GUIDELINES

# Indian Academy of Pediatrics (IAP) Recommended Immunization Schedule for Children Aged 0 through 18 years – India, 2014 and Updates on Immunization

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**Justification:** There is a need to review/revise recommendations about existing vaccines in light of recent developments in the field of vaccinology.

**Process:** Following an IAP ACVIP meeting on April 19 and 20, 2014, a draft of revised recommendations for the year 2014 and updates on certain vaccine formulations was prepared and circulated among the meeting participants to arrive at a consensus.

**Objectives:** To review and revise recommendations for 2014 Immunization timetable for pediatricians in office practice and issue statements on certain new and existing vaccine formulations.

**Recommendations:** The major changes in the 2014 Immunization Timetable include two doses of MMR vaccine at 9 and 15 months of age, single dose recommendation for administration of live attenuated H2 strain hepatitis A vaccine, inclusion of two new situations in 'high-risk category of children' in context with 'pre-exposure prophylaxis' of rabies, creation of a new slot at 9-12 months of age for typhoid conjugate vaccine for primary immunization, and recommendation of two doses of human papilloma virus vaccines with a minimum interval of 6 months between doses for primary schedule of adolescent/ preadolescent girls aged 9-14 years. There would not be any change to the committee's last year's (2013) recommendations on pertussis vaccination and administration schedule of monovalent human rotavirus vaccine. There is no need of providing additional doses of whole-cell pertussis vaccine to children who have earlier completed their primary schedule with acellular pertussis vaccine-containing products. A brief update on the new Indian Rotavirus vaccine, 116E is also provided. The committee has reviewed and offered its recommendations on the currently available pentavalent vaccine (DTwP+Hib+Hepatitis-B) combinations in Indian market. The comments and footnotes for several vaccines are also updated and revised.

**Keywords:** *Immunity, Child, Guidelines, MMR Vaccine, Vaccination*.

The IAP Advisory Committee on Vaccines and Immunization Practices (ACVIP) has recently reviewed and revised the recommended immunization schedule for children aged 0 through 18 years to ensure that the schedule reflects recommendations based on recent evidences for licensed vaccines in the country. The first annual meeting of the IAP ACVIP was held on 19th and 20th April 2014 in New Delhi. IAP ACVIP members and invited experts who attended the meeting are listed in ***Annexure* 1.** The aim of the meeting was to discuss and debate recent developments in the field, to revise recommendations for the IAP Immunization Timetable for the year 2014, and to issue recommendations for available licensed vaccines in the country. Following the meeting, a draft of revised immunization schedule for the year 2014 was prepared and circulated among the meeting participants to arrive at a consensus.

The detailed process behind issuing IAP recommendations on immunization – primarily for the pediatricians in office practice has been described earlier [1]. These recommendations provide guidelines to a pediatrician on how best to utilize available licensed vaccines in their office-practice settings. The members may use their own discretion while using them in a given situation within the framework suggested [2]. The existing National immunization schedule and government policies are also taken into account while drafting recommendations.

## AIMS AND OBJECTIVES

To revise IAP Immunization Timetable for the year 2014, and review and issue recommendations on the available licensed vaccines.

## RECOMMENDATIONS FOR IAP IMMUNIZATION TIMETABLE, 2014

The IAP ACVIP has issued recommendations for the IAP Immunization Timetable ***(Table* I and *Fig.* 1)** for the year 2014 that includes the following major changes from last year:

**TABLE I** IAP IMMUNIZATION TIMETABLE 2014

**I. IAP recommended vaccines for routine use**

| *Age (completed wks/mo/y)* | *Vaccines* | *Comments* |
|---|---|---|
| Birth | BCG<br>OPV 0<br>Hep-B 1 | Administer these vaccines to all newborns before hospital discharge |
| 6 weeks | DTwP 1<br>IPV 1<br>Hep-B 2<br>Hib 1<br>Rotavirus 1<br>PCV 1 | **DTP:**<br>• DTaP vaccine/combinations should preferably be avoided for the primary series<br>• DTaP vaccine/combinations should be preferred in certain specific circumstances/conditions only<br>• No need of repeating/giving additional doses of whole-cell pertussis (wP) vaccine to a child who has earlier completed their primary schedule with acellular pertussis (aP) vaccine-containing products<br>**Polio:**<br>• All doses of IPV may be replaced with OPV if administration of the former is not feasible<br>• Additional doses of OPV on all supplementary immunization activities (SIAs)<br>• Two doses of IPV instead of 3 for primary series if started at 8 weeks, and 8 weeks interval between the doses<br>• No child should leave the facility without polio immunization (IPV or OPV), if indicated by the schedule<br>**Rotavirus:**<br>• 2 doses of RV1 and 3 doses of RV5<br>• RV1 should be employed in 10 and 14 week schedule, instead of 6 and 10 week<br>• 10 and 14 week schedule of RV1 is found to be far more immunogenic than existing 6 and 10 week schedule |
| 10 weeks | DTwP 2<br>IPV 2<br>Hib 2<br>Rotavirus 2<br>PCV 2 | **Rotavirus:**<br>• If RV1 is chosen, the first dose should be given at 10 weeks |
| 14 weeks | DTwP 3<br>IPV 3<br>Hib 3<br>Rotavirus 3<br>PCV 3 | **Rotavirus:**<br>• Only 2 doses of RV1 are recommended at present<br>• If RV1 is chosen, the 2nd dose should be given at 14 weeks |
| 6 months | OPV 1<br>Hep-B 3 | **Hepatitis-B:**<br>• The final (third or fourth) dose in the HepB vaccine series should be administered no earlier than age 24 weeks and at least 16 weeks after the first dose |
| 9 months | OPV 2<br>MMR-1 | **MMR:**<br>• Measles-containing vaccine ideally should not be administered before completing 270 days or 9 months of life<br>• The 2nd dose must follow in 2nd year of life<br>• No need to give stand-alone measles vaccine |
| 9-12 months | Typhoid Conjugate Vaccine | • Currently, two typhoid conjugate vaccines, Typbar-TCV and PedaTyph available in Indian market<br>• PedaTyph is not yet approved; the recommendation is applicable to Typbar-TCV only<br>• An interval of at least 4 weeks with the MMR vaccine should be maintained while administering this vaccine<br>• Should follow a booster at 2 years of age |

