 and 6 months; 15–45 years, 0, 1, and 6 months	>90% against serotype-specific cervical cancer	None	Known serious hypersensitivity to vaccine components or following a previous dose
Gardasil 9	*HPV:* Type 6: 30 µg, type 11: 40 µg, type 16: 60 µg and type 18: 40 µg type 31: 20 µg, type 33: 20 µg, type 45: 20 µg, type 52: 20 µg, type 58: 20 µg and 500 µg of aluminum	Liquid vaccine	2–8°C Not to freeze	0.5 mL IM thigh/ deltoid	*9–14 years:* Girls and boys: Two-dose series (0–6 months) 15–26 years: 9vHPV (0–2–6 months) is recommended in a three-dose series. All immunocompromised should receive a three-dose schedule	>90% against serotype-specific cervical cancer	None	Known serious hypersensitivity to vaccine components or following a previous dose

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Vaccine/type/ brand name/s	*Content/Dose*	*Nature and diluent*	*Storage*	*Dose, route, and site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
PCV10-Inact Synflorix	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 Not to freeze	0.5 mL IM thigh/ deltoid	6–10–14 weeks, booster 15–18 months	95% against serotype-specific invasive disease	None	Known serious hypersensitivity to vaccine components or following a previous dose
PCV 13 Inact. Prevenar 13	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 Not to freeze	0.5 mL IM thigh/ deltoid	6–10–14 weeks, booster 15–18 months	95% against serotype-specific invasive disease, except ST3	None	Known serious hypersensitivity to vaccine components or following a previous dose
PCV10 Inact. Pneumosil	Contains capsular polysaccharides of 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, 23F, 2 µg of each and 4 µg of 6B, conjugated to CRM197, with $AlPO_4$: 0.125 mg	Liquid vaccine	2–8°C Not to freeze	0.5 mL IM thigh/ deltoid	6–10–14 weeks, booster 15–18 months	Licensed on basis of immunological noninferiority to PCV13 and PCV10-GSK	None	Known serious hypersensitivity to vaccine components or following a previous dose
PPSV23-Inact. Pneumovax-23	CPS of serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F unconjugated	Liquid vaccine	2–8°C Not to freeze	0.5 mL IM thigh/ deltoid	Single dose after 2 years Revaccination only once after 3–5 years	70% against invasive disease in high-risk children	None	Known serious hypersensitivity to vaccine components or following a previous dose
Hep A Inact. Avaxim 80, Havrix 720, HavShield, HapiBEV	• *Havrix 720:* Each 0.5 mL contains 720 E.U. of viral antigen (strain HM175), adsorbed onto 0.25 mg of aluminum. • *Avaxim 80:* GBM strain 80 U, Al. hydroxide: 150 mg, 2-PE: as preservative. *HavShield and HapiBEV:* 250 U of TZ84 strain and hydroxide	Liquid vaccine	2–8°C Not to freeze	0.5 mL IM thigh/ deltoid	Two doses 6 months apart, after 1 year of age	>95%	None	Known serious hypersensitivity to vaccine components or following a previous dose

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Vaccine/type/ brand name/s	*Content/Dose*	*Nature and diluent*	*Storage*	*Dose, route, and site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
Hep A-LAV BioVac A	6.5 log particles of H2 strain	Lyophilized, sterile water	2–8°C	0.5 mL SC	One dose after 1 year of age	>95%	None	Pregnancy, severely immuno-compromised
Varicella-LAV Varilrix, Variped, Nexipox	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	Two doses, first dose after 15 months and second dose after 3 months of first dose	70–90% with one dose >95% with two doses	Varicella-like rash in 5%	Pregnancy, severely immuno-compromised
Rotavirus human monovalent (LAV) Rotarix	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:* 6–14 weeks • *Second dose:* Before 24 weeks 4-week interval between doses	85–98% against severe rotavirus diarrhea, in HIC and MIC. Asia: 48.3%	None	SCID, history of intussusception. Known serious hypersensitivity to vaccine components or following a previous dose
Rotavirus human bovine pen-tavalent vaccine (LAV) RotaTeq	Five rotavirus reassortant strains G1, G2, G3, G4, and P1A (8)	Liquid vaccine	2–8°C Protect from light	2 mL, orally	*Three doses:* • *First dose:* 6–14 weeks • *Third dose:* Before 32 weeks 4-week interval between doses	85–98% against severe rotavirus diarrhea, in HIC and MIC. Africa: 39.3%	None	SCID, history of intussusception. Known serious hypersensitivity to vaccine compo-nents or following a previous dose

