Indian Academy of Pediatrics (IAP) Recommended Immunization Schedule for Children Aged 0 through 18 years — India, 2016 and Updates on Immunization

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ABSTRACT

Justification: There is a need to review/revise recommendations about existing vaccines in light of recent developments in the field of vaccinology where new developments are taking place regularly at short intervals.

Process: Following an IAP ACVIP meeting on May 6, 2016, a draft of revised recommendations for the year 2016 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 2016 Immunization timetable for pediatricians in office practice and issue statements on certain new and existing vaccine formulations.

Recommendations: The major change in the 2016 Immunization Timetable includes three doses of MMR vaccine at 9 months, 15 months, and between 4-6 years of age. Another change includes raising the recommended age for Japanese encephalitis (JE) vaccination to 18 years in endemic regions. The committee has also provided new guidelines on the use of inactivated poliovirus vaccine (IPV) in office practice following the Government of India's decision to use intradermal fractional dose IPV in universal immunization program (UIP) in few states, and subsequently, scarcity of IPV in private market. The committee has also approved another typhoid conjugate vaccine, PedaTyph® for prevention of typhoid fever in children. A new update on the typhoid conjugate vaccines is also provided. The committee has now devised an accreditation policy based on transparent, uniformly set parameters to evaluate different brands of a licensed vaccine in the country. Based on these parameters, a detailed review of the available monovalent varicella vaccine brands in the Indian market is conducted and its results are presented herewith. Recommendation is also offered on the use of MMRV, a combination vaccine containing measles, mumps, rubella and varicella antigens. A brief perspective on the new dengue vaccine, CYD-TDV (Dengvaxia®) is also presented. The comments and footnotes for several vaccines are also updated and revised.

Keywords: *Advisory Committee on Vaccines and Immunization Practices, Immunization Timetable 2016, Indian Academy of Pediatrics, Recommendations.*

INTRODUCTION

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 6th May, 2016 in Mumbai. IAP ACVIP

members who attended the meeting are listed in Annexure 1. The aim of the meeting was to discuss and debate recent developments in the field of immunization, to revise recommendations for the IAP Immunization Timetable for the year 2016, and to issue recommendations for available licensed vaccines in the country. Following the meeting, a draft of revised immunization schedule for the year 2016 was prepared and circulated among the meeting participants to arrive at a consensus.

Process for Issuing Recommendations

The detailed process behind issuing IAP recommendations on immunization is described earlier [1]. However, this is to reiterate that the recommendations of IAP are primarily for the pediatricians in office practice. 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.

II. AIMS AND OBJECTIVES

To revise IAP Immunization Timetable for the year 2016 and review and issue recommendations on the available licensed vaccines.

RECOMMENDATIONS FOR IAP IMMUNIZATION TIMETABLE, 2016

The IAP ACVIP has issued recommendations for the IAP Immunization Timetable **(Table I and Figure 1)** for the year 2016 that includes the following major changes from the previous schedule**:**

Measles, mumps and rubella (MMR) vaccine

Recommendation: The committee has now recommended a third dose of the MMR vaccine at 4 to 6 years of age along with two doses of the vaccine at 9 months and 15 months of age.

The need and justification: NTAGI's proposal [3] of replacing the first and the second dose of measles containing vaccine (MCV) at 9 months and 16-24 months with measles-rubella (MR) vaccine in the universal immunization program (UIP) is already being implemented in few states of the country. Resultantly, stand alone measles vaccine would cease to be available in future. However, MR is still not available in the private sector. Thus, IAP ACVIP after further considering the issue of morbidity following mumps infection, suggested that MMR be given instead of MR at both 9 months and 15 months [4]. Fairly adequate seroconversion rates for all 3 components was demonstrated in various studies with MMR at 9 and 12 months, and 12 and 15 months to suggest that schedule [5]. However, further literature review observed that some of the long term follow-ups available were in cohorts given their 1st dose of

MMR after 12 months age. Protective levels of antibodies induced by the MMR vaccine were first suggested to be lifelong; however, the levels of measles, mumps, or rubella antibodies have been shown to decline over time, faster after vaccinations than when naturally acquired especially for measles and mumps [6-10]. Rubella titres although decrease with time, high rates of seropositivity is maintained. Further, considering the long incubation period of rubella (14 to 21 days), an anamnestic response in vaccinees after exposure may offer sufficient protection, making the presence of detectable antibodies at the time of exposure unnecessary. So, two doses of measles vaccine [8] and one dose of rubella should suffice for long term protection against measles and rubella, respectively. The studies on long term follow up and risk for outbreak for mumps suggests that 'time since vaccination' seems to be a factor [9, 10] that determines the risk of outbreaks. Two doses of mumps-containing vaccine may not be as effective particularly to prevent outbreaks considering frequent and intense exposure [11, 12]. Further, a third MMR vaccine dose would control a mumps outbreak in a setting with pre-existing high 2-dose MMR coverage [13] and since 'time since vaccination' is a factor in mumps outbreaks, a 3rd dose of MMR at 4-6 yrs age be added to prevent mumps outbreaks in the adolescents.

IAP ACVIP, considering the significant burden and morbidity following mumps infection [14], suggests that MMR be given instead of MR at both 9 months and 15 months; and since 'time since vaccination' is a factor in mumps outbreaks, a 3rd dose of MMR at 4-6 years age be added to prevent mumps outbreaks in the older children and adolescents.

MMRV (MMR and varicella combination vaccine)

Recommendation: IAP ACVIP recommends that the varicella vaccine be given separately as MMR+V (varicella) at 15 months age and either the same (MMR+V) or MMRV be offered at 4-6 years of age. For catch up vaccination of children more than 48 months age, if both MMR and varicella vaccines not given earlier; two doses of MMRV or MMR + V separately be given 6 weeks to 3 months apart.

Justification and evidence: Studies comparing 2 doses of MMR +V (MMR and varicella vaccine given separately) and MMRV have shown adequate seroconversion for all four antigens [15-18]. The committee is convinced as far as the data on the efficacy of the combined MMRV vaccine against all the four components is concerned. However, reports of higher incidence of adverse events following immunization (AEFI) with MMRV when compared to MMR+V, fever and rash [19] and febrile seizures in the age group of 12 months to 23 months of age [20, 21], prompted the US CDC Advisory Committee on Immunization Practices (ACIP) to suggest a 'one-to one discussion', unless the parent or caregiver expresses a preference for MMRV vaccine, CDC ACIP recommends that MMR + V separately be given for the 1st dose in this age group'[22]. Even the immunogenicity and safety study of MMRV in India [23]

has found approximately 2-fold higher incidence of grade 3 fever (>39.5°C) in subjects who received MMRV than those who received MMR [23]. After careful review of these aforementioned studies and other relevant data, the committee has also recommended the same guidelines for this combination vaccine till further studies on MMRV in the lower age group from India are available. MMRV is thus far licensed till 12 yrs age [24] and anyone 13 or older who needs protection from these diseases should get MMR and varicella vaccines as separate shots [22].

Polio vaccination

Recommendation: The following points recapitulate the current ACVIP's recommendations with regard to polio immunization schedule:

1. The members should use 'alternative' polio immunization schedule in which primary schedule is started at 8-weeks instead of 6 weeks and completed with two doses of IPV, instead of three, administered at an interval of 8 weeks. [1].
2. A full dose of IM-IPV should be offered to the children who had already received 2 ID-fIPV doses at 6 and 14 weeks of age from government health facilities. An interval of at least 8 weeks must be maintained from the second ID-fIPV dose.
3. For the recipients of single dose of IM-IPV at 14 weeks, another full dose of IM-IPV should be offered at least 8 weeks after the first dose.
4. There is no change in the booster dose schedule of IPV, and OPV immunization schedule [1].

Justification and evidence: The committee has reviewed its existing recommendations pertaining to poliomyelitis vaccination [1] in wake of recent introduction of inactivated poliovirus vaccine (IPV) in the UIP [25, 26]. The academy's perspectives on introduction of IPV in the UIP, its scarcity in private market along with the committee's recommendations on the use of IPV in office practice have already been published [27, 28].

The main objectives of existing ACVIP polio immunization schedule as stated earlier [1] are complete protection against vaccine associated paralytic poliomyelitis (VAPP) along with maximizing both humoral and mucosal immune protection against polioviruses [1]. However, the committee believes, there is an urgent need of providing immunity against type 2 poliovirus following tOPV to bOPV switch to naive children born after the 'switch'. Considering the threat posed by circulating vaccine-derived poliovirus (cVDPV) type 2 poliovirus, this objective needs to override all other considerations for the time being.