| | | |
|---|---|---|
| 12 months | Hep-A 1 | **Hepatitis A:**<br>• Single dose for live attenuated H2-strain Hep-A vaccine<br>• Two doses for all killed Hep-A vaccines are recommended now |
| 15 months | MMR 2<br>Varicella 1<br>PCV booster | **MMR:**<br>• The 2nd dose must follow in 2nd year of life<br>• However, it can be given at anytime 4-8 weeks after the 1st dose during 2nd year |
| 16 to 18 months | DTwP B1/DTaP B1<br>IPV B1<br>Hib B1 | **Varicella:**<br>• The risk of breakthrough varicella is lower if given 15 months onwards<br>• The first booster (4th dose) may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose.<br>**DTP:**<br>• First and second boosters should preferably be of DTwP<br>• Considering a higher reactogenicity of DTwP, DTaP can be considered for the boosters |
| 18 months<br>2 years | Hep-A 2<br>Typhoid booster | • 2nd dose for killed vaccines; only single dose for live attenuated H2- strain vaccine<br>• Either Typbar-TCV® or Vi-polysaccharide (Vi-PS) can be employed as booster;<br>• Typhoid revaccination every 3 years, if Vi-polysaccharide vaccine is used<br>• Need of revaccination following a booster of Typbar-TCV® not yet determined |
| 4 to 6 years | DTwP B2/DTaP B2<br>OPV 3 Varicella 2<br>Typhoid booster | **Varicella:**<br>• 2nd dose can be given at anytime 3 months after the 1st dose |
| 10 to 12 years | Tdap/Td<br>HPV | **Tdap:**<br>• Tdap is preferred to Td followed by Td every 10 years<br>**HPV:**<br>• Only 2 doses of either of the two HPV vaccines for adolescent/pre-adolescent girls aged 9-14 years<br>• For girls 15 years and older, and immunocompromised individuals 3 doses are recommended<br>• For two-dose schedule, the minimum interval between doses should be 6 months.<br>• For 3 dose schedule, the doses can be administered at 0, 1-2 (depending on brands) and 6 months |

**II. IAP recommended vaccines for High-risk* children (Vaccines under special circumstances)**

1-Influenza Vaccine
2-Meningococcal Vaccine
3-Japanese Encephalitis Vaccine
4-Cholera Vaccine
5-Rabies Vaccine
6-Yellow Fever Vaccine
7-Pneumococcal Polysaccharide vaccine (PPSV 23)

**** High-risk category of children:*** *Congenital or acquired immunodeficiency (including HIV infection); Chronic cardiac, pulmonary (including asthma if treated with prolonged high-dose oral corticosteroids), hematologic, renal (including nephrotic syndrome) and liver disease; Children on long term steroids, salicylates, immunosuppressive or radiation therapy; Diabetes mellitus, Cerebrospinal fluid leak, Cochlear implant, Malignancies; Children with functional/ anatomic asplenia/ hyposplenia; During disease outbreaks; Laboratory personnel and healthcare workers; Travelers; Children having pets in home; Children perceived with higher threat of being bitten by dogs such as hostellers, risk of stray dog menace while going outdoor.*

## A. Measles and MMR vaccination

*Recommendation*: The committee has revised its recommendations on Measles and MMR vaccination schedule. The new schedule will have a dose of MMR at 9 months instead of measles, and another dose (2nd) at 15 months of age. The earlier recommendation of 2nd dose of MMR at 4-6 years of age has been removed.

*The need and justification*: NTAGI Standing Technical Sub-Committee (STSC) recommended two doses of Measles – Rubella (MR) vaccines in the Universal immunization program (UIP) at 9 months and 16-24 months at the time of 1st booster of DTP vaccine. Since the Academy has argued very strongly in favor of MMR instead of MR vaccine in UIP schedule, the revised recommendations will facilitate inclusion of Mumps

vaccine in the National immunization program in near future. Furthermore, it will be more in sync with the upcoming UIP schedule. The detailed reasons are discussed in another recent position paper from IAP publication [3].

*The evidence*: There are many studies both from India and from other countries demonstrating efficacy and safety of MMR vaccine given at 9 month of age [3-8].

**B. Live attenuated Hepatitis A vaccine**

*Recommendation*: The committee has revised its recommendations on administration schedule of live attenuated hepatitis A vaccine, based on the viral H2 strain (Chinese vaccine). Now a single dose of this vaccine is recommended at 12 months of age over-riding the previous recommendation [9] of two doses of the same vaccine.

*The justification and evidence*: The committee reviewed both published [11,12] and unpublished long term follow-up data on immunogenicity and safety of a single dose of this vaccine from trials in India. The data showed 79.3% of 121 children were seroprotected (anti-HAV titers >20 mIU/mL) up to 6 years follow-up in the pivotal single center study, whereas 97.3% of 111 children had shown seroprotection after 5 years of follow-up period in the multi-centric group. In the multi-centric study [12], the test subjects maintained good GMT levels even after 5 years of follow-up. The committee had earlier shown its concern on waning of seroprotection in a subgroup of individuals of original single-center study cohort [2]. However, it was later disclosed that only ten subjects had shown this phenomenon, and most of these subjects were of comparatively higher age groups than other study subjects. The decision was also facilitated by the SAGE/WHO recommendations of single dose of live attenuated hepatitis A vaccine [10].

**C. Rotavirus Vaccines**

***Monovalent rotavirus vaccine, RV1***

The committee reviewed new data on administration schedule of RV1 (Rotarix) from Pakistan [13] and Ghana [14]. In both studies, the seroconversion and GMTs were higher at delayed (10 and 14 weeks) than early (6 and 10 weeks) schedule, though not statistically significant [13, 14]. In Ghana study, the seroconversion and GMTs were significantly higher in 3-dose (6, 10 and 14 week) schedule than 2-dose early (6 and 10 week) schedule [14]. As these studies are yet unpublished, full methodology and results are not available for scrutiny. The available results do not warrant any change in the existing schedule of RV1 vaccine that includes the first dose at 10 weeks of age instead of 6 weeks in order to achieve better immune response, and the second dose at 14 weeks to fit with existing National immunization schedule [9].

***Indian rotavirus vaccine, 116 E***

This vaccine developed by Bharat Biotech (Rotavac) is a live, naturally attenuated vaccine containing monovalent, bovine human reassortant strain characterized as G9 P [11], with the VP4 of bovine rotavirus origin, and all other segments of human rotavirus origin. The vaccine strain was isolated from asymptomatic infants with mild diarrhea by Indian researchers in 1985 at AIIMS, New Delhi. Follow up of these infants indicated that they were protected against severe rotavirus diarrhea for up to 2 years. This strain was sent for vaccine development to the National Institute of Health by Department of Biotechnology, India, and later transferred to Bharat Biotech International Limited in 2001 for further development.

In a phase II study, both low ($10^4$ ffu) and high ($10^5$ ffu) dosages of 116E were found safe in infants between 8 and 20 weeks of age. IgA immunogenicity rates for the $10^5$ ffu dosage were 64.7% after 1 dose, and 89.7% after 3 doses. The vaccine virus was shed in about 20% of infants [15].

A randomized, double-blind, placebo-controlled phase III clinical trial [16] amongst 6,799 infants was conducted at three sites in India. The first year efficacy against severe rotavirus diarrhea was 53·6% (95% CI 35·0-66·9; $P$=0·001) with protection continuing into the second year of life also. The vaccine also showed 20% efficacy against all-cause severe diarrhea admission. Six cases of intussusceptions (all occurring after administration of 3rd dose) were recorded in the vaccinees and two in the control group. This vaccine has already been licensed in India and would soon be available for use in Indian market.