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Vaccine/type/ brand name/s	*Content/Dose*	*Nature and diluent*	*Storage*	*Dose, route, and site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
Rotavirus human bovine monovalent vaccine (LAV) Rotavac RotaSure Rotavac 5D	Naturally occurring reassortant 116E strain	Liquid vaccine	2–8°C for 6 months Protect from light 2–8°C throughout the shelf life of 24 months	0.5 mL orally 5 drops	*Three doses:* • *First dose:* 6–14 weeks • *Third dose:* Before 32 weeks 4-week interval between doses	54.4% against SRVGE	None	SCID, history of intussusception. Known serious hypersensitivity to vaccine components or following a previous dose
Rotavirus human bovine pentavalent vaccine-LAV Rotasiil	Five rotavirus reassortant strains G1, G2, G3, G4, and G9	Liquid	*Liquid formulation:* 2–8°C	*Liquid:* 2 mL	*Three doses:* • *First dose:* 6–14 weeks • *Third dose:* Before 1 year 4-week interval between doses	Niger: 66.8% India: 60.5%-against VS-RVGE	None	SCID, history of intussusception. Known serious hypersensitivity to vaccine components or following a previous dose
Inactivated, Kolar strain, JE vaccine, JEN-VAC	Inactivated, Kolar strain, 821564XY, JE vaccine 5.0 µg per 0.5 mL	Liquid vaccine	2–8°C	0.5 mL IM thigh/ deltoid	Two doses at 4 weeks interval from 1 year of age and onward (up to 50 years) No recommendation for boosters	>90% seroconversion and seroprotection after one dose	None, only fever and local side effects	Known serious hypersensitivity to vaccine components or following a previous dose

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Vaccine/type/ brand name/s	*Content/Dose*	*Nature and diluent*	*Storage*	*Dose, route, and site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
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 No recommendation for booster	>90% seroconversion	None, only fever and local side effects	Known serious hypersensitivity to vaccine components or following a previous dose
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	Two doses at 9 months and 15–18 months	>90% in Nepal and China with one dose India: ~70% with one dose	None	Immunodeficient patients and household contacts of such patients
• Conjugated • Quadrivalent • Meningococcal vaccine • Menactra	4 µg of Meningococcal group A, C, Y, and W 135 polysaccharides conjugated to 48 µg of diphtheria toxoid	Liquid vaccine	2–8°C	0.5 mL IM	9–23 months: Two doses 3 months apart 24 months to 55 years: Single dose	*Effectiveness*: 80–85%	None, no extra risk of GBS among vaccinees	Known serious hypersensitivity to vaccine components or following a previous dose
Menveo	Menveo: Men Gp A: 10 µg, Men Gp C: 5 µg, Men Gp W-135: 5 µg, Men Gp Y: 5 µg, each bound to CRM197	The freeze-dried MenA powder is to be reconstituted in MenCWY solution	2–8°C	0.5 mL IM	Single dose >2 years	*Effectiveness*: 80–85%	None, no extra risk of GBS among vaccinees	Known serious hypersensitivity to vaccine components or following a previous dose