Although the IAP ACVIP has not yet approved the use of intradermal fractional-dose IPV (ID-fIPV) for office practice, however, in view of the extraordinary situation in context of scarcity of IPV and the need of providing immunity against type-2 poliovirus, the committee is willing to provisionally accept

the immune-protection accorded by two ID-fIPV doses given at 6 and 14-week of age as 'moderately' effective against type-2 poliovirus. The committee however recommends another full dose of IM-IPV after an interval of at least 8 weeks following the second dose of ID-fIPV for enhanced protection. The evidences behind this recommendation are contained in the committee's earlier publication [27].

Typhoid conjugate vaccines

Recommendations

Primary schedule: IAP ACVIP has now approved the use of another typhoid conjugate vaccine, PedaTyph® for prevention of typhoid fever in pediatric population. The administration schedule of the vaccine will be the same as recommended for the other typhoid conjugate vaccine, Typbar-TCV® [4]. A single dose of the vaccine at 9-12 months of age is recommended for primary schedule. An interval of at least 4 weeks should be maintained between typhoid conjugate vaccine and MMR vaccine since the data on interference with the latter is not available.

Boosters: The primary dose of the conjugate vaccine at 9-12 months of age shall be followed by a booster of the same at 2 years of age. This recommendation will be applicable to both the typhoid conjugate vaccines, PedaTyph® and Typbar-TCV®. The committee has now indicated its preference for conjugate typhoid vaccine as a booster dose over the Vi-polysaccharide (Vi-PS) vaccine. A recently published trial of Typbar-TCV® [29] has demonstrated generation of strong anamnestic response with production of high affinity antibodies consisting of all the subclasses following a booster dose of the conjugate typhoid vaccine amongst a sub-set of test subjects [29]. Whereas Vi-PS vaccine elicited a limited IgG subclass response following the booster of Vi-PS vaccine with a significantly lower overall anamnestic response [29]. Further, this is in accordance to WHO recommendation that states, 'unconjugated Vi polysaccharide should not be administered to subjects primed with a Vi conjugate vaccine'[30]. The need of further boosters has not yet been determined since the long term follow-up data is still not available.

Catch-up schedule: Catch-up vaccination is recommended throughout the adolescent period, i.e. up to 18 years of age. The committee thinks that the Vi conjugate typhoid vaccine should be preferred over Vi-PS vaccine wherever feasible owing to generation of superior immune responses with the former. Only a single dose of either of the two available conjugate vaccines, i.e. Typbar-TCV® and PedaTyph® is recommended for children above 2 years of age. The need of the booster doses is not yet determined.

The evidence and justification: The committee's recommendations on PedaTyph® are based on the review of some recent publications on this vaccine [31-33]. A recently published school based cluster randomized trial of 1765 children, aged 6 months to 12 years with 2 doses of PedaTyph® vaccine, has demonstrated 100% (95% CI: 97.6%, 100%) efficacy of the vaccine in the first year of follow-up with

minimal adverse events post vaccination [33]. This is the first efficacy trial of any Vi conjugate typhoid vaccine in India. However, the committee has observed few limitations of this study such as lack of blinding of test subjects, small sample size considering an efficacy study, demographic differences in the test subjects and controls, and limited follow up period. Furthermore, the anti-Vi-IgG measurements expressed in ELISA units in a subgroup evaluation for immunogenicity (Table II) are based on a separate reference serum from US NIH, which was different from the one used in the Vietnam's Vi-rEPA (Vi antigen of Salmonella typhi conjugated to a recombinant exoprotein A from Pseudomonas aeruginosa) trials. Hence, the antibody measurements cannot be compared quantitatively with the original Vi-rEPA efficacy trial and other NIH publications (Personal communication, Shousun Chen Szu, Ph.D, Project leader of vaccines for salmonella, V.Cholera, E.Coli and Rotavirus, LDMI, NICHD, NIH, Bethesda, MD, USA). The committee has advised the manufacturer to provide a long term follow up data of the vaccinated subjects and to conduct an interference study on concomitant administration of PedaTyph® with MMR vaccine.

Why only a single dose of the PedaTyph® vaccine for primary vaccination?

The ACVIP has recommended single dose of the vaccine despite the fact that in the efficacy trial two doses of the vaccine are employed [33]. In two other studies with experimental Vi conjugate typhoid vaccines [34,35], two doses of the vaccines were used in children whereas a single dose was studied in the phase II/III study of Typbar-TCV® [29]. The recommendation on single dose of the PedaTyph® vaccine is based on the following evidences:

- In a sub-group analysis of 62 subjects in the post-licensure efficacy trial [33], 100% of the subjects underwent seroconversion (four fold or greater rise in IgG Vi polysaccharide antibody titer from baseline values) at 6 weeks with 21 folds higher level of GMTs (32 EU/mL (95% CI: 27.0, 39.0 EU/mL) from the baseline after the first dose (***Table* II**) [33]. In the same study, no Bactec or widal positive case was found over a period of 12 months in 140 subjects who had received only a single dose of the vaccine [33].
- In a pre-licensure study of the vaccine [36], a single dose of PedaTyph® seroconverted (>4-folds rise from baseline) 100% of study subjects aged 3 months to 2 years with reasonably good GMTs [36]. A post-licensure study on 163 subjects with single dose of the vaccine in Chennai found 83% sero-conversion (>4-folds rise from baseline) and reasonably good GMTs (9 folds rise from the baseline level) [31]. A sub-set of these vaccinated cohorts (one dose and two doses groups) were followed up to 30 months post-vaccination [32]. No significant advantage of two doses regimen over one dose was noticed. Though the GMT values of anti-Vi IgG antibodies for the two dose-cohort were slightly higher than in single dose- cohort [17 (95% CI: 7.4, 33) versus 14 (95% CI: 4.8, 29.8)], however, the difference was not found to be statistically significant [32].

- In a randomised, observer-blind, phase 2 trials of an experimental Vi-CRM typhoid conjugate vaccine in three countries, a second dose of conjugate vaccine had no incremental effect on antibody titres in children and older infants [35].
- In the efficacy trial of Vi-rEPA in Vietnam [34], both a single and two doses the vaccine showed comparable point estimates of efficacy of 87.7% and 89%, respectively, 46 months post- vaccination [34].
- In an earlier Phase II study of Vi-rEPA among 2- to 4-year olds children [37], there was no difference in the GMTs of anti-Vi IgG antibodies after 3 years of first dose among the one or two dose recipient children (5.84 vs 5.65) [37].

Are the immune responses elicited by a 5 µg Vi-PS TT conjugate sufficient for protection?

The committee has also reviewed in detail the optimum dose requirement for an ideal Vi conjugate typhoid vaccine. There is no guideline from WHO in this regard [30]. A dose finding study of the experimental Vi-rEPA vaccine [38] evaluated three different dose strengths of 5 µg, 12.5 µg and 25 µg of the vaccine and found a dose-dependent increase in anti-Vi IgG responses with 25 µg elicited the highest immune response [38]. Adopting a protective cut-off level of >4.3 µg/mL (or 3.52 Elisa Unit) for anti-Vi IgG, 12.5 µg was found to be the most optimum dose for a Vi conjugate typhoid vaccine for all ages [39]. Similar dose dependent response was also observed in the dose ranging study of Vi-CRM 197 conjugate typhoid vaccine in adults at Novartis Institute of Global Health [40]. However, in this study, even a very low antigen concentration (i.e., 1.25 µg /dose), was found similar or better than Vi-PS (25 µg/dose) [40]. However, the NVGH had chosen a dose of 5 µg of Vi-CRM197 for further development and for their Phase II study [35]. Later, re-examination of immune response and estimation of anti-Vi igG protective threshold against typhoid fever-based on the efficacy trial of Vi-rEPA conjugate in young children in Vietnam [34,41], the researchers estimated a new minimum protective level of anti-Vi IgG, between 1.4 and 2.0 µg/ml at 46 months after vaccination [42]. When the cut-off threshold was lowered from 4.3 µg/mL, the original proposed value based on the GMT level at the end of the efficacy study [34,41] to 2.0 µg/ml, nearly all children from the earlier study [38] achieved this newly proposed protective level at 10 or 52 weeks and there was no difference among the 3 dose strengths of the vaccine [42]. All the children with 5 µg dose attained this level at 10 and 52 weeks after vaccination whereas the corresponding figures were 100% and 77% , respectively when 4.3 µg/ml was used as cut-off level [42].

The manufacturer of PedaTyph® had also conducted a pre-clinical, dose escalation study using 5 µg and 25 µg dose strengths in animals. The study did not find any statistically significant difference in the immunogenicity of the two formulations. A higher incidence of local reaction (induration) was observed in animals immunized with 25 µg dose [43].

