

# 4

## Individual Vaccines

### **BACILLUS CALMETTE GUERIN (BCG) VACCINE**

#### **Background**

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

#### **Vaccine**

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

The vaccine contains 0.1–0.4 million live viable bacilli per dose. It is supplied as a lyophilized (freeze-dried) preparation

in vacuum sealed multi-dose dark colored ampoules or 2 ml vials with normal saline as diluent. The vaccine is light sensitive and deteriorates on exposure to ultraviolet rays. In lyophilized form it can be stored at 2 to 8° C for up to 12 months, without losing its potency. The long necked BCG ampoule should be cut carefully by gradual filing at the junction of its neck and body, as sudden gush of air in the vacuum sealed ampoule may lead to spillage of the contents. Diluent should be used for reconstitution. Sterile normal saline may be used if diluent is not available. As the vaccine contains no preservative, bacterial contamination and consequent toxic shock syndrome may occur if kept for long after reconstitution. The reconstituted vaccine should be stored at 2 to 8°C, protected from light and discarded within 4-6 hours of reconstitution. The recommended dose is 0.1 ml or 0.05 ml as suggested by the manufacturer of the vaccine. Dose not depend on the age and weight of the baby. Injection of BCG should be strictly intradermal, using a tuberculin syringe and a 26G/27G needle. The convex aspect of the left shoulder at level of deltoid insertion is preferred for easy visualization of the BCG scar and for optimum lymphatic drainage. Other sites such as thigh should be avoided. The selected site may be swabbed clean using sterile saline and local antiseptics should be avoided. A wheal of 5 mm. at the injection site indicates successful intradermal administration of the vaccine. Subcutaneous administration of BCG is associated with an increased incidence of BCG adenitis. The injected site usually shows no visible change for several days. Subsequently, a papule develops after 2-3 weeks, which increases to a size of 4-8 mm. by the end of 5-6 weeks. This papule often heals with ulceration and results in a scar after 6-12 weeks. The ulcer at vaccination site may persist for a few weeks before formation of the final scar. No treatment is required for this condition. Secondary infection at the vaccination site may require antimicrobials. Ipsilateral axillary/cervical lymphadenopathy may develop a few weeks/months after BCG vaccination. Antitubercular therapy is of no benefit in such situations and should not be administered.

The nodes regress spontaneously after a few months. It should also be noted that if fine needle aspiration cytology of the nodes is carried out, stain for acid-fast bacilli may be positive. These are bovine vaccine bacilli and should not be misconstrued as being suggestive of tuberculous disease. In some children the nodes may even liquefy and result in an abscess. Surgical removal of the nodes or repeated needle aspiration is the treatment of choice, again antitubercular therapy is not recommended. Disseminated BCG infection is extremely unusual but may occur in children with cellular immunodeficiency. BCG should be avoided in the immunocompromised especially those with cellular immunodeficiency; it may however be given at birth to children born to HIV positive mothers. BCG may be given with all vaccines on the same day or at any interval with the exception of measles/measles mumps rubella (MMR) vaccine where a gap of 4 weeks between the two vaccines is recommended.

### **Recommendations for Use**

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

## **POLIO VACCINES**

### **Background**

The availability of two effective vaccines against poliomyelitis for the past five decades has ensured remarkable decline in the global burden of disease. The Global Polio Eradication

initiative was launched in 1988 using oral polio vaccine (OPV) as the eradication tool and employing a four pronged strategy comprising high routine immunization coverage, supplementary immunization activities (SIAs)/pulse immunization, acute flaccid paralysis (AFP) surveillance and outbreak response/“mopping up” immunization. The initiative was hugely successful with reduction of polio cases from 350,000 in 1988 to less than a 1000 cases in 2007. Only four countries including India, Pakistan, Nigeria and Afghanistan remain endemic today and wild virus type 2 has not been isolated since 1999. However, the last leg of the journey has been difficult consisting of challenges of eradication of polio from the last remaining pockets (especially UP and Bihar), occurrence of cVDPV (circulating vaccine derived polio viruses) and meeting the funding gap.

## **Vaccines**

### *OPV*

OPV is a trivalent vaccine consisting of a suspension of attenuated poliovirus types 1, 2 and 3 grown in monkey kidney cell cultures and stabilized with magnesium chloride. It is a very heat sensitive vaccine having a shelf life of 2 years at a temperature of  $-20^{\circ}\text{C}$ , 6 months at  $2$  to  $8^{\circ}\text{C}$  and 1-3 days at room temperature. OPV should be stored at  $-20^{\circ}\text{C}$  at the state and district level and in the freezer at the clinic level. The vaccine must reach the outreach facility at  $2$  to  $8^{\circ}\text{C}$  in vaccine carriers with ice packs. Multiple freeze thaw cycles should be avoided as the virus loses its potency. The dose is 2 drops orally. When OPV is given by mouth, the vaccine viruses reach the intestines where they must establish infection (vaccine virus “take”) before an immune response may occur. For reasons that are not clearly understood, OPV “take” rates may be somewhat variable. Infection with other enteroviruses and competition between the three polioviruses impair take of the vaccine. Data from clinical trials suggest that seroconversion rates after three doses of OPV average 73%,

90% and 70% for Types I, II and III respectively or roughly 30% per dose. Multiple doses of OPV are necessary before 90-95% of children develop immune responses to all three poliovirus types. The onset of action of OPV is faster as compared to inactivated poliovirus vaccine (IPV) and thus OPV is the vaccine of choice for outbreak control. The virus is transmissible from the vaccinees to contacts. In settings where vaccine efficacy is high, OPV provides mucosal immunity including intestinal and pharyngeal immunity, reduces transmission of the wild virus and thus offers significant herd protection. Several countries have eradicated polio with use of OPV alone. IAP has recommended the administration of OPV at birth (OPV0), 3 doses at 6, 10 and 14 weeks and 2 more repeat doses; at 16-18 months and 5 years. In addition to the routine OPV doses, "Pulse OPV doses" every year on National Immunization Days (NID's) and sub-National Immunization Days (SNID's) until the age of 5 years are also mandatory. Administration of a dose at birth (zero dose) serves as a priming dose and has been shown to improve the serologic response to future doses. Administration of pulse doses replaces the wild virus from guts of all children with the vaccine virus and hence plays an important role in polio eradication.

However, AFP surveillance data systematically generated since launch of GPEI suggests that several Indian children particularly from Uttar Pradesh (UP) and Bihar develop paralytic poliomyelitis despite having received 15-20 doses of OPV. A case control study based on AFP surveillance data from India has estimated the per dose efficacy of trivalent OPV in India as 13% to as low as 9% in UP. This poor efficacy is attributed to high population densities, malnutrition, poor sanitation that increase the risk of infection with other enteroviruses and NOT due to poor vaccine potency due to breaks in cold chain. This low efficacy and associated poor mucosal immunity is responsible for poor herd effect of OPV in these settings. Monovalent OPV (mOPV) is presumably 2.5-3 times more efficacious than trivalent OPV as competition between different polio viruses is eliminated. Henceforth

monovalent OPV containing type1 virus has been introduced in India since 2005 for pulse immunization. The benefits of decline in P1 cases has been partly offset by resurgence of P3. Pulse immunization with monovalent P3 and bivalent OPV (bOPV containing P1 and P3) are strategies to offset this risk.

A rare but serious adverse effect associated with OPV is vaccine associated paralytic poliomyelitis (VAPP). VAPP occurs due to loss of attenuating mutations and reversion to neurovirulence during replication of the vaccine virus in the gut. VAPP is defined as those cases of AFP which have residual weakness 60 days after the onset of paralysis and from whose stool samples, vaccine-related poliovirus but no wild polio virus is isolated. VAPP may occur in the vaccine recipient (recipient VAPP, occurring within 4-40 days of receiving OPV) or contact of the vaccine recipient (contact VAPP). The risk of VAPP is higher with the first dose that "takes," with P2 virus and in patients with B-cell immunodeficiency. The incidence of VAPP in developed countries such as US has been reported to be 1 per 2.4 million doses distributed and 1 per 750,000 with first dose. Many countries switched to sequential IPV-OPV and then only IPV schedules once the number of VAPP cases exceeded wild polio cases. The risk of VAPP in India has been estimated to be 1 per 4.1 to 4.6 million doses distributed and 1 per 2.8 million first dose recipient risk. This lower risk of VAPP has been attributed to maternal antibodies, birth dose of OPV, early immunization with OPV and most importantly lower "take" of the vaccine (as only the vaccine that takes up can cause VAPP). Nevertheless the absolute numbers of VAPP are significant and it is estimated that 181 cases of VAPP occurred in India in 1999. Unfortunately there is lack of recent data on incidence of VAPP in India with all VAPP cases being reported as non polio AFP.

A recently recognized unanticipated major problem with use of OPV is the emergence of Vaccine Derived Polio Viruses (VDPVs). They arise due to mutation and recombination in the human gut and are 1-15% divergent from the parent vaccine virus. These viruses like those causing VAPP are

neurovirulent but additionally are transmissible and capable of causing outbreaks. They have been classified into three groups; circulating VDPV (cVDPV), VDPV in the immunodeficient (iVDPV) and VDPV of ambiguous origin (aVDPV). VDPV's have been present since OPV was in use but are recognized now since sensitive surveillance systems are in place. As many as 10 outbreaks in 9 countries affecting 209 individuals have been recognized in the last decade. Risk factors for outbreaks due to cVDPV include dropping immunization coverage (both routine and SIA's), high population densities, tropical conditions and previous eradication of wild virus. Interestingly, in the recent Nigerian outbreak in 2006-2007 due to P2 strain affecting 71 people, cVDPV coexisted with the wild virus and was less than 1% divergent from the vaccine virus. India at present is at low risk for cVDPV outbreak due to high immunization coverage. However dropping immunization coverage (especially routine immunization with trivalent vaccine), eradication of wild virus from several sites, high force of transmission and monovalent OPV use are factors conducive to a cVDPV outbreak (possibly type 2) in future. Recognition of VDPV's is the primary reason why synchronous stopping of OPV use globally and continuing to vaccinate against polio with IPV is mandatory in the post polio eradication scenario.

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

#### *Inactivated Polio Vaccines (IPV)*

IPV is formaldehyde killed poliovirus grown in monkey kidney cell/human diploid cells. Old IPV contained 20, 8 and 32 D antigen units of type 1, 2 and 3 polioviruses respectively. All currently used IPV vaccines are enhanced potency IPV (eIPV) which contain 40, 8 and 32 D antigen units of type 1, 2 and 3 respectively. Currently the term IPV means eIPV. The vaccine should be stored at 2 to 8°C and dose is 0.5 ml intramuscularly/subcutaneously. It is highly immunogenic. Seroconversion rates

are 90-100% with two doses given after the age of 2 months and at 2 months interval or in the EPI schedule of three doses at 6,10 and 14 weeks. It produces excellent humoral immunity as well as local pharyngeal and, possible intestinal immunity and thus offers herd protection. IPV can be administered along with all other childhood vaccines and can be used in combination with DTwP/DTaP, Hib and Hep B vaccines without compromising seroconversion or increasing side effects. The vaccine is very safe. As IPV contains trace amounts of streptomycin, neomycin and polymyxin B, allergic reactions may be seen in individuals with hypersensitivity to these antimicrobials.

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

### **Recommendations for Use**

#### *For EPI*

In 2008 as many as 551 cases of polio (481 P3, 70 P1) have been reported in India of which 530 are in UP and Bihar. This scenario of continuous P1 transmission and resurgence of P3 has been attributed to neglect of routine immunization, poor efficacy of OPV, extremely high force of transmission of wild polio virus in UP and Bihar and operational/political issues. The polio eradication committee of the IAP (IAP-PEC) has suggested certain corrective measures including improvement of routine immunization coverage, utilization of IPV in a campaign mode in the hotbeds of wild polio, improving performance of the NID's/SNID's, reducing the frequency and shortening the durations of SIA's, prompt outbreak response immunization, sensitive surveillance to pick up cVDPV, greater transparency on VAPP cases, rehabilitation of polio victims, conduction of appropriate research, social mobilization, adequate attention to other EPI vaccines and improvement of environmental sanitation. The IAP-PEC has further opined

that it will be unsafe to stop vaccination in the post eradication era due to risks of cVDPV and bio terrorism and thus switch to IPV is inevitable. Such a switch cannot happen overnight due to requirement of large number of doses and logistic issues. It therefore, recommends incorporation of IPV as DTP-IPV combination in addition to OPV in the routine immunization of states that are currently free of polio so that a gradual switch to IPV is facilitated.

*For Office Practice*

IAPCOI recommends continuing OPV use for birth dose, for routine immunization at 6,10 and 14 weeks, 15-18 months and at 5 years and on all NID's and SNID's. The IAPCOI also recommends offering additional use of IPV with OPV in all children who can afford the vaccine (Category 2) in the schedule discussed below. Any of the currently licensed brands may be used. The recommendation for wider use of IPV is for the following reasons:

- Excellent immunogenicity, efficacy and safety of IPV
- IAP-PEC has already recommended that the government gradually introduce IPV in polio free states to facilitate the switch to IPV in post eradication era. By promoting use of IPV in the private sector, the committee hopes to create a demand base for the vaccine, increased supply and lower cost of the vaccine.