The committee reviewed the evidence and opined it to be a moderately effective vaccine against rotavirus diarrhea in India. As this is the only vaccine that has undergone large scale field- efficacy trial in India, the level of evidence regarding its efficacy is rated higher by the committee. However, the committee stresses the need of having large scale studies, particularly post-marketing surveillance to monitor occurrence of acute intussusception amongst vaccinated children. There seems to be one excess case of intussusception for every 2000 children vaccinated. Apparently, the sample size was not adequately powered to look for statistical significance [16]. Regarding use of the vaccine in office-practice, it is not clear whether pediatricians would be able to use it in coming months since information about formulation and commercial availability of the vaccine is not yet available.

- This schedule includes recommendations in effect as of September 2014.
- These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars in Fig. 1

**FIG. 1** *IAP Recommended immunization schedule for children aged 0-18 years (with range), 2014.*

# Footnotes: Recommended Immunization Schedule for Persons Aged 0 through 18 Years — IAP, 2014

**I. General instructions:**

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

**II. Specific instructions:**

**1. BCG Vaccine**

***Routine vaccination:***

- Should be given at birth or at first contact

***Catch up vaccination:*** may be given up to 5 years

**2. Hepatitis B (HepB) vaccine**

***Routine vaccination:***

- Minimum age: birth
- Administer monovalent HepB vaccine to all newborns within 48 hours of birth.
- Monovalent HepB vaccine should be used for doses administered before age 6 weeks.
- Administration of a total of 4 doses of HepB vaccine is permissible when a combination vaccine containing HepB is administered after the birth dose.
- Infants who did not receive a birth dose should receive 3 doses of a HepB containing vaccine starting as soon as feasible.
- The ideal minimum interval between dose 1 and dose 2 is 4 weeks, and between dose 2 and 3 is 8 weeks. Ideally, the final (3rd or 4th) dose in the HepB vaccine series should be administered no earlier than age 24 weeks and at least 16 weeks after the first dose, whichever is later.
- Hep B vaccine may also be given in any of the following schedules: Birth, 1, & 6 mo, Birth, 6 and 14 weeks; 6, 10 and 14 weeks; Birth, 6 ,10 and 14 weeks, etc. All schedules are protective.

***Catch-up vaccination:***

- Administer the 3-dose series to those not previously vaccinated.
- In catch up vaccination use 0, 1, and 6 months schedule.

**3. Poliovirus vaccines**

***Routine vaccination:***

- Birth dose of OPV usually does not lead to VAPP.
- OPV in place of IPV, if IPV is unfeasible, minimum 3 doses.
- Additional doses of OPV on all SIAs.
- IPV: Minimum age - 6 weeks.
- IPV: 2 instead of 3 doses can be also used if primary series started at 8 weeks and the interval between the doses is kept 8 weeks
- No child should leave your facility without polio immunization (IPV or OPV), if indicated by the schedule!!

***Catch-up vaccination:***

- IPV catch-up schedule: 2 doses at 2 months apart followed by a booster after 6 months of previous dose.

**4. Diphtheria and tetanus toxoids and pertussis (DTP) vaccine.**

***Routine vaccination:***

- Minimum age: 6 weeks
- The first booster (4thth dose) may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose.
- DTaP vaccine/combinations should preferably be avoided for the primary series.
- DTaP may be preferred to DTwP in children with history of severe adverse effects after previous dose/s of DTwP or children with neurologic disorders.
- First and second boosters may also be of DTwP. However, considering a higher reactogenicity, DTaP can be considered for the boosters.
- If any 'acellular pertussis' containing vaccine is used, it must at least have 3 or more components in the product.
- No need of repeating/giving additional doses of whole-cell pertussis (wP) vaccine to a child who has earlier completed their primary schedule with acellular pertussis (aP) vaccine-containing products

***Catch-up vaccination:***

- Catch-up schedule: The 2nd childhood booster is not required if the last dose has been given beyond the age of 4 years
- Catch up below 7 years: DTwP/DTaP at 0, 1 and 6 months;
- Catch up above 7 years: Tdap, Td, and Td at 0, 1 and 6 months.

**5. Tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine**

***Routine vaccination:***

- Minimum age: 7 years (Adacel® is approved for 11-64 years by ACIP and 4 to 64 year olds by FDA, while Boostrix® for 10 years and older by ACIP and 4 years of age and older by FDA in US).
- Administer 1 dose of Tdap vaccine to all adolescents aged 11 through 12 years.
- *Tdap during pregnancy:*One dose of Tdap vaccine to pregnant mothers/adolescents during each pregnancy (preferred during 27 through 36 weeks gestation) regardless of number of years from prior Td or Tdap vaccination.

***Catch-up vaccination:***

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

**6. *Haemophilus influenzae* type b (Hib) conjugate vaccine**

***Routine vaccination:***

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

***Catch-up vaccination:***

- Catch-up is recommended till 5 years of age.
- 6-12 months; 2 primary doses 4 weeks apart and 1 booster;
- 12-15 months: 1 primary dose and 1 booster;
- Above 15 months: single dose.

- If the first dose was administered at age 7 through 11 months, administer the second dose at least 4 weeks later and a final dose at age 12-18 months at least 8 weeks after the second dose

**7. Pneumococcal conjugate vaccines (PCVs)**
**Routine vaccination:**
- Minimum age: 6 weeks
- Both PCV10 and PCV13 are licensed for children from 6 weeks to 5 years of age (although the exact labeling details may differ by country). Additionally, PCV13 is licensed for the prevention of pneumococcal diseases in adults >50 years of age
- Primary schedule (For both PCV10 and PCV13): 3 primary doses at 6, 10, and 14 weeks with a booster at age 12 through 15 months.

***Catch-up vaccination:***
- Administer 1 dose of PCV13 or PCV10 to all healthy children aged 24 through 59 months who are not completely vaccinated for their age.
- **For PCV 13:** Catch up in 6-12 months: 2 doses 4 weeks apart and 1 booster; 12-23 months: 2 doses 8 weeks apart; 24 mo & above: single dose
- **For PCV10:** Catch up in 6-12 months: 2 doses 4 weeks apart and 1 booster; 12 months to 5 years: 2 doses 8 weeks apart
- **Vaccination of persons with high-risk conditions:**
  - o PCV and pneumococcal polysaccharide vaccine [PPSV] both are used in certain high risk group of children.
  - o For children aged 24 through 71 months with certain underlying medical conditions, administer 1 dose of PCV13 if 3 doses of PCV were received previously, or administer 2 doses of PCV13 at least 8 weeks apart if fewer than 3 doses of PCV were received previously.
  - o A single dose of PCV13 may be administered to previously unvaccinated children aged 6 through 18 years who have anatomic or functional asplenia (including sickle cell disease), HIV infection or an immunocompromising condition, cochlear implant or cerebrospinal fluid leak.
  - o Administer PPSV23 at least 8 weeks after the last dose of PCV to children aged 2 years or older with certain underlying medical conditions.