Hence, it is felt that the 5 µg dose used in PedaTyph® may be optimal. This is to be noted that the optimal dosage in the conjugate typhoid vaccines is usually derived from fine balances of many factors including age related immunogenicity, protective efficacy, number of doses, cost and possible overloading of immunogens.

Long term persistence of immune responses following a single dose of Vi conjugate typhoid vaccine

One post-licensure follow up study of Peda Typh® showed adequate immune response at 30 months post-vaccination with a single dose (GMTs: 14 (95% CI: 4.8, 29.8) µg/ml (which is greater than the earlier seroprotective level of 4.36 µg/ml or the current seroprotective level 1.4 µg/mL to 2.0 µg/mL) [32].

According to an unpublished study of Typbar-TCV®, adequate GMTs of anti-Vi IgG antibodies and good seroconversion rates (>4-folds rise from baseline) are maintained in a sub-group of 'un-boostered' subjects from the original cohort till 3 years of vaccination with a single dose of the vaccine (***Table* III, IV**). The GMTs at 3 years are equal or even higher than 2 years levels in both the subgroups, *i.e.* in open-label trial of children 6 months-<2 years of age and in controlled group of 2-45 years old following a single dose of Typbar-TCV®. Whereas in the Vi-PS subgroup, there was decline in titers at 3 years (***Table* III**). Similarly, 72.7% and 83.6% of subjects in open-label trial and controlled trial, respectively had 4 or more folds seroconversion from the baseline at 3 years follow-up (***Table* III**). In the boostered subgroup, GMTs are 3-5 folds higher than in unboostered groups at 3 years following a booster dose of the vaccine at 2 years (***Table* IV**). [Personal communication, Raghu J Reddy, M/s Bharat Biotech International Limited (BBIL), India].

Analysis of long term data of both the vaccines, it seems that a single dose of the either vaccines administered at 9 months or later provides a reasonably good GMTs and seroconversions in most of the vaccinees at least till 2.5 to 3 years after vaccination. The frequent sub-clinical natural boosting particularly in older children (>2 years of age) may obviate the need of further boosters in this age group. The Vi-rEPA vaccine has shown continued protection against clinical typhoid fever for at least 4 years in young children (based on efficacy data) and 8 years (based on immunogenicity study) [39]. In an earlier phase II study in adults, it was seen that Vi-rEPA elicited long-lasting protection up to 10 years after vaccination with a single dose [37].

Why booster at 2 years of age after primary vaccination at 9-12 months?

Conventionally it is believed that immune responses elicited in young children (<2 years old) are inferior to older children owing to immaturity of immune system. This has been amply demonstrated in the immunogenicity studies of Vi-rEPA and Vi-CRM197 conjugate typhoid vaccines also [34, 35, 37,

41]. There is a significant drop in titers of anti-Vi IgG antibodies at 6-12 months after vaccination amongst vaccinees following an initial 'jump' in the antibody levels at 4 weeks after the first dose [33, 39]. Furthermore, there are reduced opportunities of natural boosting in children below 2 years of age owing to lower burden of the typhoid fever in younger age group. These were the reasons why the committee had recommended a booster at 2 years of age [4]. This recommendation is now validated by the excellent booster response noted in a group of vaccinees when a 2nd dose was offered after 2 years of the first dose to a subset of original Typbar-TCV® vaccinees [29]. Surprisingly, both the licensed Vi conjugate typhoid vaccines in India, have shown higher GMTs and seroconversion rates initially in younger age group children than in older children and adults [29,32,36].

Conclusions: The committee concludes that many issues pertaining to Vi conjugate typhoid vaccines like exact correlate of protection, optimum dose and schedule, long term protection after a single dose, need and timing of the booster, etc are not yet fully elucidated. Most of the recommendations including the current correlate of protection for Vi conjugate typhoid vaccines are based on the analysis and interpretation of the pivotal large efficacy trial conducted by Szu, *et al*. in Vietnam with their experimental Vi-rEPA conjugate vaccine [34,39,41,42]. This trial has set a benchmark for all the future trials of Vi conjugate candidate typhoid vaccines. The trials on currently licensed Vi conjugate typhoid vaccines are still in the variable stages of completion in India and abroad. Hence, it is extremely difficult to offer immaculate recommendations on the use of current generation of the Vi conjugate typhoid vaccines. The present recommendations are based on the inferences drawn after analyzing the currently available data of all the licensed and experimental Vi conjugate typhoid vaccines.

Japanese encephalitis vaccine

Recommendation: The committee has now raised the recommended age for Japanese encephalitis (JE) vaccination to 18 years in endemic regions. Previously, the vaccine was recommended only up to 15 years of age [4].

Justification: This change in the recommendation is based on the changing epidemiology of the disease in the country wherein older children and even adults are found affected more frequently with the disease. The recent Government of India's (GoI's) decision to introduce adult JE vaccination in few endemic districts of the country [44] has also factored in the revised recommendation.

IAP ACVIP accreditation policy framework for available brands of licensed vaccines in India

A number of different brands of a particular vaccine are available in the Indian market. Some of them are marketed by global multinational companies and some other by indigenous vaccine manufacturers. They all are licensed by the Indian national regulatory authority (NRA), *i.e.* the CDSCO (Central Drugs Standard Control Organization), on the basis of the trials submitted to them. However, all of them are not

of the same quality and many lack the clinical efficacy and safety data for which rigorous studies are needed. In some instances, different brands use different constituents/excipients to manufacture the same formulation. The claims and counter-claims of the superiority of one brand over the other and vise-a versa may sometime create confusions among the vaccine prescribers and users. As a result, there have been regular queries at different forums on the preference of one brand over the other. With this background, the committee has devised a separate proforma **(Annexure II**) with uniformly set parameters to evaluate different brands of a licensed vaccine in the country. This process shall impart some objectivity and transparency to the committee's accreditation policy.

Review of the currently available monovalent varicella vaccine brands in India

Background: Different brands of monovalent varicella vaccine are available in India now for over the last two decades. Recently, a new monovalent varicella vaccine brand has entered the Indian market. Intensive marketing strategies of vaccine manufacturers have created confusion amongst pediatricians regarding the superiority of one brand over the other. Therefore, the committee undertook a detailed review of the monovalent varicella vaccine brands in the Indian market to provide a fair assessment of the strengths and weaknesses of the different products available in the country.

Results: There are currently five different brands of monovalent varicella vaccine available in Indian market. Besides the two multinational brands, Variped® and Varilrix®, there are three other brands manufactured by three Chinese manufacturers and imported in India by different Indian vaccine companies (***Table* V**). Another Japanese product, Okavax® by Biken marketed by M/s Sanofi Pasteur is not available in Indian market. All vaccines are freeze-dried, lyophilized products and licensed for use in persons aged ≥12 months [45].

Composition

Viral strain: All the available products employ live attenuated varicella zoster virus (Oka strain). They differ in the number of plaque-forming units (PFU) per vaccine dose ranging from 1000 to 17,000 PFU [45]. Though even a dose as small as 200 PFU is found to be immunogenic [46], the strength of antigen varies from 1300 PFU to 2500 PFU in the available varicella vaccines in India (***Table* V**). There is no WHO recommendation on the minimum amount of VZV (Oka strain) antigen in a varicella vaccine and it depends on the guidelines of a licensing authority of a country [45].

Monosodium L-glutamate (MSG): Monosodium L-glutamate (MSG) is the sodium salt of an amino acid known as glutamic acid (glutamate). Glutamic acid is naturally present in our bodies and occurs naturally in many foods such as tomatoes and cheeses [47]. MSG is used as a stabilizer in some of the vaccines approved by US CDC like Adenovirus, Influenza (FluMist), MMRV, and Zoster vaccines [47]. Stabilizers are added to the vaccines to ensure that the vaccine remains unchanged when it is

exposed to heat, light, acidity or humidity. Apart from Varilrix® and Nexipox®, all the brands contain minute amount (ranging from 0.36 mg-3.0 mg) of MSG (***Table* I**). A very small minority of people may suffer from some short-term, transient, and generally mild symptoms, such as headache, numbness, flushing, tingling, palpitations, and drowsiness after eating foods that contain MSG [48]. However, these concerns are not supported by scientific research. The US FDA and the US CDC have affirmed MSG to be safe and have labelled MSG as "Generally Recognized as Safe" (GRAS) in 1959 [47]. However, many anti-vaccines websites are exploiting this issue to cause misinformation against the vaccines. Variped®, the most widely used vaccine globally does also contain trace amount of MSG. Despite the massive use of this vaccine (approximately 200 million doses) in around 40 countries, no safety issue related to use of MSG has been reported so far. There is no guideline from the WHO on the use of MSG in vaccines. Despite the lack of separate studies on the safety of MSG use in vaccines, the verdict on its safety is still unsettled. However, considering the lack of published ill-effects of the MSG in licensed vaccines in spite of their massive use, MSG can be considered as a safe excipient of vaccines, free from serious harmful effects.