OPV use should be continued at present for the following reasons:

- In concordance with the government policy of using OPV for polio eradication
- Better mucosal immunity of OPV and IPV combination schedule as compared to IPV alone
- By not giving OPV we might create confusion in the minds of the parents whose children receive only IPV about the efficacy and safety of OPV and interfere with OPV uptake on the NID's and SNID's. Also as a cascade effect there might be some individuals who may refuse immunization with OPV due to fear of side effects and neither give IPV due to non-affordability.

- The risk of VAPP with this combined OPV and IPV schedule is extremely low as the child receives OPV at the time when he/she is protected against VAPP by maternal antibodies. Subsequently he/she is protected from VAPP by IPV. Even if we adopt an all IPV schedule the child may still be at a small risk for VAPP through exposure to the oral polio vaccine virus through contacts/environment before he/she receives his/her first dose of IPV.

The IAPCOI feels that in the current scenario where polio eradication in India is at the cross roads and a highly sensitive issue, the combined OPV and IPV schedule strives to provide the best of protection to an individual child while not deviating from the national immunization policies.

#### *Dose and Schedule*

*Child who has not received any polio vaccination so far:* OPV at birth, OPV and IPV at 6, 10 and 14 weeks. OPV and IPV at 15-18 months and OPV at 5 years. OPV on all NID's and SNID's. An alternative to this schedule is birth dose of OPV, OPV at 6 weeks, OPV and IPV at 10 weeks, OPV at 14 weeks and IPV at 18 weeks, OPV and IPV at 15-18 months, OPV at 5 years and OPV on all NID's and SNID's. In this schedule though the number of IPV doses have reduced from 4 to 3 but it (a) is logistically more demanding as number of visits increase (b) is not feasible if combination vaccines are chosen (c) delays the introduction of IPV and thus lowers protection against VAPP.

*Child who has completed primary series of OPV:* IPV may be offered as catch up vaccination for children less than 5 years of age who have completed primary immunization with OPV. IPV can be given two doses at 2 month interval. OPV need not be given with these IPV doses. OPV should be given with the 1st and 2nd boosters of DTP and on all NID's and SNID's.

*Immunodeficient children and their close contacts:* IPV should be the preferred vaccine especially in patients with B-cell

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

Combination vaccines containing IPV will be discussed separately.

## **DIPHTHERIA, TETANUS AND PERTUSSIS VACCINES**

### **DTwP VACCINE**

#### **Background**

The morbidity and mortality due to diphtheria, tetanus and pertussis has reduced significantly in India since introduction of the whole cell vaccines in EPI. However coverage with 3 doses of the whole cell vaccine stands at 55% with booster coverage being even lower thus offering tremendous scope for improvement.

#### **Vaccine**

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

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

Absolute contraindications to any pertussis vaccination (including DTwP vaccine) is history of anaphylaxis or development of encephalopathy within 7 days following previous DTwP vaccination. In case of anaphylaxis further immunization with any diphtheria/tetanus/pertussis vaccine is contraindicated as it is uncertain which component caused the event. For patients with history of encephalopathy following vaccination any pertussis vaccine is contraindicated and only diphtheria and tetanus vaccines may be used. Events such as persistent inconsolable crying of more than 3 hours duration/hyperpyrexia (fever  $\geq 40.5^\circ\text{C}$ )/HHE within 48 hours of DTwP administration and seizures with or without fever within 72 hours of administration of DTwP are considered as precautions but not contraindications to future doses of DTwP because these events generally do not recur with the next dose and they have not been proven to cause permanent sequelae. Progressive/evolving neurological illnesses, is a relative

contraindication to first dose of DTwP immunization. However, DTwP can be safely given to children with stable neurologic disorders.

### **Recommendations for Use**

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

## **DTaP VACCINE**

### **Background**

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

### **Vaccine**

The components of pertussis bacilli used for preparation of the acellular vaccines include pertussis toxin (PT) as the essential component with or without filamentous hemagglutinin (FHA), pertactin (PRN) and fimbrial hemagglutinins 1, 2 and 3 (FIM). Commercially available vaccines vary in number of components, quantity of components and method of inactivation of

the components. Currently available aP vaccines in India include five component vaccines (Tripacel™- PT, PRN, FHA, FIM 2 and 3), three component vaccines (Infanrix™ - PT, FHA, PRN) and a two component combination vaccine (Pentaxim™ - PT and FHA, IPV, Hib). The vaccines should be stored at 2 to 8°C and the recommended dose is 0.5 ml intramuscularly. The efficacy and duration of protection with DTaP vaccines against diphtheria/tetanus and pertussis is similar to that afforded by the whole cell vaccines. There is considerable controversy on the relative efficacy of different acellular vaccines with varying number of components. The efficacy is influenced not only by number of components but also by quantity of antigen and method of inactivation. Even monocomponent vaccines with only PT have performed well in national programs. Review of clinical trial data and experience from field use in national programs indicates that all currently licensed acellular pertussis vaccines have similar efficacy. All DTaP vaccines show better efficacy against severe disease than mild disease.

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

### **Recommendations for Use**

DTaP vaccines are not more efficacious than DTwP vaccines, they have fewer adverse effects. It must also be remembered that serious adverse effects are rare phenomena even with the whole cell vaccine unlike popular belief. The IAPCOI

therefore unequivocally endorses the continued use of DTwP vaccine in EPI because of its low cost, proven efficacy and safety. The use of DTaP vaccine in office practice should be following one to one discussion with parents on a named child basis (Category 3). The DTaP vaccines may be preferred to DTwP vaccines in those children with history of severe adverse effects following DTwP vaccines or children with neurologic disorders if resources permit. The schedule is same as with DTwP vaccines. Like DTwP vaccines, DTaP vaccines must not be used in children 7 years or older because of increased reactogenicity. All licensed DTaP vaccines are of similar efficacy and safety as of currently available data and any one of them may be used. DTaP combination vaccines will be discussed separately.

## **TETANUS TOXOID (TT)**

### **Background**

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

### **Vaccine/Toxoid**

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

### **Recommendations for Use**

The role of standalone TT vaccines is diminishing and replacement with Td/Tdap is recommended for more comprehensive protection. In individuals who have completed primary

and booster vaccination with DTwP/DTaP, TT boosters every 10 years provide sufficient protection.

#### *TT in Pregnancy*

WHO has evolved exhaustive guidelines for administration of TT in pregnant women and recommends replacement of TT with Td in a phased manner. For pregnant women who have not been previously immunized, two doses of TT at least one month apart should be given during pregnancy so that protective antibodies in adequate titers are transferred to the newborn for prevention of neonatal tetanus. The first dose should be administered at the time of first contact/as early as possible and the second dose of TT should be administered 1 month later and at least 2 weeks before delivery. A single dose of TT would suffice for subsequent pregnancies that occur in the next 5 years; thereafter, 2 doses of TT would again be necessary. Women, who have received 5 doses of TT over a period of at least 2.5 years, get lasting protection for their reproductive years. For women who have received 3 primary doses in infancy, two doses during the 1st pregnancy are indicated. The 2nd pregnancy requires 1 more dose and gives lasting protection for the reproductive years. For women who have received three doses and 1 booster in childhood, 1 dose each in the first and second pregnancy provide lasting protection. In women who have received 3 primary doses and the two childhood boosters only 1 dose in the first pregnancy provides lasting protection. For women who have received an additional adolescent booster in addition to the 5 childhood doses no further doses are necessary in pregnancy.

#### *TT in Wound Management*

All patients presenting with skin wounds/infections should be evaluated for tetanus prophylaxis. Cleaning of the wound, removal of devitalized tissue, irrigation and drainage is important to prevent anerobic environment which is conducive to tetanus toxin production. The indications for TT and tetanus

immunoglobulin (TIG) are as below (Table 4.1). Again replacement of TT with Td/Tdap is recommended.

**Table 4.1: Indications for tetanus and tetanus immunoglobulin**

<i>Doses of TT Given in past</i>	<i>Clean, minor wounds</i>		<i>All other wounds #</i>	
	<i>TIG*</i>	<i>TT</i>	<i>TIG*</i>	<i>TT</i>
Unknown, < 3 doses, immuno- deficient	Yes	Yes	No	Yes
≥ 3 doses	No	No**	No	No***

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

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

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

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

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

### **DT VACCINE**

This vaccine comprises of diphtheria and tetanus toxoid in similar amounts as in DTwP/DTaP, should be stored at 2 to 8° C and

dose is 0.5 ml intramuscularly. It is recommended in children below 7 years of age where pertussis vaccination is contraindicated. The DT vaccine is also recommended by the Government of India in EPI as the second childhood booster at the age of 5 years instead of DTP vaccine due to fear of side effects with the pertussis component of DTwP. However, studies with DTwP in school aged children have shown no serious adverse events attributable to the vaccine. Additionally boosting of pertussis immunity is important to protect against childhood pertussis. Henceforth the IAPCOI recommends DTwP/DTaP as the 2nd childhood booster and has also recommended to the Government of India to replace DT with DTwP for the 2nd childhood booster in EPI.

## **Td VACCINE**

### **Background**

Studies show that diphtheria antibody levels decline over time resulting in increasing susceptibility of adolescents and adults to diphtheria. However good childhood vaccination coverage (at least 70%) provides herd immunity 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 1990's, massive outbreaks of diphtheria involving primarily adults have occurred. Thus it is desirable to regularly boost adult immunity against diphtheria in addition to tetanus every 10 years. The DTwP, DTaP and DT vaccines cannot be used in children aged 7 years and above due to increased reactogenicity due to the higher diphtheria toxoid and pertussis components.

### **Vaccine**

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

### **Recommendations for Use**

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

### **Tdap VACCINE**

#### **Background**

Immunity against pertussis following primary/booster DTwP/DTaP vaccination wanes over the next 6-12 years. Surveillance studies from the developed world chiefly US have shown a gradual increase in adolescent and adult pertussis cases over the past decade. This has been attributed to more awareness, better diagnosis and a real increase in pertussis cases due to loss of vaccine induced/natural immunity further reduced by lack of natural boosting. Adolescent/adult pertussis is responsible for considerable morbidity/loss of working days and is a reservoir for disease transmission to unvaccinated/incompletely vaccinated neonates and young infants. Henceforth several developed countries have instituted routine booster immunization of adolescents and adults with standard quantity tetanus toxoid and reduced quantity diphtheria and acellular pertussis vaccine (Tdap) instead of Td. The standard strength DTwP and DTaP vaccines cannot be used for vaccination of children 7 years and above due to increased reactogenicity.

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

**Vaccine**

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

**Recommendations for Use**

There is no reason to believe that the disease burden of pertussis is low in adolescents in India. A safe and efficacious vaccine is available. The IAP COI therefore recommends offering Tdap vaccine instead of Td/TT vaccine in all children/adolescents who can afford to use the vaccine (Category 2) in the schedule discussed below. It also recommends that studies aiming to determine the serosusceptibility to pertussis and prevalence of pertussis in children/adolescents/adults presenting with prolonged cough be conducted.

- In those children who have received all three primary and the two booster doses of DTwP/DTaP, Tdap should be administered as a single dose at the age of 10-12 years.

Catch up vaccination is recommended till the age of 18 years. A single dose of Tdap may also be used as replacement for Td/TT booster in adults of any age if they have not received Tdap in the past. A gap of 5 years should be maintained between Tdap and previous TT/Td vaccine. A gap of 2 years between Tdap and TT/Td is acceptable in those children/adolescents

- Who are at high risk for contracting pertussis such as during an outbreak
  - Who are at high risk for pertussis complications such as those with neurological or pulmonary diseases
  - Who are in contact with infants less than 12 months of age as infants are at the highest risk for pertussis complications.
- It is also acceptable to use Tdap as a replacement for TT/Td in wound management of children aged 10 and above if they have not received Tdap in the past, and at least 5 years have elapsed since receipt of Td/TT vaccine.
  - In children who have missed the 2nd booster of DTwP/DTaP and who are 7 years of age or more, Tdap single dose is recommended at the time of presentation.
  - In children who have not completed primary immunization with DTwP/DTaP and are more than 7 years of age, 1 dose of Tdap and 2 doses of Td at 0, 1 and 6 months are recommended.
  - The single booster dose of Tdap may be followed by Td boosters every 10 years. There is no data at present to support repeat doses of Tdap (Austria is an exception where Tdap is recommended every 10 years). No tetanus prophylaxis is required for minor wounds if less than 10 years have elapsed since receipt of Tdap. No tetanus prophylaxis is required for major wounds if less than 5 years have elapsed since receipt of Tdap; if more than 5 years (but less than 10 years) have elapsed a single dose of TT may be given.
  - In the absence of sufficient data on the efficacy, immunogenicity and duration of protection against pertussis with

Tdap used as 2nd childhood booster, the IAPCOI does not recommend the use of Tdap vaccine as an alternative to DTaP/DTwP for the 2nd childhood booster in children below the age of 7 years at present.

### **MEASLES, MUMPS AND RUBELLA VACCINES**

Several combinations for protection against measles, mumps and rubella are available. These include monovalent measles, mumps and rubella vaccines, MR vaccine and MMR vaccine. Monovalent mumps and MR vaccines are not available in India.