**8. Pneumococcal polysaccharide vaccine (PPSV23).**
- Minimum age: 2 years
- Not recommended for routine use in healthy individuals. Recommended only for the vaccination of persons with certain high-risk conditions.
- Administer PPSV at least 8 weeks after the last dose of PCV to children aged 2 years or older with certain underlying medical conditions like anatomic or functional asplenia (including sickle cell disease), HIV infection, cochlear implant or cerebrospinal fluid leak.
- An additional dose of PPSV should be administered after 5 years to children with anatomic/functional asplenia or an immunocompromising condition.
- PPSV should never be used alone for prevention of pneumococcal diseases amongst high–risk individuals.
- **Children with following medical conditions for which PPSV23 and PCV13 are indicated in the age group 24 through 71 months:**
  - o Immunocompetent children with chronic heart disease (particularly cya-notic congenital heart disease and cardiac failure); chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy), diabetes mellitus; cerebrospinal fluid leaks; or cochlear implant.
  - o Children with anatomic or functional asplenia (including sickle cell disease and other hemoglobinopathies, congenital or acquired asplenia, or splenic dysfunction);
  - o Children with immuno-compromising conditions: HIV infection, chronic renal failure and nephrotic syndrome, diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas and Hodgkin disease; or solid organ transplantation, congenital immunodeficiency.

**9. Rotavirus (RV) vaccines**
***Routine vaccination:***
- Minimum age: 6 weeks for both RV-1 [Rotarix] and RV-5 [RotaTeq])
- Only two doses of RV-1 are recommended at present
- RV1 should preferably be employed in 10 and 14 week schedule, instead of 6 and 10 week; the former schedule is found to be far more immunogenic than the later
- If any dose in series was RV-5 or vaccine product is unknown for any dose in the series, a total of 3 doses of RV vaccine should be administered.

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

**10. Measles, mumps, and rubella (MMR) vaccine**
***Routine vaccination:***
- Minimum age: 9 months or 270 completed days.
- Administer the first dose of MMR vaccine at age 9 through 12 months, and the second dose at age 15 through 18 months.
- The 2nd dose must follow in 2nd year of life. However, it can be given at anytime 4-8 weeks after the 1st dose
- No need to give stand-alone measles vaccine

***Catch-up vaccination:***
- Ensure that all school-aged children and adolescents have had 2 doses of MMR vaccine; the minimum interval between the 2 doses is 4 weeks.
- One dose if previously vaccinated with one dose
- 'Stand alone' measles/measles containing vaccine can be administered to infants aged 6 through 8 months during outbreaks. However, this dose should not be counted.

**11. Varicella vaccine**
***Routine vaccination:***
- Minimum age: 12 months
- Administer the first dose at age 15 through 18 months and the second dose at age 4 through 6 years.
- The second dose may be administered before age 4 years, provided at least 3 months have elapsed since the first dose. If the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.
- The risk of breakthrough varicella is lower if given 15 months onwards.

***Catch-up vaccination:***
- Ensure that all persons aged 7 through 18 years without 'evidence of immunity' have 2 doses of the vaccine.
- For children aged 12 months through 12 years, the recommended minimum interval between doses is 3 months. However, if the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.
- For persons aged 13 years and older, the minimum interval between doses is 4 weeks.
- For persons without evidence of immunity, administer 2 doses if not previously vaccinated or the second dose if only 1 dose has been administered.
- 'Evidence of immunity' to varicella includes any of the following:
- documentation of age-appropriate vaccination with a varicella vaccine
- laboratory evidence of immunity or laboratory confirmation of disease
- diagnosis or verification of a history of varicella disease by a health-care provider
- diagnosis or verification of a history of herpes zoster by a health-care provider

**12. Hepatitis A (HepA) vaccines**
***Routine vaccination:***
- Minimum age: 12 months
- Killed HepA vaccine: Start the 2-dose HepA vaccine series for children aged 12 through 23 months; separate the 2 doses by 6 to 18 months.
- Live attenuated H2-strain Hepatitis A vaccine: Single dose starting at 12 months and through 23 months of age

***Catch-up vaccination:***
- Either of the two vaccines can be used in 'catch-up' schedule beyond 2 years of age
- Administer 2 doses for killed vaccine at least 6 months apart to unvaccinated persons
- Only single dose of live attenuated H2-strain vaccine
- For catch up vaccination, pre vaccination screening for Hepatitis A antibody is recommended in children older than 10 years as at this age the estimated sero-positive rates exceed 50%.

**13. Typhoid vaccines**
***Routine vaccination:***
- Both Vi-PS conjugate and Vi-PS (polysaccharide) vaccines are available
- Minimum ages:
  - o Vi-PS (Typbar-TCV®): 6 months;
  - o Vi-PS (polysaccharide) vaccines: 2 years
- Vaccination schedule:
- *Typhoid conjugate vaccines (Vi-PS):* Single dose at 9-12 through 23 months and a booster during second year of life
- *Vi-PS (polysaccharide) vaccines:* Single

dose at 2 years; revaccination every 3 years;
- Currently, two typhoid conjugate vaccines, Typbar-TCV® and PedaTyph® available in Indian market;
- PedaTyph® is not yet approved; the recommendation is applicable to Typbar-TCV® only
- An interval of at least 4 weeks with the MMR vaccine should be maintained while administering Typbar-TCV® vaccine
- Primary dose of conjugate vaccine should follow a booster at 2 years of age
- Either Typbar-TCV® or Vi-polysaccharide (Vi-PS) can be employed as booster;
- Typhoid revaccination every 3 years, if Vi-polysaccharide vaccine is used
- No evidence of hypo-responsiveness on repeated revaccination of Vi-polysaccharide vaccine so far
- Need of revaccination following a booster of Typbar-TCV® not yet determined

***Catch-up vaccination:***
- Recommended throughout the adolescent period, i.e. 18 years

**14. Influenza vaccine**

***Routine vaccination:***
- Minimum age: 6 months for trivalent inactivated influenza vaccine (TIV)
- Recommended only for the vaccination of persons with certain high-risk conditions.
- First time vaccination: 6 months to below 9 years: two doses 1 month apart; 9 years and above: single dose
- Annual revaccination with single dose.
- Dosage (TIV) : aged 6–35 months 0.25 ml; 3 years and above: 0.5 ml
- For children aged 6 months through 8 years: Administer 2 doses (separated by at least 4 weeks) to children who are receiving influenza vaccine for the first time.
- All the currently available TIVs in the country contain the 'Swine flu' or 'A (H1N1)' antigen; no need to vaccinate separately.
- Best time to vaccinate:
  o As soon as the new vaccine is released and available in the market
  o Just before the onset of rainy season.

**15.Human papillomavirus (HPV) vaccines**

***Routine vaccination:***
- Minimum age: 9 years
- HPV4 [Gardasil] and HPV2 [Cervarix] are licensed and available.
- Only 2 doses of either of the two HPV vaccines (HPV4 & HPV2) for adolescent/ preadolescent girls aged 9-14 years;
- For girls 15 years and older, and immunocompromised individuals 3 doses are recommended
- For two-dose schedule, the minimum interval between doses should be 6 months.
- Either HPV4 (0, 2, 6 months) or HPV2 (0, 1, 6 months) is recommended in a 3-dose series for females aged 15 years and older
- HPV4 can also be given in a 3-dose series for males aged 11 or 12 years, but not yet licensed for use in males in India.
- The vaccine series can be started beginning at age 9 years.
- For three-dose schedule, administer the 2nd dose 1 to 2 months after the **1st** dose and the 3rd dose 6 months after the **1st** dose (at least 24 weeks after the first dose).