Gelatin: Gelatin, a protein of porcine origin has also been used to stabilize vaccines so that they remain effective after manufacture. Gelatin is present in vaccines in quantities sufficient to induce rare instances of severe, immediate-type hypersensitivity reactions [49]. Although the incidence of anaphylaxis to gelatin is extremely low (about 1 case per 2 million doses), it is the most common identifiable cause of severe allergic reactions to vaccines [49]. Both Variped® and Varivax® contain hydrolyzed gelatin which is less likely to cause hypersensitivity reactions than non-hydrolyzed gelatin. Hydrolysis converts high molecular weight gelatin (>100 000 Da) to low molecular weight gelatin (between 2000 and 5000 Da). Low molecular weight gelatin is less likely to stimulate gelatin-specific IgE than high molecular weight gelatin [49]. In a recent study [50], the recombinant human gelatin (8.5 kDa) demonstrated similar ability to stabilize the live attenuated varicella zoster vaccine (Oka/Merck) in an experimental, refrigerator-stable varicella vaccine when compared to the vaccine preparation formulated with hydrolyzed porcine gelatin used in currently marketed varicella vaccine [50]. Gelatin may be considered a potential allergen notwithstanding the extremely low rates of hypersensitivity reactions to this excipient.

Human serum albumin: Human albumin is added to live viral vaccines as a stabilizer and also to increase viral yield. Except Variped® and Biovac-V®, all other brands contain minute amount of human albumin. Since human serum albumin is derived from human blood, there is a theoretical risk that it might contain infectious agents. However, the human serum albumin used in modern-day vaccines is derived from blood of screened donors and is manufactured in a manner that would eliminate the risk of transmission of all known viruses [49].

Bovine calf serum: Only Variped® and Nexipox® contain trace amount of bovine calf serum (***Table* V**). Product insert (PI) of Varilrix® also mentions exposure to bovine derived materials during manufacturing process. There is a theoretical concern that bovine-derived materials used in vaccines might contain the agent associated with bovine spongiform encephalopathy (BSE). However, no evidence exists that any case of 'variant' Creutzfeld-Jacob disease (considered to be the human form of BSE) has resulted from the administration of any vaccine product [49]. Nevertheless, the US FDA has recently prohibited the use of bovine-derived materials obtained from countries that are known to have cattle that are infected with BSE [51]**.** There is no information regarding any such restriction from the Chinese FDA and regulators. However, the WHO has specified that the residual amount of serum albumin should be <50 ng per single human dose if animal serum is used during manufacture of any vaccine [52].

Neomycin: Apart from Biovac-V®, all other brands contain trace amount of neomycin, an antibiotic used to prevent bacterial contamination of the vaccine during the manufacturing process (***Table* I**). Though antibiotics can cause immediate type hypersensitivity reactions in children, such reactions to neomycin have not been documented [53].

Trehalose as a stabilizer: Nexipox® is the only brand that uses trehalose as a stabilizer of the varicella vaccine (***Table* I**). Trehalose is a naturally-occurring, non-reducing disaccharide of glucose which has been reported to be safe and non-toxic. Unlike some other conventional stabilizers like gelatin and MSG, no safety concern has been raised so far with this molecule. Trehalose is not a new chemical stabilizer. In fact, along with other carbohydrates like sucrose, lactose, maltose, etc and sugar alcohols such as sorbitol and mannitol, it is being used in veterinary and poultry vaccines for last 20 years [54]. Whereas the safety of trehalose is indisputable, its superiority as claimed by the manufacturer of Nexipox® over other chemical stabilizers is yet to be established. The role of trehalose as a stabilizer is evolving with possibilities of novel delivery formats and vaccine combinations [55-57]. Sucrose and trehalose have been reported to improve the stability of peste des petits ruminants (PPR) virus, camelpox virus or live-attenuated mumps vaccines during freeze drying [57-59]**.**

However, some studies on comparison with other stabilizers find formulations containing sorbitol and gelatin superior to the trehalose containing formulations [58, 60-62]. In a study analyzing the impact of four different stabilizer formulations containing trehalose, sorbitol, sucrose and fetal bovine serum for their efficacy in stabilizing a representative panel of four DNA/RNA freeze dried viruses at different storage temperatures, the sorbitol emerged as the most efficient stabilizer, particularly in sub-optimal storage temperatures [54].

The stability of live-attenuated viral vaccines is important for their efficacy. It is known that the level of virus viability after freeze drying varies according to the virus family, and the efficacy of the

protective agent (stabilizer). The choice of an appropriate stabilizer with respect to virus type is crucial for effective lyophilization. Generally, the best protective quality for enveloped viruses is achieved with gelatine-sucrose, which best maintained their infectivity and envelope morphology [63]. Though trehalose got mentioned as a safe stabilizer in the few old WHO papers [64, 65], there is no guideline from WHO regarding the use of any specific stabilizer in lyophilized vaccines. It can be safely inferred that trehalose is a safe and effective stabilizer but claims of its superiority over other stabilizers have not been validated.

Process of development: None of the varicella vaccine brands available in India or abroad is WHO prequalified. In fact, varicella vaccines are not on a high priority list of WHO for granting prequalification status. Variped® is approved by both US-FDA and European Medicines Agency (EMA) whereas Varilrix® is approved in Europe by EMA. Biovac-V® and Nexipox® are not yet approved by US FDA or EMA, though they have been approved by the Chinese health regulatory body. However, certain issues like vaccine production process, quality control and lot to lot consistency of vaccine bulk manufacturing remain to be evaluated.

Stability: The live attenuated varicella vaccine is not only freeze sensitive but is relatively unstable at elevated temperatures, even when lyophilized. All the available brands have a shelf life of 24 months except Nexipox® which is stable for 36 months at 2-8 degree centigrade. The company has ascribed this to the use of trehalose as a stabilizer in their product.

Clinical efficacy and safety data

Immunogenicity: All the vaccine brands are approved by the Central Drugs Standard Control Organization (CDSCO) after reviewing their phase II/ III clinical immunogenicity and safety studies. Only immunogenicity trial of Biovac-V® is published in a peer-reviewed journal [66] whereas Nexipox® trial has been published in a Chinese journal [67]. Varilrix® was used as a reference vaccine in most of pivotal clinical trials of different varicella vaccines conducted in India. A trial of Priorix-Tetra®, a combination MMRV vaccine has been conducted in India and the report is available in a peer reviewed journal [23]. The immunogenicity of the varicella component in combined vaccine was reported as non-inferior to that of varicella-only vaccine [23]. The immunogenicity trial of Variped® was displayed as a poster in IAP's national conference, Pedicon 2015 [68]. There is no information on any published Indian trial of Varivax® (***Table* VI**).

Efficacy: Efficacy studies are available only for Variped® and Varilrix® [69-72]. No data on any efficacy trial exists for Biovac-V®, Varivax® and Nexipox® (Table VI). However, an efficacy study for the varicella vaccine manufactured by Changchun Keygen Biological Products Co., Ltd is available [73].

Effectiveness: Most post-licensure studies were performed in the United States, and as a result, most vaccine effectiveness (VE) estimates are available for the Variped®. Studies conducted in other countries generally assessed Varilrix®, Okavax®, and various other varicella vaccines [74, 75]. In a systematic review performed by the SAGE Working Group of WHO on varicella [74], it was found that although majority of studies used the Variped® vaccine, there were several studies that used Varilrix® brand. Only very few studies are available on domestically produced Chinese vaccines including Biovac-V®, Varivax®, and Nexipox® (Table VI). Though the systematic review has concluded that VE appeared similar across products [74], however, the committee believes that the quality of evidence for Chinese products is limited owing to very few studies available in the literature. Table VII presents the VE estimates for different varicella brands by disease severity based on the WHO systematic review and another recent meta-analysis [75, 76]. It is evident that both Variped® and Varilrix® have comparable VE across all disease severity whereas there is limited information on Chinese products. In a VE study from a school in China [77], all the three varicella vaccines in use in China were found equally effective. While the Varilrix® had a VE of 86.4%, the Changchun vaccine (Varivax®) and Shanghai brand (not available in India) had 79.5% and 92.6% VE, respectively [77]**.** In yet another school-based study from Shandong province of China [78], **t**he VE for the Baike vaccine (Nexipox®) was found greater than that of the Changsheng vaccine (Biovac-V®) among those who had received vaccine within five years (91.4% *vs*. 84.5% for Baike and Changsheng, respectively, *P*=0.02) [78].