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Vaccine/type/ brand name/s	*Content/Dose*	*Nature and diluent*	*Storage*	*Dose, route, and site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
Flu vaccine Quadrivalent (IIV4) Influvac Tetra, Fluarix Tetra, FluQuadri, Vaxi-Flu4	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	0.5 mL IM	*Vaccine naïve*: Two doses, at 4 weeks interval, below 8 years, single dose yearly. 0.5 mL >6 months of age	50–75% 63.2% efficacy against moderate to severe influenza and 49.8% efficacy against influenza of any severity in children 6–35 months	None	Known serious hypersensitivity to vaccine components or following a previous dose
Flu vaccine live-attenuated influenza (LAIV) Nasovac S4	10^7 EID_{50} of two Type A and $10^{6.5}$ EID_{50} of one Type B (differs according to Northern/Southern hemisphere and usually yearly) inactivated influenza virus	Liquid formulation	2–8°C	0.25 mL in each nostril	Single dose >2 years	Vary widely, ranging from 0 to 50%	None	Severe hypersensitivity to any constituent, <2 years, h/o asthma, GBS, on antiflu medications or aspirin, pregnancy
Yellow fever vaccine-LAV Stamaril, CRI Kasauli vaccine	17D strain of yellow fever virus	Lyophilized, sterile water diluent	2–8°C	0.5 mL SC	Single dose >9 months	>90%	Rarely neurologic/ viscerotropic disease	Below 6 months, serious egg allergy severe immunodeficiency, thymus disease
Oral cholera Inact. Shanchol	1.5 mL contains killed bivalent (O1 and O139) strains of *V. Cholerae*	Liquid vaccine	2–8°C	1.5 mL orally	• >1 year, two doses 2 weeks apart • Booster may be considered after 3 years	60%	None	Known serious hypersensitivity to vaccine components or following a previous dose

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Vaccine/type/ brand name/s	*Content/Dose*	*Nature and diluent*	*Storage*	*Dose, route, and site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
Rabies vaccines Inact. Chirorab (PCEC) Rabivax-S (VeroCell) Vaxirab (VeroCell) AbhayRab and IndiRab (VeroCell)	All contain not <2.5 IU per dose	Lyophilized powder with diluent to a volume of 1 mL. *Sterile water:* Chirorab, Rabivax-S, Vaxirab. 0.9% saline for Abhayrab and IndiRab	2–8°C	1 mL IM		100% seroprotective titers of >0.5 IU, by day 14	None	None
ThRabies	Recombinant nanoparticle-based rabies G protein vaccine is prepared using VLP technology. 50 µg per dose	Liquid vaccine	2–8°C	1 mL IM	0–3–7 days Licensed for >18 years only	100% seroprotective titers of >0.5 IU, by day 14	None	None
Covid vaccines-Inact Covaxin, Corbevax, Covovax	*Covaxin*: SARS Ag: 6 µg TLR 7/8 agonist: 15 mg 2-PE: 2.5 mg *Aluminium hydroxide:* 0.25 mg Corbevax: Each dose of 0.5 mL contains RBD antigen of SARS-CoV-2: 25 µg hydroxide: 750 µg CpG 1018: 750 µg Covovax: Each dose (0.5 mL) contains SARS-CoV-2 spike protein 5 µg and is adjuvanted with Matrix-M-Fraction-A (42.5 µg and Fraction-C (7.5 µg of *Quillaja saponaria* Molina extract)	Liquid vaccine	2–8°C	0.5 mL IM	*Covaxin:* >6 years *Corbevax:* >5 years *Covovax:* >12 years Two doses 4 weeks apart	Licensed on basis of noninferiority to immunological responses in adults	None	Known serious hypersensitivity to vaccine components or following a previous dose