***Catch-up vaccination:***
- Administer the vaccine series to females (either HPV2 or HPV4) at age 13 through 45 years if not previously vaccinated.
- Use recommended routine dosing intervals (see above) for vaccine series catch-up.

**16. Meningococcal vaccine.**
- Recommended only for certain high risk group of children, during outbreaks, and international travelers, including students going for study abroad and travelers to Hajj and sub-Sahara Africa.
- Both Meningococcal conjugate vaccines (Quadrivalent MenACWY-D, Menactra® by Sanofi Pasteur and monovalent group A, PsA–TT, MenAfriVac® by Serum Institute of India) and polysaccharide vaccines (bi- and quadrivalent) are licensed in India. PsA–TT is not freely available in market.
- Conjugate vaccines are preferred over polysaccharide vaccines due to their potential for herd protection and their increased immunogenicity, particularly in children <2 years of age.
- As of today, quadrivalent conjugate and polysaccharide vaccines are recommended only for children 2 years and above. Monovalent group A conjugate vaccine, PsA–TT can be used in children above 1 year of age.

**17. Cholera Vaccine.**
- Minimum age: one year (killed whole cell vibrio cholera (Shanchol)
- Not recommended for routine use in healthy individuals; recommended only for the vaccination of persons residing in highly endemic areas and traveling to areas where risk of transmission is very high like Kumbh mela, etc.
- Two doses 2 weeks apart for >1 year old.

**18. Japanese encephalitis (JE) vaccine.**

***Routine vaccination:***
- Recommended only for individuals living in endemic areas
- The vaccine should be offered to the children residing in rural areas only and those planning to visit endemic areas (depending upon the duration of stay)
- Three types of new generation JE vaccines are licensed in India : one, live attenuated, cell culture derived SA-14-14-2, and two inactivated JE vaccines, namely '**vero cell culture-derived SA 14-14-2 JE vaccine' (JEEV® by BE India) and 'vero cell culture-derived, 821564XY, JE vaccine' (JENVAC® by Bharat Biotech)**
- **Live attenuated, cell culture derived SA-14-14-2:**
  o Minimum age: 8 months;
  o Two dose schedule, first dose at 9 months along with measles vaccine and second at 16 to 18 months along with DTP booster
  o Not available in private market for office use
- **Inactivated cell culture derived SA-14-14-2 (JEEV® by BE India) :**
  o Minimum age: 1 year (US-FDA: 2 months)
  o Primary immunization schedule: 2 doses of 0.25ml each administered intramuscularly on days 0 and 28 for children aged ≥ 1 to ≤ 3 years
  o 2 doses of 0.5 ml for children >3years and adults aged ≥ 18 years
  o Need of boosters still undetermined
- **Inactivated Vero cell culture-derived Kolar strain, 821564XY, JE vaccine (JENVAC® by Bharat Biotech)**
  o Minimum age: 1 year
  o Primary immunization schedule: 2 doses of 0.5 ml each administered intramuscularly at 4 weeks interval
  o Need of boosters still undetermined.

***Catch up vaccination:***
- All susceptible children up to 15 yrs should be administered during disease outbreak/ ahead of anticipated outbreak in campaigns

**19. Rabies vaccine:**
- Practically all children need vaccination against rabies
- Following two situations included in 'high-risk category of children' for rabies vaccination and should be offered 'Pre-exposure prophylaxis' (Pre-EP):
  o Children having pets in home;
  o Children perceived with higher threat of being bitten by dogs such as hostellers, risk of stray dog menace while going outdoor.
- Only modern tissue culture vaccines (MTCVs) and IM routes are recommended for both 'post-exposure' and 'pre-exposure' prophylaxis in office practice
- Post-exposure prophylaxis (PEP) is recommended following a significant contact with dogs, cats, cows, buffaloes, sheep, goats, pigs, donkeys, horses, camels, foxes, jackals, monkeys, mongoose, squirrel, bears and others. Domestic rodent (rat) bites do not require post exposure prophylaxis in India.
- *Post-exposure prophylaxis:*
  o MTCVs are recommended for all category II and III bites.
  o *Dose:* 1.0 ml intramuscular (IM) in antero-lateral thigh or deltoid (never in gluteal region) for Human Diploid Cell Vaccine (HDCV), Purified Chick Embryo Cell (PCEC) vaccine, Purified Duck Embryo Vaccine (PDEV); 0.5 ml for Purified Vero Cell Vaccine (PVRV). Intradermal (ID) administration is not recommended in individual practice.
  o *Schedule:* 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
  o Rabies immunoglobin (RIG) along with rabies vaccines are recommended in all category III bites.
  o Equine rabies immunoglobin (ERIG) (dose 40 U/kg) can be used if human rabies immunoglobin is not available;
- *Pre -exposure prophylaxis:*
  o 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).
  o 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.
  o RIG is not required during re-exposure therapy.

**D. Pre-exposure prophylaxis for rabies**

*Recommendations for office practice*: The committee has now recommended that practically all children need vaccination against rabies and following two situations to be included in high-risk category of children for rabies vaccination: (*i*) children having pets at home; and (*ii*) children perceived with higher threat of being bitten by dogs such as hostellers, and those with risk of stray dog bite while going outdoor. These children should be offered pre-exposure prophylaxis (Pre-EP) against rabies. This must be preceded by a one-to-one discussion with the parents. The Pre-EP is not included in the IAP immunization schedule for all children. Three doses are recommended to be given intramuscularly on days 0, 7 and 28 (day 21 may be used if time is limited, as with imminent travel, but day 28 is preferred). The intradermal schedule has been shown to be effective, but is not approved for this purpose in office practice.

There are studies to show that good antibody levels persist up to 10 years even after a 3 dose pre-exposure prophylaxis followed by a booster at one year. However, on account of the nature of the disease, for re-exposure at any point of time after completed and documented, pre-or post-exposure prophylaxis, two doses are to be given on days 0 and 3. Rabies immunoglobulins (RIG) are not needed in these children. There is no change in the IAP recommendations for post-exposure prophylaxis (PEP) of rabies.

*Public use*: The committee urges the Government of India (GoI) to urgently take remedial measures to address the huge burden of rabies in India [17]. These measures include public education campaigns, need to ensure the uninterrupted availability of vaccines and anti-rabies immunoglobulin in primary health care facilities and training of primary care providers (including pediatricians), vaccination of dogs, sterilization of stray dogs, and declaration of rabies as a notifiable disease. The committee reiterated its position that universal Pre-EP vaccination, especially for children, could reduce the number of human rabies dramatically. Use of intradermal vaccination would bring down the vaccine cost for universal vaccination program dramatically [2].

*Justifications*: The advantages of the Pre-EP include elimination of the need for RIG, reduction in the number of vaccine doses on exposure and provision of immunity to individuals whose post-exposure prophylaxis is delayed. Further, the likelihood of lack of documentation of a dog bite amongst young children who may not report scratches and small playful bites from dogs and cats are other reasons why Pre-EP would be useful. However, it was agreed upon that inclusion of Pre-EP in only IAP schedule for office practice would not serve the desired purpose since majority of deaths occur among children belonging to low socioeconomic strata and those living in remote areas [17]. WHO encourages the implementation of carefully designed studies on the feasibility, cost-effectiveness and long-term impact of incorporating 'Cell Culture Vaccines and Embryonated egg-based vaccines' (CCEEVs) into the immunization programs of infants and children where canine rabies is a public health problem [18].