### **MEASLES VACCINE**

#### **Background**

A safe, effective and reasonably inexpensive vaccine is available against measles for the past 5 decades and measles is a potentially eradicable disease. Most developed and many developing countries have significantly reduced the burden and even eliminated measles by a multi pronged strategy comprising of improved routine coverage, provision of a second dose through routine immunization or periodic supplementary immunization activities, careful surveillance and appropriate case management. Interestingly measles immunization saves more lives per unit cost than any other health intervention. However measles still kills around 6,00,000 children globally and 80,000 in India every year. Additionally, measles causes significant morbidity including malnutrition, blindness and neurologic damage. Suboptimal primary immunization coverage which in India as per National Family Health Survey-3 (NFHS-3) is only 60% is primarily responsible for this dismal scenario and needs to be urgently addressed.

#### **Vaccine**

All currently used measles vaccines are live attenuated vaccines. Most of the currently used live attenuated measles vaccine strains originate from the original Edmonston strain and

include Schwarz, Edmonston Zagreb, Moraten and Edmonston-B strains. Indian vaccines are usually formulated from the Edmonston Zagreb strain grown on human diploid cells or purified chick embryo cells. Each dose contains at least 1000 infective units and has no preservative. It is supplied freeze-dried in single dose or multidose vials with distilled water as a diluent. The vaccine may be stored frozen or at 2 to 8°C (shelf life 2 years). Reconstituted vaccine is destroyed by light and is very heat labile (loses 50% potency at 20° C and 100% at 37° C after 1 hour) and is susceptible to contamination as it does not have any preservative. For these reasons reconstituted vaccine should be protected from light, kept at 2 to 8° C and used within 4-6 hours of reconstitution. This is particularly applicable to multidose vials. The dose is 0.5 ml subcutaneously or intramuscularly, preferably over the upper arm/anterolateral thigh. Immunogenicity and efficacy depends on the age of administration due to interference by preexisting maternal antibodies. Seroconversion rates are around 60% at the age of 6 months, 80-85% at the age of 9 months and beyond 95% at the age of 12-15 months. While antibody titers wane over the years measles specific cellular immunity persists and provides lifelong protection. Secondary vaccine failures rarely occur. Immunogenicity is lower in the immunocompromised including HIV. In HIV infected infants superior seroconversion rates are seen at 6 months as compared to 9 months due to progressive immunodeficiency with age. Vaccine efficacy studies from India have reported varying efficacies ranging from 60-80% when given at the age of 9 months. Adverse reactions apart from local pain and tenderness include a mild measles like illness 7-12 days after vaccination in 2-5% of the vaccinees. Thrombocytopenic purpura may occur at a frequency of 1/30,000 vaccinees. Though depression of cell mediated immunity may occur, it recovers within 4 weeks and is considered harmless even for those with early HIV or latent/unrecognized tuberculosis. There is no data to support causal relationship between measles vaccine and encephalitis, GBS, subacute sclerosing encephalitis and autism. There is no

transmission of the vaccine virus from the vaccinees to the contacts. Measles vaccine has been the cause of several infant deaths in India due to toxic shock syndrome and use of succinylcholine instead of distilled water as the diluents. The vaccine is contraindicated in the severely immunocompromised, in those with history of severe allergic reactions to the constituents and in pregnancy. The vaccine should be administered to those with HIV infection irrespective of degree of immunocompromise as here the benefits outweigh the risks. The vaccine may be safely given to those with history of egg allergy. The vaccine may be given along with all childhood vaccines with the exception of BCG vaccine.

### **Recommendations for Use**

In view of the significant morbidity and mortality against measles the government is urged to take rapid steps such as surveillance for disease, improvement of primary coverage, supplementary immunization activities and better case management.

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

## **RUBELLA VACCINE**

### **Background**

Rubella per se is a mild exanthematous illness; but if acquired in the first trimester of pregnancy can lead to disastrous consequences in the fetus/new born such as abortion, stillbirth, mental retardation, congenital heart disease, blindness and cataract. Hence the objective of vaccination against rubella is protection against congenital rubella syndrome (CRS). Developed countries have remarkably reduced the burden of CRS by universal immunization against rubella. It is essential that when immunization against rubella is instituted more than 80% coverage is achieved. Haphazard use of rubella vaccine (monovalent or as a constituent of MMR) in young children through public health measure with sub-optimal coverage of the target population may be counter-productive as it may shift the epidemiology of rubella to the right with more clinical cases occurring in young adults leading to paradoxical increase in cases of CRS. This has been shown to occur using mathematical models. Direct evidence from some Latin American countries and Greece also corroborates these concerns. There is paucity of reliable data on occurrence of CRS in India. Other developing countries have incidence rates of 0.6-4.1 per 1000 live births. WHO estimates that 100,000 cases of CRS occur in developing countries alone. Cost benefit studies in countries with routine immunization coverage  $\geq 80\%$  show that benefits of rubella vaccine outweigh the costs particularly when combined with measles vaccination.

### **Vaccine**

Rubella vaccine currently derived from RA 27/3 vaccine strain grown in human diploid/chick embryo cell cultures. The vaccine is available in freeze dried form that should be stored frozen or at 2 to 8° C and needs to be reconstituted with sterile diluent prior to use. The reconstituted vaccine must be protected from light, stored at 2 to 8° C and used within 6 hours of reconstitution. The dose is 0.5 ml subcutaneously. A single

dose of vaccine provides lifelong protection in 95% of the vaccinees. Apart from local side effects, a mild rash may develop in 5% of the vaccinees. Joint symptoms such as arthralgia and arthritis may occur 1-3 weeks following vaccination especially in susceptible post pubertal females but is usually mild. Immune thrombocytopenic purpura may occur in a frequency of 1 per 30,000 vaccinated children. The vaccine is contraindicated in the severely immunocompromised and in pregnancy. Pregnancy should be avoided for 3 months after vaccination but babies born to women inadvertently vaccinated in pregnancy do not exhibit an increased risk of congenital malformations. Hence accidental vaccination in pregnancy is not an indication for medical termination of pregnancy.

### **Recommendations for Use**

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

## **MMR VACCINE**

### **Background**

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

### **Vaccine**

Formulations from different manufacturers have different strains of the vaccine virus. Measles and Rubella strains have

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

### **Recommendations for Use**

For the purposes of universal immunization, the vaccine should be introduced in those areas where immunization coverage is

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

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

## **HEMOPHILUS INFLUENZAE TYPE B (hib) CONJUGATE VACCINES**

### **Background**

Capsulated *H. influenzae* has six serotypes of which type b is most important. *Hemophilus influenzae type b* (Hib) is an important invasive pathogen causing diseases such as

meningitis, bacteremia, pneumonia, cellulitis, osteomyelitis, septic arthritis and epiglottitis. Most of invasive Hib disease occurs in children in the first two years of life and natural protective immunity is acquired by the age of 3-4 years. Non capsulated Hib disease including, bronchitis, otitis media, sinusitis and some pneumonia is not amenable to prevention at present and can occur at all ages. The burden of Hib disease is underestimated in India as cultures are often not sent, the organism is difficult to culture especially when antibiotics have been administered and as a large proportion of pneumonia may be non bacteremic. Data from the Invasive Bacterial Infections Surveillance (IBIS) group from six referral hospitals in India show that Hib is a common cause of meningitis in India.

### **Vaccine**

All Hib vaccines are conjugated vaccines where the Hib capsular polysaccharide (polyribosyl ribitol phosphate or PRP) is conjugated with a protein carrier so as to provide protection in the early years of life when it is most needed. Currently available vaccines include Hb OC (carrier CRM197 mutant *C. diphtheria* toxin protein), PRP-OMP (carrier *N meningitidis* protein outer membrane complex) and PRP-T (carrier tetanus toxoid). PRP-D has been withdrawn due to relatively poor efficacy. HbOC and PRP-T vaccines show only a marginal increase in antibody levels after the first dose with a marked increase after the second and even better response after the third dose. On the other hand, PRP-OMP shows an increase in antibody level after the first dose itself with only marginal increases after the second and third doses. The onset of protection with PRP-OMP is thus faster. Additionally while 3 doses of HbOC and PRP-T are recommended for primary vaccination, only 2 doses of PRP-OMP are recommended for this purpose. Only HbOC and PRP-T are currently available in India. The vaccines should be stored at 2 to 8° C and the recommended dose is 0.5 ml intramuscularly. Efficacy trials have demonstrated 90-100% efficacy against culture proven

invasive Hib disease for 1 year after vaccination. A trial in Gambian infants has shown 21% protection against episodes of severe pneumonia. The serologic correlate of protection at the time of exposure has been fixed at 0.15 µg/ml and that for long term protection as 1µg/ml. Side effects are mild and usually local. Developed countries where the vaccine was introduced for universal immunization have witnessed virtual elimination in Hib disease with no serotype replacement. The vaccine has also been shown to impart herd protection by reducing nasopharyngeal carriage. A notable exception to the Hib success story was an increased incidence of Hib disease in vaccinated children between the years 1999-2003 in the UK occurring after a remarkable initial decline in Hib disease in the early 1990's. Most of the cases of invasive Hib disease occurred in the late 2nd year of life. The major factor responsible for this phenomenon was omission of the 2nd year booster. Vaccine induced immunity wanes over time and reduced carriage of the organism in the environment compounds the problem by lack of natural boosting. It is also now recognized that immunological memory is insufficient for protection against Hib disease. Hence a booster dose is mandatory for sustained protection.

### **Recommendations for Use**

The IAPCOI recommends offering the Hib vaccine to all parents who can afford the vaccine (Category 2). The Government of India has also approved introduction of Hib vaccine in EPI in a phased manner. The vaccination schedule for Hib consists of three doses when initiated below 6 months, 2 doses between 6-12 months and 1 dose between 12-15 months, with a booster at 18 months. For children aged more than 15 months a single dose suffices. The interval between two doses should be at least 4 weeks. As Hib disease is essentially confined to infants and young children, catch up vaccination is not recommended for healthy children above 5 years. However the vaccine should be administered to all individuals with functional/anatomic

hyposplenism irrespective of age. Hib vaccines are now used mostly as combination vaccines with DTwP/DTaP/Hep B/IPV details of which will be discussed separately.

## **HEPATITIS B (hep B) VACCINE**

### **Background**

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

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

### **Vaccine**

The plasma derived Hep B vaccine is no longer available. The currently available vaccine containing the surface antigen of Hepatitis B is produced by recombinant technology in yeast and adjuvanted with aluminium salts and preserved with thiomersol (thiomersol free vaccines is also available, Revac-Bmcf). Hep B vaccine is available as single and multidose vials and should be stored at 2 to 8° C. The vaccine should not be frozen; frozen vaccine should be discarded. The dose in children and adolescents (aged less than 18 years) is 0.5 ml/

10 µg and in those 18 years and older is 1 ml/20 µg. It should be injected intramuscularly in the deltoid/anterolateral thigh. Gluteal injections should be avoided due to low immunogenicity. The vaccine is extremely safe and well tolerated. The classical schedule is 0, 1 and 6 months. The vaccine is highly immunogenic and seroconversion rates are greater than 90% after a three dose schedule. Seroconversion rates are lower in the elderly, the immunocompromised and those with chronic renal failure. Four doses at 0, 1, 2 and 12 months of double dose may be given in these patients. Routine testing for anti HBsAg levels 1 month after completion of the immunization schedule is recommended in children born to HBsAg positive mothers, health care workers and those with comorbidities. Antibody titers greater than 10 mIU/ml signify a response and are considered protective. Non responders should be tested for Hepatitis B carrier status. If found to be negative the same three dose schedule should be repeated. 50% of non responders may respond to the second series; the rest are permanently susceptible. Routine boosters are not needed in healthy children and adults. Studies have shown that individuals who had responded to the vaccination series and had levels of 10 mIU/ml after vaccination are protected against hepatitis B disease for life even if the levels drop to below protective levels or are undetectable later. This is due to immune memory. In the immunocompromised and those with co morbidities such as chronic renal disease, levels should be checked periodically and booster vaccination given whenever levels drop to below protective levels.

### **Hepatitis B Immunoglobulin (HBIG)**

HBIG provides passive immunity and is indicated along with Hep B vaccine in management of perinatal/occupational/sexual exposures to Hepatitis B in susceptible individuals. The dose of HBIG in adults is 0.06 ml/kg and in neonates/infants 0.5 ml. HBIG should be stored at 2 to 8° C and should not be frozen. HBIG provides temporary protection lasting 3-6 months. HBIG should never be given intravenously. HBIG is also used alone

following exposure to Hepatitis B in patients who are non responders to Hepatitis B vaccination (genetic reasons/ immunocompromised status). In this situation two doses of HBIG 1 month apart are indicated.

### **Recommendations for Use**

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

For office practice, the IAPCOI recommends offering hepatitis B vaccine to all children who can afford the vaccine (Category 2).

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

- a. Birth, 1 and 6 months
- b. Birth, 6 and 14 weeks
- c. 6, 10 and 14 weeks

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

Catch up vaccination with Hep B vaccine as a 0, 1, 6 schedule should be offered to all children/adolescents who have not been previously vaccinated with Hep B vaccine. This is to address problems related to horizontal mode of transmission of the virus. Pre vaccination 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. Pre vaccination screening for HBsAg should be done in these contacts.

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

#### **Management of an Infant Born to Hepatitis B Positive Mother**

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

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

If the mother is HBsAg positive (and especially HBeAg positive), the baby should be given Hepatitis B Immune Globulin (HBIG) along with Hep B vaccine within 12 hours of birth, using two separate syringes and separate sites for injection. The dose of HBIG is 0.5 ml IM. HBIG may be given upto 7 days of birth but the efficacy of HBIG after 48 hours is not known. Two more doses of Hep B vaccine at 1 month

and 6 months are needed. The closely spaced schedule should not be used. If HBIG is not available (or is unaffordable), Hep B vaccine may be given at 0, 1 and 2 months with an additional dose between 9-12 months. The efficacy of prophylaxis with both HBIG and Hep B vaccine is 85-95% and that with Hep B vaccine alone (1st dose at birth) is 70-75%. All infants born to HBsAg positive mothers should be tested for HBsAg and anti HBsAg antibodies at the age of 9-15 months to identify carriers/non responders.