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Vaccine/type/ brand name/s	*Content/Dose*	*Nature and diluent*	*Storage*	*Dose, route, and site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
Specific immunoglobulins/Mabs:								
Rabies:								
HRIg: Kamrab Berirab	150 IU/mL 2 mL vials	Liquid	2–8°C	20 IU/kg to a maximum of 1,500 IU. Maximum volume to be infiltrated into depth of wound. No need for IM administration of remaining volume				
ERIg: Equirab	300 IU/mL 5 mL vials	Liquid	2–8°C	40 IU/kg to a maximum of 3,000 IU. Maximum volume to be infiltrated into depth of wound. No need for IM administration of remaining volume				
Rabishield	50 IU/1.25 mL 100 IU/2.5 mL	Liquid	2–8°C	3.33 IU/kg. Maximum volume to be infiltrated into depth of wound. No need for IM administration of remaining volume				
Twinrab	600 IU/mL 1,500 IU/mL/2.5 mL	Liquid	2–8°C	40 IU/kg. Maximum volume to be infiltrated into depth of wound. No need for IM administration of remaining volume				
Hepatitis B:								
Hepabsv	100 IU/1 mL	Liquid	2–8°C	100 IU for newborn 0.06 mL/kg for others IM	IM			
Hepabig	200 IU/mL/2 mL	Liquid	2–8°C	100 µ for newborn 0.06 mL/kg for others IM	IM			
Tetanus:								
TetGlob	250 IU 500 IU	Liquid	2–8°C	250–500 µ IM	IM			

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Vaccine/type/ brand name/s	*Content/Dose*	*Nature and diluent*	*Storage*	*Dose, route, and site*	*Schedule*	*Protective efficacy*	*Major adverse effects*	*Contraindications*
Diphtheria:								
Diphtheria antitoxin: Equine	10,000 µ in 10 mL	Liquid	2–8°C	• Pharyngeal or laryngeal disease of 2 days' duration: 20,000–40,000 • Nasopharyngeal disease: 40,000–60,000 • Extensive disease of 3 or more days duration, or any patient with diffuse swelling of neck: 80,000–100,000 • Skin lesions only (rare case where treatment is indicated) • 20,000–40,000 • Administered IM. Larger volumes may be administered IV • Sensitivity testing essential prior to administration				

(BCG: bacillus Calmette–Guérin; bOPV: bivalent oral polio vaccine; CFU: colony-forming unit; CPS: capsule polysaccharide; DT: diphtheria and tetanus; DTaP: diphtheria, tetanus, and pertussis; DTwP: diphtheria tetanus whole-cell pertussis; ERIg: equine rabies immunoglobulin; FHA: filamentous hemagglutinin; GBM: glioblastoma multiforme; GBS: Group B *Streptococcus*; HBsAg: hepatitis B surface antigen; HBIg: hepatitis B immune globulin; HBV: hepatitis B virus; HHE: hemiconvulsion-hemiplegia epilepsy; Hib: *Haemophilus influenzae* type b; HIC: high-income countries; ID: intradermal; IIV: inactivated influenza vaccine; IM: intramuscular; IPV: inactivated polio vaccine; ITP: immune thrombocytopenic purpura; IV: intravenous; JE: Japanese encephalitis; LAV: live attenuated vaccines; MIC: middle-income countries; MMR: measles, mumps and rubella; NID: national immunization day; NTHi: nontypeable *Haemophilus influenzae*; PFU: plaque-forming unit; PPSV: pneumococcal polysaccharide vaccine; PT: pertussis toxoid; RBD: receptor-binding domain; SARS-COV-2: severe acute respiratory syndrome coronavirus 2; SC: subcutaneous; SNID: subnational immunization day; Td: tetanus and diphtheria; TdaP: tetanus, diphtheria, and pertussis; TLR: toll-like receptor; TT: tetanus toxoid; VAPP: vaccine-associated paralytic polio; VDPV: vaccine-derived poliovirus; VLP: virus-like particles)

IV

Annexure

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 H H M M Y Y Y Y

Describe AEFI (signs and symptoms):

Suspected adverse event(s) (tick at least one):

☐ Severe local reaction ○ *>3 days* ○ *beyond nearest joint* ☐ Seizures ○ *febrile* ○ *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:

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- New chapters on Future Vaccines and Vaccine Hesitancy.

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