**E. Typhoid conjugate vaccines**

***Recommendation for office practice***

Primary schedule*:* The committee has now created a new slot for typhoid conjugate vaccine for primary immunization at 9-12 months of age in the IAP Immunization schedule. There are currently two typhoid conjugate vaccines (Typbar-TCV and PedaTyph), available and licensed in the country. However, this recommendation would be applicable only to the former as the committee is awaiting more data on the latter. Only a single dose of the vaccine is recommended for primary series. An interval of at least 4 weeks with the measles/ MMR vaccine should be maintained since the data on interference with the measles/MMR vaccine are not yet available.

*Boosters*: Those who received a dose of conjugate vaccine at 9-12 months can be prescribed booster of either Vi-polysaccharide (Vi-PS) or the conjugate vaccine at 2 years of age. Those who have received booster of Vi-PS vaccine will need revaccination every 3 years till the intended duration of protection. There is no evidence of hypo-responsiveness on repeated vaccination so far. The need of further boosters after conjugate vaccine is not yet determined since long term data are not yet available.

*Catch-up schedule*: Catch-up vaccination is recommended throughout the adolescent period, i.e. up to 18 years of age. Below 2 years, only conjugate vaccine is recommended while above 2 years of age any of the two can be employed. The details about further schedule should be followed as described above in the 'boosters' section.

***Recommendations for public use***

The committee strongly urges the GoI to include universal typhoid vaccination in its UIP all over the country at the earliest.

*Evidence and justification*: The committee believes that considering the epidemiology of typhoid in the country, there is definite need of protection against typhoid fever below 2 years of age. The Vi-PS vaccines are ineffective below 2 years of age and provide modest and short lasting protection. There is definite need of typhoid conjugate

vaccines, effective below 2 years of age and capable of providing superior long-lasting protection. The committee reviewed the published [19] and unpublished data of new typhoid conjugate vaccines, (BBIL's Typbar-TCV, BioMed's PedaTyph and Novartis's Vi-CRM197). All these vaccines can be administered at and around 9 months of age. Only a single dose is sufficient for adequate seroconversion for primary immunization, and the second dose failed to show incremental effect on antibody titers (data after 2nd dose of PedaTyph are not yet available). In the published trial of Novartis's Vi-CRM197 conjugate typhoid vaccine [19], a low response was noted to measles, hepatitis B and H influenza type b both in reference (PCV13) and test vaccine (conjugate typhoid vaccine) groups, with a non-significant reduction in the rate of measles seroconversion in the test vaccine group in one center. The committee has thus recommended maintaining an interval of at least 4 weeks with the measles/MMR vaccine while administering this vaccine. The committee has also asked the manufacturer to undertake a 'measles/ MMR interference study' with vaccination at 9 months.

Regarding the need and timing of boosters, the data provided by the manufacturer of Typbar-TCV vaccine show almost 100% seroprotection (>7.2 EU/mL) of test vaccine in both the cohorts (6 mo-2 years and 2-45 years) till 18 months of follow-up, although both seroconversion (>4-fold rise of antibody level) and GMT levels waned significantly in both cohorts. Regarding comparison of Vi-PS non-conjugate vaccine with the Vi-PS conjugate vaccine, both fared equally well above 2 years of age as far as immediate and long-term seroconversion are concerned, although the latter had significantly higher GMTs and slightly better seroconversion rates than the former. The committee has thus recommended either of the vaccines as a booster at 2 years of age. The need of repeat doses/boosters for conjugate vaccine shall only be determined after long-term efficacy data are available.

**F. Human Papillomavirus (HPV) vaccination schedule**

*Recommendations*: Two doses of HPV vaccine are advised for adolescent/pre-adolescent girls aged 9-14 years; for girls 15 years and older, current 3 dose schedule will continue. For two-dose schedule, the minimum interval between doses should be 6 months. The interval between the first and second dose may be extended upto12 months, should this facilitate administration – say in school settings. For girls, primed before the age of 15 years, even if older at the time of second dose, a two-dose schedule will be applicable. However, for immuno-compromised individuals, including HIV-infected, the three-dose schedule is recommended, irrespective of age.

*Evidence and justification*: IAP had recommended use of HPV vaccine in its immunization schedule way back in 2007. Though there is no coverage data on uptake of this vaccine through private sector, the common perception is that acceptance is poor and the coverage still remains miniscule. The move to revise HPV vaccine immunization schedule for adolescent girls from existing three to two doses would not only be cost-saving, but would also simplify logistics like increased flexibility of the intervals, and annual doses for school-based delivery. Hence, the revised recommendations may help in improving acceptance, facilitating delivery, and enhancing coverage of the vaccine.

The WHO's Strategic Advisory Group of Experts (SAGE) working group (WG) on HPV has recommended revision of vaccination schedule for pre-adolescent and adolescent girls from three primary doses to two in its April 2014 meeting [20]. The committee has reviewed the background material and various trials conducted in this regard so far [21]. The main source of evidence is provided by a systematic review commissioned by SAGE WG [22]. The other sources include review of the data from observational studies on 2 *versus* 3 dose schedule, and proceedings of an Ad hoc Expert Consultation on HPV vaccine schedules organized in Geneva, 2013 [21]. The European Medicines Agency (EMA) has also approved two doses for pre-adolescent and adolescent girls aged 9-14 years for the bivalent HPV vaccine and also offered positive opinion for a similar schedule for quadrivalent vaccine [23]. Many countries have either already adopted or are planning to adopt a two-dose schedule [21]. Few countries like Brazil, Mexico, Columbia and British Columbia are running an extended schedule (2+1, *i.e.* 0, 6, 60 months) where the last dose at 5 years depends on follow-up assessment of the need [21]. In Costa Rica, strong 4 year protection was reported in women who received just one dose of bivalent HPV vaccine [21].

The systematic review [22] has identified various studies that include both randomized and non-randomized trials of both the vaccines, bivalent and quadrivalent, from various high income group countries like Canada, Australia, Sweden, Denmark, Germany, and low and middle income (LMI) countries like Uganda, Mexico, and India. In randomized comparisons of two-dose and three-dose schedules (overall 3 RCTs), seroconversion and seropositivity were non-inferior or inconclusive at all-time points. In non-randomized comparisons, all available data for seroconversion and seropositivity showed non-inferiority of the 2-dose compared with the 3-dose schedule. The efficacy against virological endpoints in initially HPV-naïve subjects who received 2 doses of bivalent vaccine at 48th month indicates that the two-dose

schedule prevents HPV-16/18 infection in subjects who did not receive a complete 3-dose vaccination course. The review also compared different intervals between doses of HPV vaccine. The 6-month interval resulted in superior GMCs compared with the 2-month interval one month after the last vaccine dose in all the age groups enrolled.