## **COMBINATION VACCINES**

### **Background**

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

**Combination Vaccines Currently Licensed in India***DTwP+Hib, DTwP+Hep B, DTwP+Hib+Hep B*

These are available in two forms. 1) As ready to use liquid preparations: DTwP+ Hep B (Tritanrix HB<sup>TM</sup>, SII Q-Vac<sup>R</sup>, Comvac<sup>TM</sup>4-HB, Shantetra), DTwP+Hib (Easy four, ShanHib-DPT), DTwP+Hep B+ Hib (Shan5, Easy five, Comvac<sup>TM</sup>5) and 2) When lyophilized Hib needs to be reconstituted with DTwP/DTwP + Hep B from the same manufacturer: DTwP + Hib (Tetraact Hib), DTwP+ Hib + Hep B (Tritanrix HB<sup>TM</sup> + Hiberix<sup>TM</sup>, SII Q-Vac<sup>R</sup> + Hibpro<sup>R</sup>, Comvac<sup>TM</sup>4-HB + BioHib<sup>TM</sup>). Though the antibody response to Hib is reduced in these combination vaccines as compared to separate administration, most subjects attain the seroprotective level of 1 µg/ml and there is no reduced efficacy against Hib disease. The antibody responses to diphtheria, pertussis, tetanus and Hep B are unchanged. The liquid and the lyophilized formulations have similar immunogenicity and safety for both primary and booster immunization.

*DTaP+Hib, DTaP+Hib+IPV*

Currently the DTaP/Hib is available as lyophilized Hib which needs to be reconstituted with liquid DTaP just prior to administration (Infanrix<sup>TM</sup> + Hiberix<sup>TM</sup>, Tripacel<sup>TM</sup> + ActHib<sup>TM</sup>) or with DTaP + IPV (Pentaxim<sup>TM</sup>). Antibody responses to diphtheria, pertussis, tetanus and if applicable polio are satisfactory and comparable to those obtained after administration as separate doses. The primary concern and debate with these vaccines is Hib immunogenicity as studies showed a significant reduction in Hib titer/percentage of children achieving the long term protective level of 1 µg/ml, when these combination vaccines are used as compared to separate administration of Hib vaccines in primary immunization. This reduction in Hib immunogenicity is not noted when these vaccines are used for booster vaccination even in subjects who had been administered combination

vaccines for primary immunization. The reduction in Hib antibody titers was noted across all studies with different formulations of DTaP (exception Canadian five component DTaP vaccine) and different Hib conjugate vaccines and was more significant when vaccination was administered earlier in life and in premature babies. Studies with the five component Canadian vaccine combination vaccine with Hib did not show reduced Hib immunogenicity. Experts did not attach much significance to lower Hib immunogenicity of these combination vaccines as the serologic correlates of protection for Hib were derived from studies with the polysaccharide vaccines which provided poor quality antibodies and no immunologic memory. Hence DTaP+ Hib combination vaccines were initially licensed in Europe for both primary and booster immunization but in the USA only for booster vaccination. An increased incidence of Hib disease was noted in the UK but not in other European countries following shift to DTaP+ Hib combination vaccines. This was initially attributed to the lower immunogenicity of the combination vaccine but later conclusively attributed to other factors mainly non administration of a booster dose at 18 months. The US FDA and ACIP has recently approved DTaP (5 component) + IPV + Hib combination vaccine (Pentacel™) for primary immunization (June 2008).

#### *Hep A + Hep B*

Available in adult formulation (for those aged 18 and above, Twinrix™) and pediatric formulation (Twinrix junior™). The recommended schedule is three doses at 0, 1 and 6 months. These combination vaccines show acceptable and comparable immune response against Hep A and Hep B as compared to separate administration. A rapid immunization schedule particularly suitable for travelers at 0, 7 and 21 days has acceptable short and long term efficacy. The adult formulation may also be used effectively in children aged 1-15 years as two doses at 0 and 6 months.

**Internationally Available Combination Vaccines***DTwP+IPV, DTwP+IPV+Hib*

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

*DTaP+IPV, DTaP+Hep B, DTaP+IPV+Hep B, DTaP+Hib+Hep B, DTaP+IPV+Hep B+Hib*

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

*MMRV Vaccine*

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

combination MMRV vaccine licensed in Europe is Priorix tetra with comparable immunogenicity and efficacy but an increased risk of fever as compared to separate administration of vaccines.

#### *Hep A + Typhoid*

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

#### *Hep B + Hib*

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

### **Recommendations for Use**

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

## **TYPHOID VACCINES**

### **Background**

Enteric fever (typhoid and paratyphoid) is a major public health problem in India. Population based studies from urban population in India suggest that incidence of typhoid fever is 2730 per 100,000 populations per year in 0-4 year old children, 1170 per 100,000 per year in 5-19 year age group and 110 per 100,000 per year in 20-40 year age group. The incidence of paratyphoid fever is increasing in India, and may account for 20-40% cases of enteric fever. High prevalence of antimicrobial resistance particularly to quinolones has made enteric fever a difficult disease to treat. All these factors have made vaccines

against typhoid and paratyphoid fever of immense need in our country.

### **Vaccine**

Several vaccines have been available against typhoid/paratyphoid fever.

#### *Whole Cell Inactivated Typhoid/Paratyphoid Vaccines (TA/TAB)*

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

#### *Oral Live Attenuated Ty21a Vaccine*

Salmonella typhi Ty21a is a live attenuated strain with a mutation in gal E gene and lacks the enzyme UDP-gal 4 epimerase. It is genetically stable and is not known to revert to virulence. It provides protection by inducing local gut immunity, but there is no biological marker of immunity for this vaccine. Since the bacteria are acid labile, the vaccine is supplied in an enteric coated formulation as capsules or liquid formulation. Efficacy drops over time and the cumulative efficacy at three years of 3 doses of the capsule formulation against culture confirmed typhoid fever has been reported as 48% in a Cochrane metanalysis. The liquid formulation has superior efficacy but is not available commercially. The vaccine should be stored at 2 to 8° C. The commercially available capsular form can only be given to children five years of age and above as the capsules have to be swallowed intact. Three doses on alternate days on an empty stomach with cool liquid are recommended. The vaccine should not be given during

diarrhoea and antimicrobials active against typhoid bacillus should not be used 3 days before and 3 days after oral typhoid vaccine administration as these may interfere with the vaccine "take". The vaccine may be administered with all other childhood vaccines including live vaccines. Protection begins within a week after completion of the course. Revaccination is recommended every 3-7 years. No adverse effects were noted in clinical trials. The vaccine should be avoided during pregnancy and in the immunocompromised (may be given in HIV infected with CD4 count more than 200 cells/ $\mu$ l). This vaccine has long been withdrawn from the Indian market.

#### *Vi-capsular Polysaccharide Vaccine*

The vaccine contains highly purified antigenic fraction of Vi-capsular polysaccharide antigen of *S typhi* which is a virulence factor of the bacteria. Each dose contains 25-30  $\mu$ g of purified polysaccharide in 0.5 ml of phenolic isotonic buffer for intramuscular or subcutaneous use. The vaccine should be stored at 2 to 8°C and should not be frozen. Since it is a pure polysaccharide vaccine, it is not immunogenic in children below 2 years of age and has no immune memory. The biological marker is anti Vi antibodies and 1  $\mu$ g/ml is proposed as the serologic correlate of protection. The vaccine does not interfere with the interpretation of the WIDAL test. Efficacy drops over time and the cumulative efficacy at 3 years against culture confirmed typhoid fever is reported as 55%. It is recommended for use as a single dose in children aged 2 years and above and can safely be given with all other childhood vaccines. Revaccination is recommended every 3 years. The adverse effects are mild and include pain and swelling at injection site. The vaccine is contraindicated only in those with previous history of hypersensitivity to the vaccine and can be safely given in the immunocompromised including HIV infected.

#### *Vi conjugate Typhoid Vaccines*

Conjugation of the Vi antigen with a protein carrier is desirable as it would induce a T-cell dependent immune response

including immunogenicity in children aged below 2 years and immune memory. Conjugation of Vi antigen with non toxic recombinant *Pseudomonas aeruginosa* exotoxin A (rEPA) has been evaluated in safety, immunogenicity and efficacy trials in Vietnam. Two doses administered 6 weeks apart showed immunogenicity superior to Vi polysaccharide vaccine and a cumulative 3 year efficacy of 89% in 2-5 year old children. Another conjugate vaccine which has recently been licensed in India has Vi antigen conjugated with tetanus toxoid (Peda typh). In a multicentric study from India in 169 subjects aged 12 weeks and more, at least four-fold rise in antibody titer was seen in all subjects following a single dose of the vaccine. The vaccine was well tolerated with no major local or systemic side effects. No data on duration of immunity and efficacy is available. The manufacturer recommends 2 doses of 0.5 ml intramuscularly at an interval of 4-8 weeks, followed by a booster every 10 years. In children aged less than 2 years an extra booster 2-2½ years after the first dose is recommended. Since the immunogenicity trial assessed response to only single dose and did not assess duration of immunity the dosing schedule seems arbitrary. The extrapolation of efficacy of the vaccine from the Vietnamese trial is invalid due to fundamental differences between the two vaccines, age groups and dosing schedule.

### **Recommendations for Use**

The public health burden of enteric fever in India is huge. Improvements in hygiene and sanitation are still a distant dream. The IAPCOI therefore recommends the inclusion of typhoid vaccines in the national immunization schedule. For office practice, the IAPCOI recommends the administration of the currently available Vi polysaccharide vaccine 0.5 ml IM every three years beginning the age of 2 years till age of 18 years in all children/adolescents who can afford to use the vaccine (Category 2). A child with history of suspected/confirmed enteric fever may be vaccinated 4 weeks after recovery if he/she has not received the vaccine in the past 3 years.

The committee awaits further data on the conjugate typhoid vaccines before recommending them for routine use. It also stresses the need for development of vaccines against paratyphoid fever for both better individual protection and reduction of enteric fever burden.

## **HUMAN PAPILLOMA VIRUS (HPV) VACCINES**

### **Background**

Globally, cervical cancer is the second most common cancer in women with approximately 5,00,000 cases annually and 350,000 deaths. Additionally, cervical cancer may occur early and strike at the productive period of a woman's life. It is well recognized that HPV is a necessary cause of cervical cancer. 100 serotypes of HPV have been discovered of which 15-20 are oncogenic. Types 16 and 18 account for 70% of the cases of invasive cervical cancer globally. The lag period between infection with oncogenic HPV and invasive cervical cancer is 15-20 years. Oncogenic HPV serotypes have also been implicated in causation of anal, vulvar, vaginal, penile and oropharyngeal cancers. Additionally, non-oncogenic HPV serotypes 6 and 11 are responsible for more than 90% of anogenital warts and most recurrent respiratory papillomatosis.

Data from national cancer registries in India indicate that cervical cancer is the most common cancer/cause of cancer related death in Indian women. Approximately 1,32,000 cases occur annually with 74,000 deaths. Indian women face a 2.5% cumulative lifetime risk of cervical cancer and 1.4% cumulative risk of death from cervical cancer. HPV types 16 and 18 account for 76.7% of cervical cancer in India. There is no data on burden of anogenital warts in the general community; warts have been reported in 2-25.2% of STI clinic attendees in India.

### **Vaccines**

Two vaccines have been licensed globally; a quadrivalent vaccine marketed as Gardasil<sup>TM</sup> and the other a bivalent vaccine

marketed as Cervarix™. Both are manufactured by recombinant DNA technology that produces non-infectious virus like particles (VLP) comprising of the HPV L1 protein, the major capsid protein of HPV. Clinical trials with both vaccines have used efficacy against cervical intraepithelial neoplasia (CIN) 2/3 and adenocarcinoma in situ (AIS) caused by HPV strains contained in the concerned vaccine as primary end points. Both vaccines do not protect against the serotype with which infection has already occurred before vaccination. Both vaccines have been licensed in several countries world over.

Gardasil™ now available in India is a mixture of L1 proteins of HPV serotypes 16, 18, 6 and 11 with aluminium containing adjuvant. Clinical trials with three doses at 0, 2 and 6 months in more than 16,000 women aged 16-26 years from 5 continents including Asia have shown 99% efficacy at a median follow up of 1.9 years against types 16, 18 related CIN- 2/3 and AIS in per protocol analysis (women who received all three doses of the vaccine and who remained uninfected with vaccine HPV type at onset and for 1 month after completion of the vaccine schedule). Additionally 99-100% efficacy was seen against vaccine type related genital warts, vaginal intraepithelial neoplasia (VaIN) and vulvar intraepithelial neoplasia (VIN). Follow up studies in a subset of participants over 5 years show persistent protection, and good response to booster immunization indicative of immune memory. Immunogenicity studies in females 9-15 years showed antibody titers non-inferior to those aged 16-26 years. Local adverse effects reported were pain at the injection site in 83% of vaccinees (mainly mild-moderate intensity) and swelling and erythema in 25%. Systemic adverse effects such as fever reported in 4% of vaccines. No serious vaccine related adverse events have been reported either in trials or post marketing surveillance studies.