Duration of protection and Breakthrough rates: The duration of protection offered by a single dose of varicella vaccine is difficult to study and remains incompletely understood for the time being. It is unclear whether varicella vaccines provide long-term protection or whether immunity wanes with time [74,75]. The figures cited on duration of protection and breakthrough rates in the Table VII, are based on few studies and may not be entirely accurate.

Population impact data: Till 2015, 24 countries (8 in Europe, 10 in the Americas, 4 in the Eastern Mediterranean, and 2 in the East Pacific) have introduced varicella vaccine in their national immunization schedule [79]. The impact studies on varicella-associated hospitalizations rates have been conducted and published in 7 countries (US, Uruguay, Canada, Germany, Australia, Spain, Italy) [79]. All these countries have adopted either Variped® or Varilrix® or both in their national schedules. So far none of the Chinese vaccines are being used in the national immunization schedule of any country so far. (***Table* VI**).

Safety and post-marketing surveillance: There is strong evidence on the safety of monovalent varicella vaccines [45,75]. Only minor adverse events have been reported despite millions of doses used globally. Most of the data available on the safety including post-marketing surveillance (PMS) trials are

available only for Variped® and Varilrix®. The committee considers all the available varicella vaccines to be safe though the evidence in favor of Chinese vaccines is limited. Despite the presence of gelatin, MSG and other excipients like human serum, bovine products, cellular residues, DNA, etc in some products, no added risk of hypersensitivity reactions or other harmful effects have been documented. The presence of gelatin and traces of bovine materials in the Variped® is of some concern though no safety concerns have been noted till date despite its massive use in many countries including India (***Table* VI**).

Cost: All the currently available monovalent varicella vaccines are costing between INR 1560-1699 per dose barring the Nexipox® which is available at a cost of INR 2259 (Table V). It is felt that the product is overpriced considering all the attributes and the available evidences on the safety and efficacy of the vaccine formulation.

Conclusions: The ACVIP approves all the available monovalent varicella vaccine brands in the Indian market for use in pediatric population for prevention of varicella disease. However, the evidence in favor of efficacy and safety of the two brands which have been available and being used, Variped® and Varilrix® far outweigh the other brands.

A brief update on CYD-TDV (Dengvaxia®) dengue vaccine

The committee reviewed the first ever licensed dengue vaccine, Dengvaxia® (CYD-TDV) in its meeting. Dengvaxia® (CYD-TDV) is a tetravalent live attenuated chimeric vaccine with yellow fever virus as the backbone developed by M/s Sanofi Pasteur for use in individuals aged 9-45 years old. The vaccine is licensed in the Mexico, Philippines, Brazil, El Salvador and Paraguay for use in individuals 9-45 years old (9-60 years old in Paraguay) living in dengue-endemic areas. The Philippines has already introduced this vaccine in their national immunization program (NIP). Few more countries are planning to introduce it in their NIP, and WHO is in the process of bringing out first ever position paper on dengue vaccines. Dengvaxia® is evaluated in Phase III trials in Asia (CYD14; 5 countries, 10 275 children aged 2–14 years) and Latin America (CYD15; 5 countries, 20 869 children, aged 9–16 years) [80,81].

Vaccine efficacy against symptomatic virologically confirmed dengue (VCD) was estimated to be 56.5% in Asia and 60.8% in Latin America [80,81]. However, there is heterogeneity in the efficacy noted after the first year of long-term follow up [82]. The vaccine is found less effective against DENV2 and DENV1 (higher protection against DENV 3 and 4), in younger age-group children (higher protection in older children), in baseline sero-negative (higher protection in participants who had already been exposed to dengue virus), and against milder form of disease (higher protection against hospitalized and severe dengue) [82]. Furthermore, variable efficacy is seen in different countries. In Malaysia, a country having comparatively low sero-positivity at baseline (47.0%), had high vaccine efficacy (79.0%) than Indonesia

(vaccine efficacy: 54.3%) despite having high baseline seropositivity (80.9%). The pooled efficacy against all four virus sub-types (DENV 1-4) in 9-16 years individuals is 65.6%. Among individuals aged 9 years and older, efficacy of vaccine was 65.6% whereas it was only 44.4% in younger children. However, in those children first vaccinated at ages 2-5 years in Asia, a statistically significant increased risk of hospitalized dengue was seen in vaccine recipients in the third year after the first dose, though this risk was not seen in years 4 and 5 [83].

SAGE recommendations: The WHO Strategic Advisory Group of Experts (SAGE) on immunization has recommended countries consider introduction of CYD---TDV only in geographic settings (national or sub national) with high endemicity, as indicated by seroprevalence of approximately 70% or greater in the age group targeted for vaccination or other suitable epidemiologic markers. The vaccine is not recommended when seroprevalence is below 50% and for use in children under 9 years of age, because of the safety signal of increased risk of hospitalized and severe dengue identified in the 2---5 year age group, as consistent with current labeling [82].

CYD-TDV should be administered as a 3-dose series given as a 0, 6, and 12-month schedule. Administration with other live vaccines and killed vaccines is permissible, though data on interference is lacking. No short or long term risks have been associated with the vaccine as far as studied [83]. However, there is an urgent need for large, multicenter phase 3 trials to test investigational dengue vaccines in heterogeneous epidemiologic settings, and to obtain confirmatory data for serotype-specific efficacy.

Current status of CYD-TDV vaccine in India: The dengue vaccine has finished phase II trials in India. The phase III trials have not been started as yet. India has a three-level approval process for new drugs and vaccines, with applications scrutinized by Subject Expert Committee (SEC), technical committee and the apex committee in the Ministry of Health and Family Welfare. The SEC consists of health secretary, Indian council of medical research (ICMR) director, director general of health services (DGHS), and drug controller general of India. The SEC had recommended market authorization without phase III trials, considering the fact that dengue is a health problem of major concern in the country. The SEC, however, stipulated that phase IV clinical trials would have to be conducted in a time-bound manner. In May 2016, the apex committee noted that evidence is not sufficient to waive conduct of clinical trial in the country [84]. Hence dengue vaccine introduction in India might be delayed.

IAP ACVIP perspectives: According to the National Vector Borne Disease Control Programme (NVBDCP), 18 states are endemic to dengue in India [85]. As per the recent review, all four serotypes are circulating in different regions of the country, highlighting the need of a vaccine having a 'pan-serotype' efficacy [86]. Due to repeated dengue outbreaks and epidemics, there has been a significant increase in

the financial burden to the health care sector. The committee believes that there is definitely a need of an effective dengue vaccine considering the significant burden of the disease in the country. However, the current dengue vaccine may not have desired impact on the burden and transmission of the disease in the country owing to its various limitations. Thus, there is an urgent felt need of a more effective vaccine that can be administered safely especially to young children and has 'pan-serotype efficacy' irrespective of the immune status of an individual.

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ANNEXURE I

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Key updates and major changes in recommendations for IAP Immunization Timetable, 2016

MMR and MMRV vaccines

- Three doses of MMR at 9 months, 15 months, and between 4-6 years
- No stand alone measles dose at 9 months;
- MMRV is approved for use at 4-6 years of age only

Polio immunization

- The 'alternative' two-dose schedule of 8 and 16 weeks for IPV to be preferred over 3-dose schedule for primary immunization;
- A full dose of IM-IPV for children who had already received 2 ID-fIPV doses at 6 and 14 weeks or single dose of IM-IPV at 14 weeks
- An interval of at least 8 weeks to be maintained between the additional dose and the last dose of ID or IM-IPV;
- No change in the booster dose schedule of IPV, and OPV immunization schedule;

Typhoid immunization

- PedaTyph®, the other typhoid conjugate vaccine is now approved for prevention of typhoid fever in children;
- Both the typhoid conjugate vaccines, i.e. Typbar-TCV® and PedaTyph® to have the same administrative schedule;
- Typhoid conjugate vaccine to be preferred over Vi-polysaccharide vaccine for both booster dose and catch-up vaccination;
- No change in the booster recommendations;
- Additional updates on typhoid conjugate vaccines provided

Japanese encephalitis vaccination

- The recommended age for Japanese encephalitis (JE) vaccination raised to 18 years in endemic regions

Varicella vaccines

- A review along with grading of the available brands of monovalent varicella vaccine presented;
- All the available vaccine brands are approved for use in pediatric population for prevention of varicella;
- Varilrix® and Variped® score over other brands as far as the evidence on efficacy and safety is concerned

Other updates and changes

- A brief update on the new dengue vaccine, CYD-TDV (Dengvaxia®) is offered
- A new accreditation policy for evaluation of different brands of a licensed vaccine in the country is announced;
- The comments and footnotes for several vaccines are also updated and revised.