The mathematical models also support the two-dose schedule for girls aged 9-14 years. In one such model it was shown that in high-income settings (such as the UK and Canada), if it was documented that a 2-dose vaccination conferred more than 10-20 years protection then adding the third dose would not be cost-effective [21]. The cost-effectiveness of 2-dose *vs*. 3-dose vaccination in low/middle income settings still needs to be explored.

The committee's recommendations are also facilitated by the evidence generated by an ongoing multi-centric RCT on alternative dosing schedule of quadrivalent HPV vaccine in India [24-26]. In this trial, comparisons favored the 2-dose schedule and the ratio of antibody levels was higher in the 2-dose group than in 3-dose group [25,26]. The GMCs for HPV18 in the 2-dose group were non-inferior to that in the 3-dose group. However, on clinical outcomes basis, the RCT provided only limited data, and incident infections with any of the vaccine types in the quadrivalent vaccine were more common in the 2-dose than in the 3-dose group [25,26].

The magnitude of the vaccine response is determined by the age at the first dose. The review of different trials have shown that 100% adolescents can be primed with a single dose of the vaccine and the second dose after 6 months results in higher (almost twice) peak titers in adolescents than in adults. These antibodies then plateau for about 12 months after the peak and decline very slowly providing a long lasting protection [21]. There are limited data from HIV-infected individuals receiving a 3-dose schedule and no data from HIV-infected individuals receiving a 2-dose schedule.

The committee concludes that two doses of HPV vaccine in girls 9-14 years of age are non-inferior in terms of immunogenicity when compared to three doses in girls 9-14 years or 15-24 years of age. A 2-dose vaccine schedule is likely to be as efficacious as three doses, even though long-term outcome and clinical efficacy data are not yet available. The committee stresses the need of long-term studies on efficacy/effectiveness of alternative schedules.

### G. Update on Pertussis immunization

*Recommendation*: In lieu with its earlier recommendations on pertussis vaccination [9], the committee clarifies that there is no need of repeating or giving additional doses of whole-cell pertussis (wP) vaccine in order to boost immunity in children who have earlier completed their primary schedule with acellular pertussis (aP) vaccine-containing products. However, it should be ensured that all the remaining doses are wP vaccine-containing products. This is to be reiterated here that wP vaccine is permitted till 7 years of age.

*Justification:* Although it is reported that presence of even a single dose of wP vaccine in the primary infant series of pertussis immunization was found to be providing superior priming and more durable immunity than the schedule completed with only aP containing vaccines [9,27], nevertheless, the aP vaccines are also effective and do offer protection against the disease. Since no stand-alone preparation of wP vaccine is available in the market, it is not advisable to administer too many doses of pertussis-containing combo products (that usually also contain diphtheria and tetanus toxoids) that may inadvertently enhance the frequencies of undesirable adverse events associated with their use.

### H. Pentavalent (DTwP+Hib+Hepatitis-B) vaccine

There are concerns amongst pediatricians related to the quality, suitability and preference of available different wP-vaccine containing pentavalent vaccines in the market since the publication of IAP recommendations on pertussis immunization [9]. Intensive marketing strategies of vaccine manufacturers have further aggravated this confusion. There are no data on either efficacy/ effectiveness of individual wP product or comparative evaluation of different available wP combinations in Indian market. ACVIP has urged the National Regulatory Authority (NRA) to setup indigenous National guidelines to manufacture and market different pertussis vaccines in the country [27]. In this background, the committee reviewed the evidence related to available wP-based pentavalent combinations in the country. There are currently six different brands available in Indian market (***Table* II**). All pentavalent vaccines, except Quinvaxem-TM contain PRP-T as carrier protein conjugated with Hib PRP antigen whereas CRM-197 is used in the latter. Both these carrier proteins are consistently highly immunogenic after completion of three primary doses in infants [28-31]. Similarly, no statistically significant difference was found in the safety profile of Hib vaccines containing these two carrier proteins after completion of three doses [28]. Regarding the adjuvant, all the pentavalent products contain Aluminium phosphate in a WHO-prescribed quantity (<1.25 mg) [32]. All the pentavalent combinations, except Quinvaxem, contain thiomersal as preservative. Even the latter also has traces of thiomersal as residue. The committee supports the WHO policy on

**TABLE II** COMPARATIVE STUDY OF CURRENTLY AVAILABLE LIQUID WHOLE-CELL PERTUSSIS VACCINE BASED PENTAVALENT PRODUCTS IN INDIA

| *Brand Name* | *Manu-facturer* | *Composition* | | | *Clinical efficacy data* | | | | | *Safety data (Reactogenicity), %* | | | | *WHO-PQ* | *World wide usage* | *Cost (MRP in Rs.)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *Hib conju gate* | *Alum. Phos. (AIO4) per 0.5 mL* | *Thio mersal* | *Immunogenicity date (seroprotection) (%)* | | | | | *Efficacy/ PMS trial* | *Pain (Gr 3)* | *Swelling (>5cm)* | *Fever* | | | |
| | | | | | *D* | *P* | *T* | *Hib* | *Hep-B* | | | | | | | |
| Pentavac | Serum Institute of India | PRP-T | < or equal to 1.25 mg | Yes, (0.005 %) | 100 | 95.3 | 100 | 100 | 100 | No | 22.4 | 39.1 | 17.5 | Yes | 40 million | 585 |
| Comvac-5 | Bharat Biotech | PRP-T | 0.3 mg | Yes (0.025 mg) | 98 | 76 | 98 | 100 | 98 | No | 9.2 (Un) | 4.4 (Un) | 24 (Un) | No | - | 600 |
| Easyfive- TT | Panacea | PRP-T | 0.25 mg | Yes (0.025 mg) | 97.7 | 65-72 | 99 | 89.5 | 97.3 | No | - | 42.3 (Un) | 73 (warm to touch) | Yes | 55 million | 600 |
| Shan5 | Shantha Biotech | PRP-T | 0.625 mg | Yes (<0.050 mg) | 99.4 | 89.9 | 99.4 | 98.3 | 97.8 | No | 36.3 | 2.6 | 5.7 | Yes | 24 million | |
| Quinvaxem | Novartis vaccines | HbOC-CRM-197 | 0.3 mg | No (only in traces) | 99 | 99 | 100 | 100 | 98 | Phase IV PMS trial* | 10 | 4 | 13 | Yes | >400 million doses | 1645 |
| ComBEfive | Biological Evans | PRP-T | <1.25 mg | Yes, (0.01% w/v) | 98.3 | 96.5 | 100 | 89.5 | 94.7 | No | 13 | 4 | 28 | Yes | - | 580 |

*NP-not published; D-Diphtheria; P-Pertussis; T-Tetanus; Hib-Hemophilus influenza type b; Hep-B-Hepatitis-B; PMS-Post-marketing surveillance; *PMS trial in Guatemala; Un-unspecified.*

this issue which continues to recommend the use of thiomersal in vaccines used for global immunization programs since the benefits of using such products far outweigh any theoretical risk of toxicity [32,33].