Cervarix™ is a mixture of L1 proteins of HPV serotypes 16 and 18 with ASO4 as an adjuvant. Clinical trials with three doses at 0, 1 and 6 months in more than 18000 women globally

has shown 90% efficacy against type 16/18 related CIN2/3 and AIS at 15 month follow up in modified intention to treat analysis (included women who were at baseline negative for HPV DNA of vaccine type virus and who received at least 1 dose of the vaccine). Follow up studies in a subset of participants over 4-5 years show no evidence of waning immunity. Local side effects reported were pain (mild and moderate intensity) in 90% and swelling and erythema in 40%. Systemic side effects such as fever were seen in 12%. No serious vaccine related adverse effects were observed.

### **Recommendations for Use**

Cervical cancer is responsible for significant morbidity/mortality in Indian women and affects women of all socio economic strata. Compliance with cervical Papanicolou (PAP) smear screening is low in India. The currently available vaccines are safe and efficacious. The HPV vaccines are thus of public health importance. The IAPCOI recommends offering HPV vaccine to all females who can afford the vaccine (Category 2) in the schedules discussed below. Since protection is seen only when the vaccine is given before infection with HPV, the vaccine should preferably be given prior to sexual debut. The vaccine should preferably be introduced to parents as a cervical cancer preventing vaccine and not as a vaccine against a sexually transmitted infection (STI). Vaccines are not 100% protective against cervical cancer and not a replacement for periodic screening. Hence screening programs should continue as per recommendations. Need for boosters and potential for serotype replacement would be known in future. Both the available vaccines are equally efficacious and safe for protection against cervical cancer and precancerous lesions as of currently available data. The quadrivalent vaccine additionally protects against anogenital warts.

### *Dose and Schedule*

The vaccines should be stored at 2 to 8° C, must not be frozen and protected from light. The dose is 0.5 ml intramuscular in

deltoid. The recommended age for initiation of vaccination is 10-12 years. As of current licensing regulations in India, catch up vaccination is permitted up to the age of 26 years. Three doses at 0, 2 and 6 months are recommended with Gardasil<sup>TM</sup> (minimum interval between 1st and 2nd dose is 4 weeks and second and third dose is 12 weeks) and 0, 1 and 6 months with Cervarix<sup>TM</sup>. HPV vaccines can be given simultaneously with other vaccines such as hepatitis B and Tdap. As a precaution against syncope following any vaccine in adolescents, the vaccinee should be counseled prior to vaccination, vaccine be administered in a sitting/lying down position and the patient observed for 15 minutes post vaccination. Both vaccines are contraindicated in those with history of previous hypersensitivity to any vaccine component and should be avoided in pregnancy. The vaccines may be administered in the immunocompromised but immunogenicity and efficacy may be lower. At present there is no data to support use of boosters.

## **PNEUMOCOCCAL VACCINES**

### **Background**

*S. pneumoniae* is responsible for 15-50% of all episodes of community acquired pneumonia, 30-50% of all cases of acute otitis media and a significant proportion of bacterial meningitis and bacteremia. It is estimated that 50% of the 2 million deaths due to pneumonia globally every year are attributable to *S. pneumoniae*. Ninety serotypes of *S. pneumoniae* have been described of which a handful are responsible for most cases of invasive pneumococcal disease (IPD). Serotypes 14, 6, 19, 18, 9, 23, 7 are responsible for 85% of invasive pneumococcal disease in the developed world. Children under the age of 2 years are at greatest risk for invasive pneumococcal disease.

Data on prevalence of pneumococcal disease is scanty in India but it has been estimated that *S. pneumoniae* causes 6.6-22 million episodes of pneumonia and 200,000 deaths yearly from pneumonia in India. Results of the IBIS study in patients

with invasive pneumococcal disease (IPD) indicate that serotypes 6, 1, 19, 14, 4, 5, 45, 12, 7, 23 are the most prevalent with serotypes 1 and 5 accounting for 30% of invasive pneumococcal disease. It is also known that serotypes causing pneumonia and otitis media differ from that causing invasive pneumococcal disease and usually reflect those serotypes present in the nasopharyngeal carriage.

### **Pneumococcal Vaccines**

Two vaccines are available; the unconjugated pneumococcal polysaccharide vaccine and the conjugate vaccines.

#### *Pneumococcal Polysaccharide Vaccine*

The unconjugated polysaccharide vaccine is a 23 valent vaccine (PPV 23) containing the following serotypes – 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F. It is a T-cell independent vaccine that is poorly immunogenic below the age of 2 years, has low immune memory, does not reduce nasopharyngeal carriage and does not provide herd immunity. It has at best 70% efficacy against prevention of invasive pneumococcal disease in the high-risk population but offers no protection against non-bacteremic pneumonia/otitis media. It is stored at 2 to 8° C and the dose is 0.5 ml subcutaneous/intramuscularly. It is a safe vaccine with occasional local side effects. Not more than two life time doses are recommended as repeated doses may cause immunologic hyporesponsiveness.

#### *Pneumococcal Conjugate Vaccines*

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

licensed PCV till date is CRM 197 PnC-7v (henceforth referred to as PCV 7) containing polysaccharide antigen of serotypes 4, 6B, 9V, 14, 18C, 19F and 23 linked to CRM 197. The landmark randomized controlled NCKP trial in the US in around 40,000 children with three primary doses at 2, 4, 6 months and 1 booster at 12-15 months demonstrated 95% protection against IPD due to vaccine serotypes, 89% protection against any serotype, 4% protection against clinically diagnosed pneumonia, 30% protection against radiological pneumonia, 6% protection against acute otitis media and 20% protection against placement of tympanostomy tubes over a 5 year follow up. No serious adverse effects were noted; 15-20% of the vaccinees had local side effects. The PCV 7 vaccine has been licensed for universal immunization in the US and 19 more countries of the developed world since the year 2000. The benefits seen in trials were replicated in program settings in USA, Canada and Australia among many other countries with dramatic declines noted in IPD, pneumonia admissions, AOM outpatient visits, prescription of antimicrobials for AOM, placement of tympanostomy tubes and antimicrobial resistance. Apart from the direct benefits, a significant decline in pneumococcal disease in unvaccinated contacts including young infants, adults and the elderly was noticed due to herd effect resulting from reduced nasopharyngeal carriage. Though increase in disease due to non vaccine serotypes particularly 19A has been small till date compared to a vast decrease in overall burden of disease; continued surveillance to monitor serotype replacement is warranted. Trials with an experimental 9 valent vaccine (CRM 197 as carrier) which incorporates serotypes 1 and 5 in South Africa showed a 20% decline in radiologically positive pneumonia in HIV non infected children and 13% decline in HIV infected. A trial in Gambia with 3 primary doses of the same 9 valent vaccine showed reduction in the incidence of invasive disease due to all serotypes by 50%, radiologically diagnosed pneumonia by 37%, clinical pneumonia by 7%, hospital admissions by 15% and all cause childhood mortality by 16%. The non significant protection against clinical pneumonia noted in trials is probably due to

poor specificity of the case definition that allowed inclusion of several children with reactive airway disease and viral pneumonia. A trial in the Czech Republic with an 11 valent vaccine (conjugated with protein D of Hib, additional serotypes of 1, 3, 5 and 7) has shown 30% protection against AOM. The US and South African but not the Gambian trials have noted an increased incidence of reactive airway disease in vaccine recipients as compared to controls but causal association is not clear. Trials are currently underway with a 10 valent (protein D carrier and additional serotypes 1, 5, 7) and 13 valent vaccines (CRM 19 as carrier and additional serotypes 1, 3, 5, 6A, 7F and 19A). Studies with alternative schedules and fewer doses are also underway. An expert committee of the WHO has proposed 0.35 µg/ml as the serologic correlate for protection against IPD.

### **Recommendations for use**

#### *For EPI*

The burden of pneumococcal disease is the greatest among the underprivileged children in India. The conjugate pneumococcal vaccines are thus of public health importance and ideally should be available to all children. However the high cost of PCV vaccines and the limited coverage of the currently available vaccine are impediments. GAVI has offered to supply PCV at a cost of 0.15–0.3 USD/dose to India for inclusion in the national immunization schedule and commits to extending this support till the year 2015. Also, broader serotype vaccines will be available in future. IAPCOI feels that Government of India should avail of this opportunity and apply for GAVI support, establish a pneumococcal disease surveillance system and set into motion a process for inclusion of PCV in EPI once broader serotype vaccines are available.

#### *High Risk Children*

Children at high risk of pneumococcal disease are listed in Table 1. The IAP COI recommends offering both PCV and

PPV 23 to all high-risk children who can afford the vaccine in schedules discussed below. The PCV vaccines provide robust immune response and immune memory while PPV 23 provides expanded serotype coverage. If PCV is not affordable, at least PPV 23 should be given to high-risk children above 2 years of age.

### *Healthy Children*

Pneumococcus is a cause of significant morbidity and mortality in children (especially those less than 2 years) and merits prevention. However as of current data, PCV7 covers only 55% of pneumococcal serotypes prevalent in India. Therefore IAPCOI recommends offering the currently available conjugate pneumococcal vaccine (PCV 7) after one to one discussion with parents in healthy children aged less than 2 years (Category 3) in schedule discussed below. The risk of invasive pneumococcal disease is significantly lower in healthy children above the age of 2 years and thus benefit achieved with vaccination of these children is likely to be low. Vaccination with single dose of PCV vaccine may be considered in children aged 2-5 years if demanded by parents. Since induction of immune system memory, reduction in carriage, efficacy against serotypes causing most invasive disease, and effectiveness against noninvasive syndromes (e.g., non bacteremic pneumonia and AOM) are superior with PCV, PCV is preferred to PPV 23 in this setting. There is no data to support pneumococcal vaccination in healthy children aged 5 years and above and is not recommended.

### *Dose and Schedule*

#### *Healthy children (PCV vaccine)*

- Dose is 0.5 ml IM
- Routine Vaccination: 3 doses at 6,10,14 weeks and 1 booster at 15-18 months
- Catch up vaccination
  - 6-12 months: 2 doses 4-8 weeks apart and 1 booster at 15-18 months

- 12-23 months: 2 doses 8 weeks apart
- 24-59 months: single dose

*High risk children (PCV and PPV 23) (Table 4.2)*

- If affordable, PCV should be given first. For children aged less than 5 years follow the schedule mentioned above. For children older than 5 years a single dose of PCV is recommended (Currently available PCV 7 though licensed upto age 9 years, has been shown to be safe and immunogenic in children older than 9 years as well).
- In children aged 2 years or more, PPV 23 should also be given as a single dose of 0.5 ml IM. If PCV has been given earlier, a gap of 2 months must be maintained between PCV and subsequent PPV 23.
- A high-risk child who has received PPV 23 in the past but not PCV vaccine may be offered a single dose of PCV vaccine at the time of presentation if 2 months have elapsed since receipt of PPV 23.

Only one repeat dose of PPV 23 is recommended only for children who have sickle cell disease, hyposplenism, asplenia, congenital/acquired immunodeficiency, those on immunosuppressive therapy, renal failure and nephrotic syndrome. The repeat dose of PPV 23 may be given after 3-5 years if the child is less than 10 years of age and after 5 years if child is aged more than 10 years.

**Table 4.2:** *Children at high risk for pneumococcal disease*

- 
- Congenital immunodeficiency
  - HIV
  - Immunosuppressive therapy
  - Organ transplant recipients
  - Sickle cell disease, asplenia/hyposplenism
  - Chronic cardiac disease
  - Chronic pulmonary disease excluding asthma unless on high dose oral steroids
  - Chronic liver disease
  - Chronic renal failure, nephrotic syndrome
  - Diabetes mellitus
  - Cerebrospinal fistula, cochlear implants
-

## HEPATITIS A VACCINES

### Background

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

Countries are classified as low/medium or highly endemic for Hepatitis A. In countries with high endemicity like India, most individuals acquire natural infection in childhood and burden of disease including incidence of outbreaks is low. As a shift occurs towards medium endemicity due to improvements in hygiene and sanitation a certain proportion of children remain susceptible till adulthood. Thus burden of symptomatic disease and incidence of outbreaks paradoxically increase. Epidemiologic data from India though limited, suggests a shift in epidemiology of disease and HAV susceptibility in 30-40% of adolescents and adults belonging to the high socioeconomic class.

### Vaccines

#### *Inactivated Vaccines*

Most of the currently available vaccines are derived from HM 175/GBM strains and grown on MRC5 human diploid cell lines. The virus is formalin inactivated and adjuvanted with aluminium hydroxide. The vaccine is stored at 2 to 8° C. The vaccines are given in a two dose schedule, 6 months apart intramuscularly. The adult formulation should be used after the recommended cut-off age of 15 years (Avaxim™) and 18 years (Havrix™). Protective antibodies are seen in 95-100% 1 month after the 1st dose and almost 100% after the second dose. Serologic correlate of protection has been fixed at

20 mIU/ml. The protective efficacy is around 90-100% and onset of protection is 2 weeks – 1 month after the 1st dose of the vaccine. The vaccine efficacy is lower in the elderly, immunocompromised, those with chronic liver disease, in transplant recipients and those with pre existing maternal antibodies. The vaccine may be safely given with other childhood vaccines and interchange of brands is permitted though not routinely recommended. Immunity is lifelong due to anamnestic response and no boosters are recommended at present in the immunocompetent. Adverse reactions are minor and usually include local pain and swelling.