REFERENCES

1. Indian Academy of Pediatrics Committee on Immunization (IAPCOI). Consensus recommendations on immunization and IAP immunization timetable 2012. Indian Pediatr. 2012;49:549-64.
2. Vashishtha VM, Choudhury P, Bansal CP, Yewale VN, Agarwal R. Editors. IAP Guidebook on Immunization 2013-2014. National Publication House, Indian Academy of Pediatrics, Gwalior, 2014.
3. Universal immunization program. Available from: http://www.mohfw.nic.in/WriteReadData/l892s/5628564789562315.pdf. Accessed on May 16, 2016.
4. Vashishtha VM, Choudhury P, Kalra A, Bose A, Thacker N, Yewale VN, *et al*. Indian Academy of Pediatrics (IAP) Recommended Immunization Schedule for children aged 0 through 18 years – India, 2014 and Updates on Immunizations. Indian Pediatr 2014;51:785-804.
5. Vashishtha VM, Yewale VN, Bansal CP, Mehta PJ; Indian Academy of Pediatrics, Advisory Committee on Vaccines and Immunization Practices (ACVIP). IAP perspectives on measles and rubella elimination strategies. Indian Pediatr. 2014;51:719-22.
6. Dai B, Chen ZH, Liu QC, Wu T, Guo CY, Wang XZ, *et al*. Duration of immunity following immunization with live measles vaccine: 15 years of observation in Zhejiang Province, China. Bull World Health Organ. 1991;69:415-23.
7. Krugman S. Further-attenuated measles vaccine: characteristics and us. Rev Infect Dis. 1983;5:477-81.
8. Markowitz LE, Preblud SR, Fine PE, Orenstein WA. Duration of live measles vaccine-induced immunity. Pediatr Infect Dis J. 1990;9:101-10.
9. Cortese MM, Jordan HT, Curns AT, Quinlan PA, Ens KA, Denning PM, *et al*. Mumps Vaccine Performance among University Students during a Mumps Outbreak. Clin Infect Dis. 2008;46:1172-80.
10. Vandermeulen C, Roelants M, Vermoere M, Roseeuw K, Goubau P, Hoppenbrouwers K. Outbreak of mumps in a vaccinated child population: a question of vaccine failure? Vaccine. 2004;22:2713-6.
11. Fahlgren K. Two doses of MMR vaccine--sufficient to eradicate measles, mumps and rubella? Scand J Soc Med. 1988;16:129-35.

12. Kutty PK, McLean HQ, Lawler J, Schulte C, Hudson JM, Blog D, *et al*. Risk factors for transmission of mumps in a highly vaccinated population in Orange County, NY, 2009-2010. Pediatr Infect Dis J. 2014;33:121-5.
13. Ogbuanu IU, Kutty PK, Hudson JM, Blog D, Abedi GR, Goodell S, *et al*. Impact of a Third Dose of Measles-Mumps-Rubella Vaccine on a Mumps Outbreak. Pediatrics. 2012;130:1567-74.
14. Vashishtha VM, Yadav S, Dabas A, Bansal CP, Agarwal RC, Yewale VN, *et al*. IAP Position Paper on Burden of Mumps in India and Vaccination Strategies. Indian Pediatr. 2015;52:505-14.
15. Czajka H, Schuster V, Zepp F, Esposito S, Douha M, Willems P. A combined measles, mumps, rubella and varicella vaccine (Priorix-Tetra): immunogenicity and safety profile. Vaccine. 2009;27:6504-11.
16. Knuf M, Zepp F, Helm K, Maurer H, Prieler A, Kieninger-Baum D, *et al*. Antibody persistence for 3 years following two doses of tetravalent measles-mumps-rubella-varicella vaccine in healthy children. Eur J Pediatr. 2012;171:463-70.
17. Lalwani S, Chatterjee S, Balasubramanian S, Bavdekar A, Mehta S, Datta S, *et al*. Immunogenicity and safety of early vaccination with two doses of a combined measles-mumps-rubella-varicella vaccine in healthy Indian children from 9 months of age: A phase III, randomised, non-inferiority trial. BMJ Open. 2015;5: e007202.
18. Ma SJ, Li X, Xiong YQ, Yao AL, Chen Q. Combination Measles-Mumps-Rubella-Varicella Vaccine in Healthy Children: A Systematic Review and Meta-analysis of Immunogenicity and Safety. Medicine. (Baltimore). 2015;94:e1721.
19. Leung JH, Hirai HW, Tsoi KK. Immunogenicity and reactogenicity of tetravalent vaccine for measles, mumps, rubella and varicella (MMRV) in healthy children: A meta-analysis of randomized controlled trials. Expert Rev Vaccines. 2015;14: 1149-57.
20. Committee on Infectious Diseases. Policy statement — Prevention of varicella: update of recommendations for use of quadrivalent and monovalent varicella vaccines in children. Pediatrics. 2011;128:630-2.
21. Schink T, Holstiege J, Kowalzik F, Zepp F, Garbe E. Risk of febrile convulsions after MMRV vaccination in comparison to MMR or MMR+V vaccination. Vaccine. 2014;32:645-50.
22. Marin M, Broder KR, Temte JL, Snider DE, Seward JF; Centers for Disease Control and Prevention (CDC). Use of combination measles, mumps, rubella, and varicella vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rec. 2010;59(RR-3):1-12.

23. Lalwani S, Chatterjee S, Balasubramanian S, Bavdekar A, Mehta S, Datta S, *et al*. Immunogenicity and safety of early vaccination with two doses of a combined measles-mumps-rubella-varicella vaccine in healthy Indian children from 9 months of age: a phase III, randomised, non-inferiority trial. BMJ Open. 2015;5:e007202.
24. CDC fact sheet on MMRV. Available from: *http://www.cdc.gov/vaccines/hcp/vis/vis-statements/mmrv.html*. Accessed May 16, 2016.
25. Prasad R. A vaccine boost to India's polio fight. The Hindu, November 29, 2015. Available from: *http://www.thehindu.com/opinion/op-ed/a-vaccine-boost-to-indias-polio-fight/article7927744.ece*. Accessed December 26, 2015.
26. Deliberations at Mini-India Expert Advisory Group (IEAG) on Polio Eradication held on 26th February, 2016, New Delhi.
27. Vashishtha VM, Choudhary J, Yadav S, Unni JC, Jog P, Kamath SS, *et al*. Perspectives on Introduction of Inactivated Poliovirus Vaccine in National Immunization Program and Polio Endgame Strategy. Indian Pediatr. 2016 Apr 23. pii: S097475591600001.
28. Indian Academy of Pediatrics. FAQs on tOPV to bOPV switch and IPV roll out in India. Available from: *http://iapindia.org/files/FAQs-on-switch-n-IPV%20roll-out.docx*. Accessed July 8, 2016.
29. Mohan VK, Varanasi V, Singh A, Pasetti MF, Levine MM, Venkatesan R, *et al*. Safety and immunogenicity of a Vi polysaccharide-tetanus toxoid conjugate vaccine (Typbar-TCV) in healthy infants, children, and adults in typhoid endemic areas: A multicenter, 2-cohort, open-label, double-blind, randomized controlled phase 3 study. Clin Infect Dis. 2015; 61:393-402.
30. World Health Organization. Guidelines on the quality, safety and efficacy of typhoid conjugate vaccines, 2013. Available from: *http://www.who.int/biologicals/areas/vaccines/TYPHOID_BS2215_doc_v1.14_WEB_VERSION.pdf*. Accessed July 12, 2016.
31. Chinnasami B, Mangayarkarasi V, Prema A, Sadasivam K, Davis MJ. Safety and Immunogenicity of Salmonella Typhi Vi conjugate vaccine (PedaTyph™) in children upto five years. Int J Sci Res Publications (IJSRP). 2013;3:1-5. Available from: *http://www.ijsrp.org/research-paper-0213/ijsrp-p1477.pdf*. Accessed June 21, 2016.
32. Chinnasami B, Sadasivam K, Vivekanandhan A, Arunachalam P, Pasupathy S. A Study on Longevity of Immune Response after Vaccination with Salmonella Typhi Vi Conjugate Vaccine (Pedatyph™) in Children. J Clin Diagn Res. 2015; 9:SC01-3.