All the brands are approved by Indian National Regulatory Authority (NRA), Central Drugs Standard Control Organization (CDSCO), MoHFW, GoI after reviewing their phase III clinical immunogenicity and safety studies. However, only the trials of Pentavac, Shan5 and Quinvaxem are published in peer-reviewed journals and available in public domain [34-36]. Information about other brands (Easyfive-TT, Comvac-5, and ComBEfive) are obtained through clinical trial data submitted to CDSCO and package inserts [37-40].

*Efficacy:* Though direct comparisons are not possible – due to differences in data collection, assays used for evaluation of the immune response, and analysis methods – the seroconversion rates for all the five antigens except for pertussis antigen (which were found lower for Comvac5 and Easyfive-TT) were comparable for all the six brands (***Table* II**). However, the seroconversion rates of Comvac5 and Easyfive-TT against pertussis were comparable to the comparator vaccines' arms. It has to be noted that till date no known single correlate of protection for pertussis exists, nor any established protective antibody levels are known. Antibody responses to pertussis antigens are variable amongst wP vaccines, likely related to the variability of antigen content amongst them. Furthermore, many different assays are used by manufacturers for the assessment of the immunogenicity.

*Reactogenicity*: Regarding reactogenicity profile of available brands, a marked diversity was noted. Pentavac was found to be the most reactogenic while Quinvaxem the least. However, it is to be noted that no comparator vaccine was used in Indian trial of Quinvaxem [36] and the reactogenicity profile of the former was found comparable or even superior to the CRM197-based comparator (Easyfive) vaccine (34). Similarly, in the case of Easyfive-TT, the test vaccine fared equally well to the comparator vaccine (Tritanrix+Hiberix) as far as reactogenicity profile is concerned [38,39]. Further, they did not provide information regarding the number of subjects having fever >38ºC. There is no study where all these products are compared 'head-to-head' with each other at the same time. On the other hand when one product was compared with another, they fared comparably well against each other. Hence, the committee concludes that all the available pentavalent products are comparable as far as immunogenicity and reactogenicity profile are concerned.

There is no efficacy, effectiveness or post-marketing surveillance (PMS) study from India available in public domain for any of these pentavalent products. There is a large PMS adverse event surveillance study of around 3000 children from Guatemala for Quinvaxem [41].

*WHO pre-qualification and world-wide usage*: All the products except Comvac-5 are now WHO prequalified [42]. While the Quinvaxem (since 2006), Pentavac (since 2010), and ComBEfive (since 2012) have never been delisted since attaining pre-qualification, the Easyfive-TT (2011-12) and Shan5 (2010-2013) had to be delisted after attaining this status for variety of reasons. Quinvaxem is the most widely used pentavalent vaccine with >400 million doses used globally [43].

The wP vaccines are standardized by protection in the 'mouse cerebral test', not by specific antigen content. The committee acknowledges the fact that the process for standardization of quality and efficacy of pertussis vaccines is challenging. Since randomized controlled studies of protective efficacy are no more permitted now owing to ethical and logistic reasons, the post-marketing surveillance and population-based 'vaccine effectiveness studies' assume great significance. WHO has made it mandatory to conduct periodic post-marketing surveillance of any newly launched wP based product to monitor its safety since limited safety data are obtained in pre-licensure studies [32].

WHO pre-qualification guidelines for a new wP vaccine, or a new formulation, require proof of concept in a relevant animal model in terms of both potency and safety. The NRAs are guided to ensure potency and safety of a new wP vaccine in preclinical evaluation through 'intracerebral mouse protection test' and 'mouse weight gain test' before granting clinical testing of a new wP vaccine containing product [32]. Regarding clinical evaluation, determination of antibody response to individual, specific antigens (at least one assay used should determine antibodies against pertussis toxin) is recommended rather than the measurement of antibodies against whole cell or whole cell extracts. The WHO uses very stringent protocol for awarding pre-qualification status to a wP vaccine product [44]. They issue guidelines to NRAs to ensure their application while licensing a wP-based combination in a country. Hence, achieving WHO pre-qualification assumes a very high significance as far as potency, efficacy and safety of any wP based product is concerned. The ACVIP also acknowledges that achieving WHO pre-qualification, which is a dynamic ongoing process with periodic assessment, is a must for all these products to achieve the committee's approval.

*Cost*: All the currently available liquid pentavalent combinations cost around INR 600, except Quinvaxem which is around 2.5 times more expensive (***Table* II**). The

**MAJOR CHANGES IN RECOMMENDATIONS FOR IAP IMMUNIZATION TIMETABLE, 2014**

*Measles and MMR immunization*

- Two doses of MMR at 9 and 15 months
- No stand alone measles dose at 9 months
- No MMR at 4-6 years of age

*Typhoid immunization*

- Slot for 'typhoid conjugate vaccine' for primary immunization at 9-12 months of age
- Recommendation applicable only for Typbar-TCV
- Booster of either Typbar-TCV or Vi-polysaccharide (Vi-PS) vaccine at 2 years of age
- Typhoid revaccination every 3 years, if Vi-polysaccharide vaccine is used
- Need of revaccination following a booster of Typbar-TCV not yet determined

*Hepatitis-A immunization*

- Single dose administration of live attenuated H2 strain hepatitis A vaccine at 12 months
- Previous recommendations of two-dose is now scrapped
- Two doses for inactivated (killed) Hepatitis-A vaccine

*Human Papillomavirus (HPV) vaccination*

- Two doses of HPV vaccine for adolescent/preadolescent girls aged 9-14 years
- For two-dose schedule, the minimum interval between doses should be 6 months
- Three dose schedule for adolescent girls aged 15 years and older to continue

*Rabies immunization*

- Two new situations, children having pets in home and children perceived with higher threat of being bitten by dogs to be included in 'high-risk category of children' for rabies vaccination
- These groups of children should now be offered 'pre-exposure prophylaxis' against rabies

*Pertussis immunization*

- No change in pertussis immunization recommendations of 2013
- No need of repeating/giving additional doses of wP vaccine to children who had earlier completed their primary schedule with aP vaccine-containing products
- Review and recommendations on the currently available wP vaccine containing pentavalent (DTwP+Hib+ Hepatitis-B) products in Indian market

*Other changes*

- A brief update and recommendation on use of new Indian Rotavirus vaccine, 116E
- The comments and footnotes for several vaccines are also updated and revised

committee thinks the price of the product cannot be justified considering all the attributes and performance.

*Conclusions*: The ACVIP concludes that all the available liquid pentavalent combinations satisfy the licensing criteria set by the Indian NRA and fulfills the requirement of WHO prequalification, except Comvac-5. There is nothing to choose between these products as far as their composition, efficacy and reactogenicity profiles are concerned. However, the lack of published studies on immunogenicity and safety of Comvac-5 and Easyfive-TT, and non-attainment of WHO pre-qualification by the former are indeed source of concern to the committee. Although, Quinvaxem has got highest experience as far as worldwide usage is concerned, the committee believes the product is definitely overpriced. There is an urgent need of conducting large scale PMS studies on the safety and effectiveness of these products in India. The committee urges the CDSCO, MoHFW, GoI to issue notices to the manufacturers to conduct, generate and submit data through PMS studies on the safety and effectiveness of their products.

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