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

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

#### *Live Attenuated Vaccine*

This vaccine is derived from the H2 strain of the virus attenuated after serial passage in Human Diploid Cell (KMB 17 cell line). It has been in use in China since the 1990's in mass vaccination programs. The vaccine meets requirements of the Chinese drug authority and the WHO. It is also now licensed and available in India (Biovac A). The recommended dose is 1 ml SC (10 (6.5) CCID<sub>50</sub>/ml) in children aged 1-15 years. Immunogenicity studies with single dose show seroconversion rates of more than 98% 2 months after vaccination and persistence of protective antibodies in more than 80% of vaccines at 10 year follow up. Uncontrolled studies show an

efficacy of almost 100% sustained over 10 years despite decline in seroprotection rates and antibody titers. Recent immunogenicity studies from India have shown > 95% seroconversion, 6 weeks following single dose of the vaccine and sustained protection over at least 2 years, though antibody titers are significantly lower than those achieved with inactivated vaccines though above the protective level. Some observational Chinese studies have reported inability of single dose of the vaccine to protect against subclinical infection. Chinese studies with 2 doses of the vaccine have shown better seroprotection rates and higher antibody titers over prolonged follow up as compared to historical controls who received single dose. No horizontal transmission or serious adverse effects have been noted. The vaccine is not effective as post-exposure prophylaxis.

### **Recommendations for Use**

The IAPCOI recommends offering the vaccine to healthy children of parents who can afford the vaccine after explaining the pros and cons to the parents on a one-to one “named child” basis (Category 3).

The vaccine is recommended for use in all individuals who can afford the vaccine in certain risk groups as enumerated below.

- Patients with chronic liver disease
- Carriers of Hep B and Hep C
- Congenital or acquired immunodeficiency
- Transplant recipients
- Adolescents seronegative for HAV who are leaving home for residential schools
- Travelers to countries with high endemicity for Hepatitis A.

Vaccination with inactivated vaccines may also be offered to household contacts of patients with acute Hep A virus infection within 10 days of onset of illness in the index case. It may not always be effective under such circumstances when the contact has had the same source of infection as the index patient.

If a decision to administer the vaccine is taken any of the licensed vaccines may be used as all have nearly similar efficacy and safety (exception for post exposure prophylaxis/immunocompromised patients where only inactivated vaccines may be used). Two doses 6 months apart are recommended for all vaccines. The manufacturers of the live attenuated vaccine claim that a single dose is sufficient for long term protection. Evidence supporting this claim is equivocal and hence till more information is available IAPCOI recommends two doses of even the live attenuated vaccine to primarily guard against primary vaccine failures. All Hep A vaccines are licensed for use in children aged 1 year or older. However in the Indian scenario it is preferable to administer the vaccines at age 18 months or more when maternal antibodies have completely declined. Vaccination at this age is preferable to immunization later as it is easier to integrate with the existing schedule, protects those who have no antibodies and protects children by the time children attend day care. Pre vaccination screening for Hepatitis A antibody is likely to be cost effective in children older than 10 years at which age the estimated seropositive rates exceed 50%.

## **VARICELLA VACCINE**

### **Background**

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

climates higher proportion of varicella cases may occur among adults and varicella morbidity and mortality may be higher than that described in developed countries. A seroprevalence study from India reported 15% seronegativity and susceptibility to varicella in adults.

### **Vaccine**

Takahashi et al developed a live attenuated vaccine from the Oka strain in Japan in the early seventies. Varicella vaccines in use today are all derived from the original Oka strain grown in human diploid cells but the virus contents may vary from one manufacturer to another. The recommended dose is 0.5 ml subcutaneously and the minimum infectious virus content should be 1000 Plaque Forming Units. It is available as a lyophilized vaccine, storage requirements vary with the brand of the vaccine and manufacturer instructions should be followed. It should be protected from light and needs to be used within 30 minutes of its reconstitution. The vaccine may be given with all other childhood vaccines. Vaccination induces both humoral and cellular immunity. Immunogenicity studies report overall seroprotection rates of 86% following single dose of the vaccine (immunogenicity reducing with increasing age) and persistence of protective antibodies for up to 10 years after vaccination. Pre licensure efficacy and post licensure effectiveness studies have shown the efficacy of a single dose of the vaccine to range from 70-90% against any disease and  $\geq 95\%$  against combined moderate and severe disease for 7-10 years after vaccination. Administration of 2 doses three months/4 years apart improves seroprotection rates to 99% and results in higher GMT's by at least 10 fold. This translates to superior efficacy of 98.3% against any disease/100% against moderate/severe disease and reduces incidence of breakthrough varicella as compared to single dose by 3.3 fold. Like with all other live attenuated vaccines the second dose of the vaccine is primarily to take care of primary vaccine failures. Breakthrough varicella is defined as varicella developing more than 42 days after immunization and usually occurs 2-5 years

following vaccination. Breakthrough disease in 70% of instances is typically mild, with <50 skin lesions, predominantly maculopapular rather than vesicular rash, low or no fever, and shorter (4-6 days) duration of illness. Nevertheless, breakthrough varicella is contagious, can result in outbreaks and has occasionally cause deaths in the immunocompromised. Risk factors for vaccine failure and breakthrough disease though equivocal include young age at vaccination ( $\leq 15$  months), increasing time since vaccination, receipt of steroids within 3 months of breakthrough disease and administration of vaccine within 28 days of MMR vaccine but not on the same day.

Adverse reactions documented carefully in prelicensure/postlicensure studies include local reactions such as pain, redness and swelling at vaccination site, injection site rash, fever and a systemic varicella like rash in around 5%. Transmission of the vaccine virus from vaccinees to contacts is rare especially in the absence of a vaccine related rash in the vaccinees. However vaccine recipients who develop a rash should avoid contact with persons without evidence of varicella immunity who are at high risk for severe complications. Herpes zoster in vaccine recipients is known to occur due to both the vaccine virus and the wild virus; however the overall incidence of herpes zoster in vaccinated children was noted to be much lower than unvaccinated children in pre licensure trials. The side effect profile is similar with the 2 dose schedule. The vaccine is contraindicated during pregnancy, in those with clinically manifest HIV infection and in the immunocompromised (exceptions listed below). When used in adult females, pregnancy should be avoided for 3 months after vaccination.

### **Recommendations for Use**

The IAPCOI recommends offering the vaccine to healthy children with no prior history of varicella who can afford the vaccine after one to one discussion with parents (Category 3).

The vaccine is recommended for use in all children belonging to certain high risk groups as enumerated below.

- Children with humoral immunodeficiencies.
- Children with HIV infection but with CD4 counts 15% and above the age related cut-off.
- Leukemia but in remission and off chemotherapy for at least 3-6 months.
- Children on long term salicylates. Salicylates should be avoided for at least 6 weeks after vaccination.
- Children likely to be on long term steroid therapy. The vaccine may be given at any time if the children are on low dose steroids/alternate day steroids but only 4 weeks after stopping steroids if the patients have received high dose steroids ( $\geq 2$  mg/kg) for 14 days or more.
- In household contacts of immunocompromised children.
- Adolescents who have not had varicella in past and are known to be varicella IgG negative especially if they are leaving home for studies in a residential school/college.
- Children with chronic lung/heart disease.
- Seronegative adolescents and adults if they are inmates of or working in the institutional set up e.g. school teachers, day care center workers, military personnel and health care professionals.
- For post-exposure prophylaxis in susceptible healthy non pregnant contacts preferably within 3 days of exposure (efficacy 90%) and potentially up to 5 days of exposure (efficacy 70%, against severe disease 100%).

The vaccines are licensed for age 12 months and above. However the risk of breakthrough varicella is lower if given 15 months onwards. Hence the IAPCOI recommends administration of varicella vaccine in children aged 15 months or older. For healthy children a single dose of 0.5 ml SC is recommended in children below 13 years and two doses 4-8 weeks apart in children 13 years or older. All high risk children should however receive two doses 4-8 weeks apart irrespective of age. The immunization committee of the USA (ACIP) has recently recommended administration of two doses

of varicella vaccine in all children owing to the inability of the single dose regimen to effectively control disease burden and the superior immunogenicity/efficacy of the 2 dose regimen. US children below the age of 13 years receive two doses at 12-15 months and 4-6 years (minimum interval 3 months between doses) and older children two doses 4-8 weeks apart. There is no change in recommendations for healthy Indian children as of date.

A live attenuated vaccine against herpes zoster is now licensed and available in the US (Zostavax<sup>TM</sup>) but not in India.

### **Varicella Zoster Immunoglobulin (VZIG)**

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

- Neonates born to mothers who develop varicella 5 days before or 2 days after delivery. The risk of varicella related death in these infants as per older estimates is likely to be 30%. Other full-term healthy newborns are not at increased risk for complications and do not merit prophylaxis if exposed to varicella.
- All neonates born at less than 28 weeks of gestation/with birth weight less than 1000 gms, exposed to varicella in the neonatal period.

- All preterm neonates born at more than 28 weeks of gestation and exposed to varicella in the neonatal period only if their mothers are negative for anti-varicella IgG.
- Pregnant women exposed to varicella.
- All immunocompromised children especially neoplastic disease, congenital or acquired immunodeficiency or those receiving immunosuppressive therapies. Patients who received IVIG @ 400 mg/kg in the past 3 weeks are deemed protected.

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

## **ROTA VIRUS VACCINES**

### **Background**

Rotavirus is a major cause of diarrhea related morbidity and mortality in children worldwide. Although rotavirus illness rates are similar in both the developed and developing world and in children of all socioeconomic status, mortality due to rotavirus disease is more in the developing world and in the poor and malnourished. It has been estimated that rotavirus causes 6,10,000 under five deaths globally every year. Rotavirus is an icosahedral RNA virus and seven serogroups have been described (A-G); Group A rotaviruses cause most human disease. The viral outer capsid is made of VP7 and VP4

proteins. The VP7 protein determines the G serotypes and the VP4 protein the P serotypes. Variability of genes coding for the VP7 and VP4 proteins is the basis for classification into genotypes. All G genotypes correspond with serotypes; there are more P genotypes than serotypes. Each rotavirus strain is designated by its G serotype number followed by P serotype number and then P genotype number in square brackets, e.g., G1P1A[8].

Epidemiologic studies from India indicate that 6-45% (median 20%) of all childhood diarrheas that need hospitalization are due to rotavirus. It is further estimated that rotavirus causes around 100,000 deaths in children below age 5 years annually in India. Seroepidemiologic studies show that G1, G2, G3 and G4 in combination with P8, P6 and P4 account for 65-70% of rotavirus infections in India. In addition to the common G and P serotypes, newer serotypes, mixed forms and untypable serotypes are frequently seen. Intra country differences exist between North, South, East and West.

### **Vaccine**

The observation that initial infection with rotavirus prevents from subsequent severe infections has been the rationale for vaccine development. The first clinically licensed rotavirus vaccine (1998) was Rotashield, a live oral tetravalent vaccine comprising of three rhesus human reassortant and one rhesus rotavirus strain. This vaccine was withdrawn soon after licensure due to occurrence of vaccine associated intussusception. Currently two live oral vaccines are licensed and marketed worldwide, Rotarix™ and RotaTeq™. A vaccine based on Indian neonatal strains is undergoing clinical trials.

Rotarix™ now available in India is a monovalent attenuated human rotavirus vaccine derived from the human rotavirus strain 89-12 grown in vero cells and contains the G1P1 [8] strain administered orally in a 2-dose schedule to infants of approximately 2 and 4 months of age. RotaTeq™ is a human bovine reassortant vaccine and consists of five reassortants between the bovine WC23 strain and human G1, G2, G3, G4 and P1A [8]

rotavirus strains grown in vero cells and administered orally in a three dose schedule at 2, 4 and 6 months. Large phase 3 double blind placebo controlled trials with both vaccines in around 70,000 infants each (11 countries mainly US, Finland for Rotateq™ and Latin America and Finland for Rotarix™) have shown 85-98% efficacy against severe rotavirus gastroenteritis and 42-59% efficacy against hospitalization due to diarrhea of any cause. Both vaccines have been demonstrated to be extremely safe with no increased risk of intussusception as compared to placebo. Shedding of the vaccine virus was observed in 10% of vaccinees with Rotateq and more than 50% of vaccinees with Rotarix. Similar high efficacy extends into the second year of follow up with the vaccine. Results from a recent trial with Rotarix™ in 10,000 infants in Hong Kong, Singapore and Taiwan showed efficacy and safety similar to that seen in earlier trials. Both vaccines have been licensed and introduced into the national immunization program of several countries worldwide. Efficacy trials in developing countries of Africa and Asia are ongoing and results are awaited.

Studies show no interference between rotavirus vaccines and other childhood vaccines including IPV, pneumococcal, Hib, DTaP and Hep B. Data is insufficient for pertussis immunity. Immunogenicity studies about simultaneous administration of rotavirus vaccines with OPV are available for Rotarix™ and Rotateq™, which show no reduction in immunogenicity against polio and no significant reduction in immunogenicity against rotavirus. Additionally an efficacy study shows no reduction in efficacy of Rotarix™ against severe rotavirus gastroenteritis when co administered with OPV.