33. Mitra M, Shah N, Ghosh A, Chatterjee S, Kaur I, Bhattacharya N, *et al*. Efficacy and safety of vi-tetanus toxoid conjugated typhoid vaccine (PedaTyph™) in Indian children: School based cluster randomized study. Hum Vaccin Immunother. 2016;12:939-45.
34. Lin FY, Ho VA, Khiem HB, Trach DD, Bay PV, Thanh TC, *et al*. The efficacy of a Salmonella typhi Vi conjugate vaccine in two-to-five-year-old children. N Engl J Med. 2001;344:1263-9.
35. Bhutta ZA, Capeding MR, Bavdekar A, Marchetti E, Ariff S, Soofi SB, *et al*. Immunogenicity and safety of the Vi-CRM197 conjugate vaccine against typhoid fever in adults, children, and infants in south and southeast Asia: Results from two randomised, observer-blind, age de-escalation, phase 2 trials. Lancet Infect Dis. 2014;14:119-29.
36. Garg P, Garg S, Sharma MK. Clinical trial of Tetanus Toxoid Conjugated Vi Polysaccharide Typhoid Vaccine in infants and young children. Biotechnology International 2014; 7(4): 90-100. Available from: *http://bti.org.in/wp-content/uploads/2015/05/BTI-7.4.2.pdf*. Accessed June 21, 2016.
37. Kossaczka Z, Lin FY, Ho VA, Thuy NT, Van Bay P, Thanh TC, *et al*. Safety and immunogenicity of Vi conjugate vaccines for typhoid fever in adults, teenagers, and 2- to 4-year-old children in Vietnam. Infect. Immun. 1999;67:5806-10.
38. Canh DG, Lin FY, Thiem VD, Trach DD, Trong ND, Mao ND, *et al*. Effect of dosage on immunogenicity of a Vi conjugate vaccine injected twice into 2- to 5-year-old Vietnamese children. Infect. Immun. 2004;72:6586–8.
39. Szu SC. Development of Vi conjugate - a new generation of typhoid vaccine. Expert Rev Vaccines. 2013;12:1273-86.
40. van Damme P, Kafeja F, Anemona A, Basile V, Hilbert AK, De Coster I, *et al*. Safety, immunogenicity and dose ranging of a new Vi-CRM_{197} conjugate vaccine against typhoid fever: randomized clinical testing in healthy adults. PLoS One.. 2011;6:e25398.
41. Mai NL, Phan VB, Vo AH, Tran CT, Lin FY, Bryla DA, *et al*. Persistent efficacy of Vi conjugate vaccine against typhoid fever in young children. N Engl J Med. 2003;349:1390-1.
42. Szu SC, Klugman KP, Hunt S. Re-examination of immune response and estimation of anti-Vi IgG protective threshold against typhoid fever-based on the efficacy trial of Vi conjugate in young children. Vaccine. 2014;32:2359-63.
43. Preclinical dose escalation study (unpublished), Data on file with M/s BioMed Private Limited.
44. Vashishtha VM, Ramachandran VG. Vaccination Policy for Japanese Encephalitis in India: Tread with Caution! Indian Pediatr. 2015; 52:837-9.

45. World Health Organization. Varicella and herpes zoster vaccines: WHO position paper, June 2014. Wkly Epidemiol Rec. 2014;89:265-87.
46. Gershon AA, Takahashi M, Seward JF. Varicella vaccine. Chapter 37. *In*: Plotkin SA, Orenstein WA, Offit PA *(ed*) Vaccines 6th Edition, Elsevier Saunders 2013. *P*.837-69.
47. Parpia R. Monosodium glutamate used as a stabilizer in vaccines. Available from: *http://www.thevaccinereaction.org/2016/06/monosodium-glutamate-used-as-a-stabilizer-in-vaccines*/. Accessed June 29, 2016.
48. Questions and Answers on Monosodium glutamate (MSG). Available from: *http://www.fda.gov/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/ucm328728.htm. Accessed* June 29, 2016.
49. Offit PA, Jew RK. Addressing parents' concerns: do vaccines contain harmful preservatives, adjuvants, additives, or residuals? Pediatrics. 2003;112:1394-7.
50. Liska V, Bigert SA, Bennett PS, Olsen D, Chang R, Burke CJ. Evaluation of a recombinant human gelatin as a substitute for a hydrolyzed porcine gelatin in a refrigerator-stable Oka/Merck live varicella vaccine. J Immune Based Ther Vaccines. 2007;5:4.
51. Marwick C. FDA calls bovine-based vaccines currently safe. JAMA. 2000;284:1231-2.
52. World Health Organization. Requirements for varicella vaccine (live), WHO Technical Report Series, No. 848, 1994. Available from: *http://www.who.int/biologicals/publications/trs/areas/vaccines/varicella/WHO_TRS_848_A1.pdf* . Accessed July 3, 2016.
53. Kwittken PL, Rosen S, Sweinberg SK. MMR vaccine and neomycin allergy. Am J Dis Child. 1993;147:128-9.
54. Pastorino B, Baronti C, Gould EA, Charrel RN, de Lamballerie X. Effect of chemical stabilizers on the thermostability and infectivity of a representative panel of freeze dried viruses. PLoS One. 2015;10:e0118963.
55. Gribbon EM, Sen SD, Roser BJ, Kampinga J. Stabilisation of vaccines using trehalose (Q-T4) technology. Dev Biol Stand. 1996;87:193-9.
56. Kim YC, Quan FS, Song JM, Vunnava A, Yoo DG, Park KM, *et al*. Influenza immunization with trehalose-stabilized virus-like particle vaccine using microneedles. Procedia Vaccinol. 2010;2:15-9.
57. Jamil RK, Taqavian M, Sadigh ZA, Shahkarami MK, Esna-Ashari F, Hamkar R, *et al*. Evaluation of the thermal stability of a novel strain of live-attenuated mumps vaccine (RS-12 strain) lyophilized in different stabilizers. J Virol Methods. 2014; 199:35-8.

58. Sarkar J, Sreenivasa BP, Singh RP, Dhar P, Bandyopadhyay SK. Comparative efficacy of various chemical stabilizers on the thermostability of a live-attenuated peste des petits ruminants (PPR) vaccine. Vaccine. 2003;21:4728-35.
59. Prabhu M, Bhanuprakash V, Venkatesan G, Yogisharadhya R, Bora DP, Balamurugan V. Evaluation of stability of live attenuated camelpox vaccine stabilized with different stabilizers and reconstituted with various diluents. Biologicals. 2014;42:169-75.
60. Kang MS, Jang H, Kim MC, Kim MJ, Joh SJ, Kwon JH, *et al*. Development of a stabilizer for lyophilization of an attenuated duck viral hepatitis vaccine. Poult Sci 2010;89:1167-70.
61. Bora DP, Bhanuprakash V, Venkatesan G, Balamurugan V, Prabhu M, Yogisharadhya R. Effect of Stabilization and Reconstitution on the Stability of a Novel Strain of Live Attenuated Orf Vaccine (ORFV MUK59/05). Asian J Anim Vet. Adv 2015; 10:365-375. Available from: *http://scialert.net/qredirect.php?doi=ajava.2015.365.375and linkid=pdf.* Accessed July 2, 2016.
62. de Rizzo E, Tenório EC, Mendes IF, Fang FL, Pral MM, Takata CS, *et al*. Sorbitol-gelatin and glutamic acid-lactose solutions for stabilization of reference preparations of measles virus. Bull Pan Am Health Organ. 1989;23:299-305.
63. Malenovská H. The influence of stabilizers and rates of freezing on preserving of structurally different animal viruses during lyophilization and subsequent storage. J Appl Microbiol.. 2014;117:1810-9.
64. WHO Drug Information, Volume 12, Number 2, 1998, World Health Organization, Geneva. Available from: *http://apps.who.int/medicinedocs/documents/s14168e/s14168e.pdf*. Accessed July 2, 2016.
65. Lloyd J. Technologies for vaccine delivery in the 21st century: A white paper of WHO, UNICEF, USAID and PATH. World Health Organization, Geneva, 1999. Available from: *http://pdf.usaid.gov/pdf_docs/Pcaaa999.pdf.* Accessed July 4, 2016.
66. Mitra M, Faridi M, Ghosh A, Shah N, Shah R, Chaterjee S, *et al*. Safety and immunogenicity of single dose live attenuated varicella vaccine (VR 795 Oka strain) in healthy Indian children: a randomized controlled study. Hum Vaccin Immunother. 2015;11:443-9.
67. ZHU Chang-lin, ZHAO Zhen-yi, TAO Hang, XU Na, WU Jin-chang. Safety and immunogenicity of freeze-dried live attenuated varicella vaccine in India, Chinese Journal of Biologicals 2015; 28: 711-714. Available from: *http://caod.oriprobe.com/neworder.htm?id=46282001.* Accessed July 4, 2016.
68. Safety, Tolerability and Immunogenicity of Oka/Merck Varicella Vaccine in Indian Children. Poster presented at Pedicon-2015, New Delhi. Abstract No:OTH-P-464. IAP No:L/1980/S-4.