### **Recommendations for Use**

The IAPCOI acknowledges the morbidity and mortality burden of rotavirus and need for a rotavirus vaccine. Such a vaccine would be most needed in the national immunization program as the disease consequences are the most serious in the underprivileged. However the IAPCOI is concerned about

(a) lack of immunogenicity studies from India where response to other oral vaccines such as OPV has been observed to be suboptimal (b) lack of efficacy studies from India where there is tremendous diversity in circulating strains and thus results from studies abroad cannot be readily extrapolated. Till such data is available IAPCOI recommends use of the vaccine after one to one discussion with parents (Category 3). If the decision to administer the vaccine is taken, either vaccine may be chosen as they have similar efficacy and safety profiles as of currently available data.

#### *Dose and Schedule*

Vaccination should be strictly as per schedule discussed below, as there is a potentially higher risk of intussusception if vaccines are given to older infants. Vaccination should be avoided if age of the infant is uncertain. There are no restrictions on the infant's consumption of food or liquid, including breast-milk, either before or after vaccination. Vaccines may be administered during minor illnesses. Though there is limited evidence on safety and efficacy of rotavirus vaccines in preterm infants, vaccination should be considered for these infants if they are clinically stable and at least 6 weeks of age as preterms are susceptible to severe rotavirus gastroenteritis. Vaccination should be avoided in those with history of hypersensitivity to any of the vaccine components or previous vaccine dose. Vaccination should be postponed in infants with acute gastroenteritis as it might compromise efficacy of the vaccine. Immunocompromised infants are susceptible to severe and prolonged rotavirus gastroenteritis but safety and efficacy of either of the two vaccines in such patients is unknown. Risks versus benefits of vaccination should be considered while considering vaccination for infants with chronic gastrointestinal disease, gut malformations, previous intussusception and immunocompromised infants.

#### *Rotarix<sup>TM</sup>*

It is available as a lyophilized vaccine to be reconstituted with liquid diluent prior to administration. The vaccine and the

diluents should be stored at 2 to 8° C and must not be frozen. The vaccine should be administered promptly after reconstitution as 1 ml orally. The first dose can already be administered at the age of 6 weeks and should be given no later than at the age of 12 weeks. The interval between the 2 doses should be at least 4 weeks. The 2-dose schedule should be completed by age 16 weeks, and no later than by 24 weeks of age. If the infant spits out or regurgitates the entire vaccine dose then the dose may be repeated at the same visit (as per drug insert of Rotarix™).

#### *RotaTeq™*

The vaccine is available as a liquid virus mixed with buffer and no reconstitution is needed. It should be stored at 2 to 8° C. The recommended schedule is 3 oral doses at ages 2, 4 and 6 months. The first dose should be administered between ages 6-12 weeks and subsequent doses at intervals of 4-8 weeks. Vaccination should not be initiated for infants aged >12 weeks. All 3 doses should be administered before the age of 32 weeks. The manufacturer does not recommend readministration of vaccine if a dose is spit out or regurgitated.

## **RABIES VACCINES**

### **Background**

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

**Vaccine**

The nerve tissue vaccines are no longer available due to poor efficacy and life threatening adverse effect of neuroparalytic reactions. The currently available vaccines are the modern tissue culture vaccines (MTCV) and include Purified Chick Embryo Cell (PCEC, Rabipur) vaccine, Human Diploid Cell Vaccine (HDCV, Rabivac), Purified Vero Cell Vaccine (PVRV, Verorab, Indirab, Abhayrab), Purified Duck Embryo Vaccine (PDEV, Vaxirab). The vaccines are available in lyophilized form with sterile water as diluent, are stable for 3 years at 2 to 8° C and should be used within 6 hours of reconstitution. All tissue culture vaccines have almost equal efficacy and any one of these can be used. These vaccines induce protective antibodies in more than 99% of vaccinees following pre/post exposure prophylaxis. The main adverse effects are local pain, swelling and redness and less commonly fever, headache, dizziness and gastrointestinal side effects. Systemic hypersensitivity reactions in vaccinees have been reported with HDCV particularly following booster injections but not with PCEC/PVRV. Intradermal vaccination may cause more local irritation as compared to the intramuscular route. Along with proper wound care and rabies immunoglobulin (RIG) post exposure prophylaxis is effective in preventing 100% of rabies cases. Failures occur due to delay in initiation or non use of RIG when indicated.

**Rabies Immunoglobulin (RIG)**

RIG contains specific anti rabies antibodies that neutralize the rabies virus and provide passive protection till active immunity is generated. There are 2 types of RIG: (1) Human rabies immunoglobulin (HRIG – dose is 20 U/kg body weight, maximum dose 1500 IU) and (2) Equine rabies immunoglobulin (ERIG–dose is 40 U/kg body weight, maximum dose 3000 IU). HRIG is preferred, but if not available/unaffordable, ERIG may be used. Most of the new ERIG preparations are potent, safe, highly purified and less expensive as compared to HRIG

but do carry a small risk of anaphylaxis. As per latest recommendations from WHO, skin testing prior to ERIG administration is not recommended as skin tests do not accurately predict anaphylaxis risk and ERIG should be given whatever the result of the test.

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

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

### **Post Exposure Prophylaxis (PEP)**

Post exposure prophylaxis is a medical emergency and is indicated following a significant contact (discussed in detail below) with any warm blooded animal. These include dogs, cats, cows, buffaloes, sheeps, goats, pigs, donkeys, horses, camels, foxes, jackals, monkeys, mongoose, bears and others. In case of bites by pet animals, PEP may be deferred only if the pet at the origin of exposure is more than a year old and has a vaccination certificate indicating that it has received at least 2 doses of a potent vaccine, the first not earlier than 3 months of age and the second within 6 to 12 months of the first dose and in the past 1 year. If vaccination is deferred, the

pet should be observed for 10 days; if the dog shows any sign of illness during the observation period, the patient should receive full rabies post-exposure prophylaxis urgently. Rabies due to rodent bites has not been reported in India till date and post exposure prophylaxis is not *normally* recommended for these bites. Post exposure prophylaxis should be initiated as soon as possible and should not be delayed till results of lab tests or animal observation is available. Infancy, pregnancy and lactation are never contraindications for PEP. Persons presenting several days/months/years after the bite should be managed in a similar manner as a person who has been bitten recently (with RIG if indicated) as rabies may have a long incubation period and the window of opportunity for prevention remains.

Rabies exposure may be classified as per WHO into three categories (Table 4.3).

**Table 4.3:** *Categories of rabies exposure*

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

The first step is thorough cleansing of the wound with soap and flushing under running water for 10 minutes. This should be followed by irrigation with a virucidal agent such as 70% alcohol or povidone iodine. Antimicrobials and tetanus

toxoid should be given if indicated. RIG should be infiltrated in and around the wound in category 3 bites as discussed earlier. Any suturing of wound should be avoided. When suturing is unavoidable for purpose of hemostasis, it must be ensured that RIG has been infiltrated in the wound prior to suturing. All category 2 and 3 bites merit rabies vaccine. Any of the MTCV may be used intramuscularly in anterolateral thigh or the deltoid. Rabies vaccine should never be injected in the gluteal region. The dose is same at all ages and is 1 ml IM for HDCV, PCEV, PDEV and 0.5 ml for PVRV. The standard schedule (Essen protocol) is five doses on days 0, 3, 7, 14 and 30, with day '0' being the day of commencement of vaccination. A sixth dose on day 90 is optional and may be offered to patients with severe debility or those who are immunosuppressed. Interchange of vaccines is permitted only in special circumstances but should not be done routinely. If RIG is not available then two doses of the vaccine may be given on day 0 (this is however not a substitute for RIG). If the animal remains healthy over a 10 day observation period, further vaccination may be discontinued. It is however desirable to administer one more dose on day 28 in order to convert to the pre exposure prophylaxis schedule.

Several other schedules of rabies vaccination have been proposed. These include the 2-1-1 intramuscular schedule (Zagreb schedule) — two IM doses on day 1, one IM dose on day 7 and one IM dose on day 21. This schedule is however not approved for use in India. Intradermal vaccination is cost effective alternative to intramuscular vaccination as the dose required is only 0.1 ml. The intradermal schedules have been used successfully in Thailand, Philippines and Sri Lanka. The unit dose of 0.1ml for ID should have at least 0.25 units. Based on the recommendations of the expert group as well as WHO, the Drug Controller General of India (DCGI) has recently decided to allow ID route administration of tissue culture based anti rabies vaccine for post exposure prophylaxis in a phased manner in certain government antirabies centres. The schedules permitted in the 1st phase include the Thai Red Cross

Regimen (2-2-2-0-1-1, two intradermal doses on the deltoid on days 0,3,7 and 1 dose on day 30 and 90) and the Updated Thai Red Cross Regimen (2-2-2-0-2-0, two doses on days 0, 3, 7 and 30). Another schedule not currently approved by DCGI is the 8 site regimen (8-0-4-0-1-1, 8 intradermal doses on each upper arm, each lateral lower abdominal quadrant, each thighs and each suprascapular regions on day 0, 4 doses on day 7 on each thigh and upper arm and 1 dose on day 30 and 90 on upper arm). Vaccines currently recommended for ID route administration in India are purified vero cell rabies vaccine and purified chick embryo cell vaccine. The intradermal route should not be used for immunocompromised patients and those on chloroquine therapy.

The criteria for selection of Antirabies centre for ID use are

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

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

### **Pre-exposure Prophylaxis**

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

- Continuous exposure: Lab personnel involved with rabies research and production of rabies biologics. Source and exposure may be unrecognized.
- Frequent exposure: Veterinarians, laboratory personnel involved with rabies diagnosis, medical and paramedical

staff treating rabies patients, dog catchers, zoo keepers, forest staff.

- Infrequent exposure
  - Postmen, policemen, courier boys
  - Travelers to rabies endemic countries particularly those who intend to backpack/trek.
  - Most Indian children are at risk for rabies. Therefore IAPCOI recommends offering pre exposure prophylaxis to children at high risk of rabies exposure after discussion with parents.

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

## **INFLUENZA VACCINES**

### **Background**

The influenza virus is an orthomyxovirus and is capable of causing disease in humans, birds and animals. In the industrialized world morbidity, absenteeism, economic burden and mortality due to influenza is well quantified and significant. Unfortunately there is scanty data on the burden of influenza

in India. The emergence of avian influenza and a consequent human pandemic is a matter of great concern in the current scenario.

Influenza A and B cause significant human disease. Influenza A is further classified into several subtypes based on hemagglutinin and neuraminidase. The currently circulating influenza virus strains are Type A H1N1 and H3N2 and influenza B virus. Influenza virus is characterized by frequent mutations — antigenic drifts (minor antigenic change, both A and B) and antigenic shifts (major antigenic change, only A). Vaccines elicit a relatively strain-specific humoral response, have reduced efficacy against antigenically drifted viruses and are ineffective against unrelated strains. It is of the utmost importance, therefore, that the vaccine should incorporate the current strain prevalent during that time. The influenza vaccine is therefore unique as the precise composition has to be changed periodically in anticipation of the prevalent influenza strain expected to circulate in a given year. The WHO reviews data obtained from its chain of reference laboratories from world over and recommends vaccine composition on a biannual basis; in September/October for the Southern Hemisphere and in February/March for the Northern Hemisphere. This gives the vaccine manufacturer's 4-6 months to manufacture the vaccine in time for the flu season for the respective hemisphere.

## **Vaccines**

### *Inactivated Influenza Vaccines (TIV)*

The inactivated influenza vaccines are produced from virus grown in embryonated hen's eggs, and are of three types: whole virus, split-product, subunit surface-antigen formulations. Whole-virus vaccines are associated with increased adverse reactions, especially in children, and are currently not used. Most influenza vaccines are split-product vaccines, produced from detergent treated, highly purified influenza virus, or surface-antigen vaccines containing purified hemagglutinin and neuraminidase. Vaccines are trivalent

(TIV); containing 15 µg each of the WHO recommended two influenza A strains (H1N1 and H3N2) and one influenza B strain. They should be stored at 2 to 8°C and never be frozen. These vaccines are licensed for use in children aged 6 months and older. Provided there is good antigenic match, the vaccines provide 70-90% efficacy against laboratory confirmed disease in healthy adults, 25-40% reduction in hospitalizations in elderly non institutionalized patients and 40-75% reduction in mortality in influenza seasons. The efficacy of vaccine is lower and around 50% in children below 5 years and in individuals with high risk conditions. The vaccine is administered intramuscularly, the dose being 0.25 ml in children below three years and 0.5 ml thereafter. Side effects are mild and include fever, rash and injection site reactions. The link between currently available influenza vaccines and Gullain Barre Syndrome (GBS) is equivocal and if present is less than 1 case per million people vaccinated. However the vaccine should preferably be avoided in patients with history of GBS and who are not at high risk of severe influenza related complications. The vaccine should be administered with caution in patients with history of severe egg allergy only if expected benefits outweigh risks.

#### *Live Attenuated Influenza Vaccines (LAIV)*

The live attenuated influenza vaccine (LAIV) FluMist® has been recently approved by US FDA for use in healthy non pregnant individuals 2-49 years of age. The vaccine is composed of the live attenuated reassortants of the three WHO recommended strains and is administered as a nasal spray. It is stored at 2 to 8° C. This vaccine has superior efficacy as compared to the inactivated vaccines in young healthy children especially below 5 years of age. However unlike the inactivated vaccine it has not been licensed in individuals with any chronic disease, pregnant women and children aged less than 2 years due to lack of efficacy and safety studies. This vaccine should also be avoided in children less than 5 years of age with history of reactive airway disease, those with history of

hypersensitivity to eggs/vaccine components and those with history of GBS in the past. Side effects include mild fever, runny nose and sore throat. This vaccine is currently not available in India.

### **Recommendations for Use**

The infection rates with influenza are highest in children aged 5-9 years but complications and mortality are greatest in children aged less than 2 years, the elderly and in patients with chronic diseases. The vaccine is recommended for use in the following patient groups

- Congenital or acquired immunodeficiency
- Chronic cardiac, pulmonary, hematologic, renal, liver disease and diabetes mellitus
- Children on long term aspirin therapy
- Any neurologic disease that might cause respiratory compromise or impair ability to handle secretions
- Asthma requiring oral steroids
- Elderly aged more than 65 years.

In countries like the USA, influenza vaccine is additionally recommended for all women likely to be pregnant in the influenza season, health care workers, all children aged 6 months to 18 years and all contacts of children with high risk conditions/healthy children less than 5 years of age. However due to lack of accurate data on the burden of disease in India and competing health priorities, the IAPCOI does not recommend the use of the vaccine in these groups.

The influenza vaccines are given before the peak influenza season. However unlike temperate countries where the peak influenza season is in winters, in tropical countries like India the illness occurs all year round. The vaccine should therefore be given as soon as the new vaccine are released in the market or at the time of presentation to the health care provider. When used for the first time in children 6 months to less than 9 years of age the vaccines (TIV/LAIV) are given as 2 doses 1 month apart; only one dose is sufficient 9 years and above. Revaccination is recommended with a single annual dose

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

### **Pre-pandemic Influenza Vaccine**

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

## **MENINGOCOCCAL VACCINES**

### **Background**

*Neisseria meningitidis* accounts for 30-40% cases of meningitis in children up to the age of 15 years. Disease can be endemic or epidemic. Endemic disease occurs primarily in children and adolescents, with highest attack rates in infants aged 3-12 months. Certain other groups are also at high risk as discussed later. Severe meningococcal disease is associated with high case-fatality rates (5-15%) even where adequate medical facilities are available and permanent disability in survivors. Chemoprophylactic measures are in general insufficient for the control of this disease because secondary cases comprise only 1-2 % of all meningococcal cases.

There are 13 known serogroups but 90% of the disease causing isolates belong to serogroups A, B, C, Y and W-135. The burden of meningococcal disease is greatest in the African meningitis belt which extends across Africa from Senegal to Ethiopia. In these areas, disease occurs endemically in the dry season and also as epidemics every 7-14 years and is usually due to serogroups A and W-135. Disease outbreaks in Haj

Pilgrims have been attributed to A and W-135. Disease in industrialized countries is primarily due to B, C and Y. In India endemic cases are mainly due to group B and epidemic disease due to Group A [Surat, Gujarat (1985-87), areas adjoining Delhi (1966-1985 and more recently 2005)]. Globally more than 50% of meningococcal disease in infants under the age of 1 year is attributed to serogroup B against which no vaccine was available due to diversity of circulating strains and molecular mimicry between serogroup B capsule and neural adhesion molecules. However several trials involving novel meningococcal B vaccines are currently in progress in Norway, France and New Zealand.

### **Vaccines**

#### *Unconjugated Meningococcal Polysaccharide Vaccine (MPSV)*

These are either bivalent (A + C) or quadrivalent (A, C, Y, W135) and contain 50 µg of each of the individual polysaccharides, available in lyophilized form, reconstituted with sterile water and stored at 2 to 8°C. These “thymus-independent” vaccines do not induce immunological memory and the response in children younger than two years is poor. Hence these are indicated for adults and children older than 2 years (only under special circumstances in children three months to two years of age). The antibody responses to each of the four polysaccharides in the quadrivalent vaccine are serogroup-specific and independent. Protective antibody levels are usually achieved within 7-10 days of vaccination. The serogroup A polysaccharide induces antibody in some children as young as three months of age, although a response comparable with that occurring in adults is not achieved until age 4-5 years. The serogroup C component is poorly immunogenic in children less than 2 years. The serogroup A and C vaccines have good immunogenicity, with clinical efficacy rates of 85 percent or higher among children five years of age or older and adults. Serogroup Y and W-135 poly-

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

#### *Conjugated Meningococcal Polysaccharide Vaccine (MCV)*

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

A conjugate meningococcal serogroup C vaccine (conjugated to CRM 197 or TT) has been part of routine immunization in the United Kingdom since November 1999. These vaccines were licensed on basis of safety and immunogenicity studies without any data on clinical efficacy. The dosing schedule was three doses at interval of 4-8 weeks interval in children below 6 months, 2 doses in age group 6-12 months and a single dose in older children. A dramatic decline in meningococcal disease in both vaccinated and unvaccinated was noted following introduction of the vaccine; effectiveness of the vaccine within the first year of vaccination ranged from 88% to 98% among different age groups; however efficacy dropped by 80% after the first year. No serotype replacement has been observed till date.

A quadrivalent A, C, Y and W-135 conjugate vaccine has been licensed for use in individuals aged 11-55 years in USA (2-55 years in Canada). This vaccine contains 4 µg each of A,

C, Y and W-135 polysaccharide conjugated to 48 µg of diphtheria toxoid (Menactra). A single dose of 0.5 ml IM is recommended. This vaccine had comparable immunogenicity to the previously used polysaccharide vaccine. It is associated with minor local side effects such as pain, swelling and can be safely administered with Td and typhoid vaccines. While not observed in clinical trials, Guillain-Barré syndrome (GBS) was noted as a possible but unproven risk in some adolescents following immunization with Menactra, occurring in an estimated 1 in 1 million vaccine recipients. As a precaution, people who have previously been diagnosed with GBS should not receive this vaccine unless they are at increased risk of meningococcal disease. This vaccine is currently not available in India. A quadrivalent meningococcal vaccine conjugated with CRM 197 is currently under evaluation and has shown promising results in infants and toddlers as well.

### **Recommendations for Use**

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

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

- As an adjunct to chemoprophylaxis in close contacts of patients with meningococcal disease (HCW in contact with secretions, household contacts, day care contacts).
- Students going for study abroad (mandatory in most universities in the USA).

The conjugate vaccines are preferred but currently unavailable in India. At present only the quadrivalent and bivalent polysaccharide vaccines are available in India. The quadrivalent vaccine is preferred for Haj pilgrims and international travelers and students as it provided added protection against emerging W-135 and Y disease in these areas. A single dose 0.5 ml SC/IM is recommended. In infants aged 3 months to 2 years, 2 doses 3 months apart are recommended. Revaccination with one more dose of the vaccine (conjugate preferred) 2-5 years after the first dose of polysaccharide vaccine may be considered in those children who are remain at high risk of infection or who have been vaccinated at age younger than 4 years. There are at present no recommendations for revaccination for those who have previously received the conjugate vaccines.

## **JAPANESE ENCEPHALITIS VACCINES**

### **Background**

Japanese encephalitis (JE) is one of the most important causes of viral encephalitis in Asia. Japan, South Korea, North Korea, Taiwan, Vietnam, Thailand, and the Peoples Republic of China (PRC) practice routine childhood immunization against JE. In India, JE is believed to be responsible for approximately 2000-3000 clinical cases and 500-600 deaths every year. JE has been reported from all states and union territories in India except Arunachal, Dadra, Daman, Diu, Gujarat, Himachal, Jammu, Kashmir, Lakshadweep, Meghalaya, Nagar Haveli, Orissa, Punjab, Rajasthan, and Sikkim. Highly endemic states include West Bengal, Bihar, Karnataka, Tamil Nadu, Andhra Pradesh, Assam, Uttar Pradesh, Manipur, and Goa. The risk is highest in children aged 1-15 years, in rural areas and in the

monsoon/post monsoon season. Periods of greatest risk are May to October in Goa, October to January in Tamil Nadu, August to December in Karnataka (second peak, April to June in Mandya District), September to December in Andhra Pradesh, and July to December in Northern States. Urban cases have been reported from Lucknow. JE vaccination remains the single most important control measure in JE endemic states of India.

### **Vaccines**

#### *Mouse Brain-Derived Inactivated JE Vaccine*

This vaccine is prepared from either the Nakayama/Beijing strain of JE virus grown in mice brain, purified, inactivated by formalin and preserved with thiomersol. No myelin basic protein is detectable in the finished product. Efficacy trials in Taiwan and Thailand demonstrated 80-91% efficacy with two doses of the vaccine. The vaccine is given subcutaneously – 0.5 ml in children 1-3 years, and 1 ml in older children. Primary immunization consists of three doses given on 0, 7 and 30 days. In special circumstances when time is short a 0, 7 and 14 day schedule may be used. Two doses 7 days apart provide only short term immunity in 80% of vaccinees for 6 months and may be used in travelers for logistic reasons. The last dose should be given at least 10 days prior to travel to the endemic area. For long term protection regular boosters every 2-3 years are recommended. Common adverse reactions include fever, malaise, local tenderness and redness in 20% of recipients. Acute neurologic events have been reported in 1-2.3 per million vaccinees. Allergic reactions mainly Type I hypersensitivity reactions including anaphylactic shock have been reported at a frequency of 1-100 per 10,000 traveler vaccinees varying with different batches of the vaccine. The risk of reactions is higher in those with history of hypersensitivity. All vaccinees should be cautiously monitored for possible allergic reactions and asked to remain in the vicinity of medical facility for 10 days after vaccination. Owing to

drawbacks (high cost, complicated dosing schedule, requirement of numerous doses and boosters, concerns about side-effects and reliance on neurological tissue for production) and availability of better vaccines, the production and availability of this vaccine has markedly declined in the current scenario.

#### *Cell Culture Derived Inactivated Vaccine*

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

#### *Cell Culture Derived Live SA-14-14-2 Vaccine*

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

In 2005 India witnessed a massive outbreak of JE which resulted in 2000 deaths and even greater disability. In response to this outbreak the Government of India with support of Program for Appropriate Technology in Health (PATH) initiated a pilot project in 2006 of immunizing children in hyperendemic districts against JE. 7 districts in UP, 2 in Assam and one each in West Bengal and Karnataka were targeted.

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

### **Recommendations for Use**

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

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

## **YELLOW FEVER VACCINE**

### **Background**

Yellow fever is a mosquito borne illness confined to certain countries in sub Saharan Africa and Central/South America and varies in severity from influenza like illness to severe hepatitis and hemorrhagic fever. The overall risk of serious illness and death in travelers to yellow fever endemic areas ranges from .05–0.5 per 100,000 travelers. Though yellow fever

does not exist in India, conditions are conducive for its spread in the country due to the widespread presence of the mosquito vector *Aedes aegypti* and favorable environmental conditions. Therefore the government of India has strict regulations in place to restrict the entry of susceptible and unvaccinated individuals from yellow fever endemic countries.

### **Vaccine**

It is a live attenuated vaccine derived from 17D strain of the virus grown in chick embryo cells. The vaccine is available as a freeze dried preparation in single/multidose vials that should be stored at 2 to 8° C (must not be frozen) along with sterile saline as diluent. The reconstituted vaccine is heat labile, must be stored at 2 to 8° C and discarded within 1 hour of reconstitution. The dose is 0.5 ml subcutaneously. It can be safely given along with all other childhood vaccines. Immunogenicity and efficacy are greater than 90%. Immunogenicity is lower in pregnancy and immunocompromised. Protective immunity is attained by 10th day of vaccination and lasts for at least 10 years. Adverse reactions usually minor local and systemic side effects are seen in 25% of the vaccines. Rare and serious adverse events of neurologic disease (YEL-AND, encephalitis, acute disseminated encephalomyelitis, GBS) and yellow fever vaccine-associated viscerotropic disease (YEL-AVD, which mimics wild yellow fever and is often fatal) have been reported at an incidence of 1 per 400,000 doses distributed. The risk of neurologic and viscerotropic disease is higher and hence the vaccine is contraindicated in infants below the age of 6 months, those with history of thymus disease and the severely immunocompromised including HIV with severe immunosuppression (CD4 count  $\leq$  15% of age related cutoff) and those with history of serious egg allergy. The vaccine is preferably avoided in infants aged 6-9 months, individuals aged  $\geq$  65 years and in pregnant and lactating women.

### **Recommendations for Use**

The vaccine is mandatory for all travelers to yellow fever endemic zones as per International Health Regulations. The list of endemic countries can be obtained at <http://wwwn.cdc.gov/travel/yellow> Book Ch4-YellowFever.aspx All vaccinees receive an international certificate for vaccination duly dated, stamped and signed by the centre administering the vaccine. The certificate is valid from the 10th day after vaccination for a period of 10 years. Individuals with medical contraindications for vaccination are advised to avoid or postpone travel. In case travel is unavoidable, an exemption certificate/waiver letter should be taken from the treating physician and vector control measures should be practiced. The waiver letter does not guarantee entry and the person may face refusal of entry, quarantine or onsite vaccination. In the Indian context, a valid certificate is required for all individuals aged more than 6 months entering India after travel to yellow fever endemic zones even if it was mere transit. Individuals lacking this certificate and sometimes even those with medical contraindications for vaccination are placed under quarantine for 5 days on entry to India. This vaccine is currently available only at select government controlled centers in India and is not within the domain of private vaccination clinics. Unfortunately it is often in short supply causing significant problems to travelers.