69. Weibel RE, Neff BJ, Kuter BJ, Guess HA, Rothenberger CA, Fitzgerald AJ, *et al*. Live attenuated varicella virus vaccine. Efficacy trial in healthy children. N Engl J Med. 1984;310:1409-15.
70. Kuter BJ, Weibel RE, Guess HA, Matthews H, Morton DH, Neff BJ, *et al*. Oka/Merck varicella vaccine in healthy children: final report of a 2-year efficacy study and 7-year follow-up studies. Vaccine. 1991;9:643-7.
71. Varis T, Vesikari T. Efficacy of high-titer live attenuated varicella vaccine in healthy young children. J Infect Dis. 1996;174:S330-4.
72. Prymula R, Bergsaker MR, Esposito S, Gothefors L, Man S, Snegova N, *et al*. Protection against varicella with two doses of combined measles-mumps-rubella-varicella vaccine versus one dose of monovalent varicella vaccine: a multicentre, observer-blind, randomised, controlled trial. Lancet. 2014;383:1313-24.
73. e-Ma FB, Luo LY, Zhang LH. [Study on epidemiological effect of the freeze-dried attenuated live varicella vaccine]. Zhongguo yi miao he mian yi. 2009;15:193-195.
74. World Health Organization. Systematic review of available evidence on effectiveness and duration of protection of varicella vaccines. Available at: *http://www.who.int/immunization/sage/meetings/2014/april/4_Systematic_review_on_effectiveness_and_duration_of_protection_of_varicella_vaccines.pdf?ua=1* Accessed July 2, 2016.
75. World Health Organization. Background Paper on Varicella Vaccine SAGE Working Group on Varicella and Herpes Zoster Vaccines Available from: *http://www.who.int/immunization/sage/meetings/2014/april/1_SAGE_varicella_background_paper_FINAL.pdf* . Accessed July 2, 2016.
76. Marin M, Marti M, Kambhampati A, Jeram SM, Seward JF. Global Varicella Vaccine Effectiveness: A Meta-analysis. Pediatrics. 2016;137:e20153741.
77. Fu C, Wang M, Liang J, Xu J, Wang C, Bialek S. The effectiveness of varicella vaccine in China. Pediatr Infect Dis J. 2010;29:690-693.
78. Wang Z, Yang H, Li K, *et al*. Single-dose varicella vaccine effectiveness in school settings in China. Vaccine. 2013;31:3834-8.
79. Hirose M, Gilio AE, Ferronato AE, Ragazzi SL. [The impact of varicella vaccination on varicella-related hospitalization rates: global data review]. Rev Paul Pediatr 2016; pii: S0103-0582(16)00008-3.

80. Capeding MR, Tran NH, Hadinegoro SR, Ismail HI, Chotpitayasunondh T, Chua MN, *et al*. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: A phase 3, randomised, observer-masked, placebo-controlled trial. Lancet. 2014;384:1358-65.
81. Villar L, Dayan GH, Arredondo-García JL, Rivera DM, Cunha R, Deseda C, *et al*. Efficacy of a tetravalent dengue vaccine in children in Latin America. N Engl J Med. 2015;372:113-23.
82. World Health Organization. Summary of the April 2016 meeting of the Strategic Advisory Group of Experts on immunization (SAGE). Available from: *http://www.who.int/immunization/sage/meetings/2016/april/SAGE_April_2016_Meeting_Web_summary.pdf*. Accessed July 12, 2016.
83. World Health Organization. Safety of CYD-TDV dengue vaccine. Available from: *http://www.who.int/vaccine_safety/committee/topics/dengue/Aug_2015/en/* Accessed July 12, 2016.
84. Health Ministry panel rejects Sanofi's clinical waiver plea for dengue vaccine. ET Bureau May 5, 2016. available from: *http://articles.economictimes.indiatimes.com/2016-05-05/news/72859178_1_sanofi-india-dengue-vaccine-sanofi-pasteur*. Accessed July 2, 2016.
85. National Vector Borne Disease Control Programme, Directorate General of Health Services, Ministry of Health and Family Welfare, India, 2016. Dengue situation in India. Available from *http://nvbdcp.gov.in/den-cd.html*. Accessed July 10, 2016.
86. Mathews JL, Agarwal A and Balasubramanian S. Tetravalent Dengue Vaccine for Children-Viewpoint. Indian Pediatr. 2015;52:237-40.

FIGURE 1. IAP Recommended immunization schedule for children aged 0-18 years (with range), 2016

Age ▶ Vaccine ▼	Birth – 2 weeks	6 wk	10 wk	14 wk	18 wk	6 mo	9 mo	12 mo	15 mo	18 mo	19-23 mo	2-3 Yr	4-6 Yr	7-10Yr	11-12 Yr	13-18Yr
BCG	BCG															
Hep B	Hep B1	Hep B2				Hep B3										
Polio	OPV 0	IPV1	IPV2	IPV3		OPV1	OPV2	IPV B1					OPV3			
DTP		DTP 1	DTP 2	DTP 3					DTP B1				DTP B2			
Tdap															Tdap	
Hib		Hib 1	Hib 2	Hib 3				Hib-booster								
Pneumococcal		PCV 1	PCV 2	PCV 3				PCV -booster					PCV			
PPSV23												PPSV				
Rotavirus		RV 1	RV 2	RV 3												
MMR							MMR 1		MMR 2				MMR 3			
Varicella									VAR 1				VAR 2			
Hep A								Hep A1 & Hep A2								
Typhoid							Typhoid CV (TCV)					Booster				
Influenza						Influenza (yearly)										
HPV															HPV	
Meningococcal												Meningococcal				
Cholera								Cholera 1 & 2								
JE								Japanese Encephalitis								
Rabies	Rabies (Pre-EP & PEP)															

Range of recommended ages for all children

Range of recommended ages for certain high-risk groups

Range of recommended ages for catch-up immunization

Not routinely recommended

- 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 Figure 1

Footnotes: Recommended Immunization Schedule for Persons Aged 0 through 18 Years — IAP, 2016

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.
- Once the protective cap on a single-dose vial has been removed, the vaccine should be discarded at the end of the immunization session because it may not be possible to determine if the rubber seal has been punctured
- 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 nonstandard 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 (3^{rd} or 4^{th}) 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!
- **Intradermal vaccination:** ACVIP does not approve the use of 'intradermal fractional-dose IPV' (ID-f IPV) for office-practice. However, considering the extreme shortage of IPV and the urgent need of providing immunity against type-2 poliovirus, the committee has now provisionally accepted the immune-protection accorded by two ID-fIPV doses given at 6 and 14-week as moderately effective against type-2 polioviruses. However, another full dose of IM-IPV should be offered at least at 8 weeks interval of the second dose of ID-fIPV.
    - If a child has received one dose of ID-fIPV at 6 weeks, two more full doses of IM-IPV should be offered at least 8 weeks after the first dose.
    - The minimum interval between the 2nd and 3rd dose should also be at least 8 weeks.

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.
- ACVIP does not approve the use of Tdap as second booster of DTP schedule!

- 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.
- Tdap vaccine should not be used as second booster for DTP series.

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:**
  - PCV and pneumococcal polysaccharide vaccine [PPSV] both are used in certain high risk group of children.
  - For children aged 24 through 71 months with certain underlying medical conditions, administer 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.
  - 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.
  - 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:**
  - Immunocompetent children with chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure); chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy), diabetes mellitus; cerebrospinal fluid leaks; or cochlear implant.
  - Children with anatomic or functional asplenia (including sickle cell disease and other hemoglobinopathies, congenital or acquired asplenia, or splenic dysfunction);
  - Children with immunocompromising 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 all available brands (RV-1 [Rotarix], RV-5 [RotaTeq] and RV-116E [Rotavac])
- Only two doses of RV-1 are recommended
- 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 RV-116E 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, the second dose at age 15 through 18 months, and final (the 3rd) dose at age 4 through 6 years.
- 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 at least 2 doses of MMR vaccine (3 doses if the 1st dose is received before 12 months) ;
- The minimum interval between the 2 doses is 4 weeks.
- One dose if previously vaccinated with one dose (2 doses if the 1st dose is received before 12 months) ;
- 'Stand alone' measles/any measles-containing vaccine or MMR 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
- Inactivated 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 of inactivated 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:
  - Vi-PS conjugate (Typbar-TCV®): 6 months;
  - Vi-PS conjugate (Pedatyph®): 6 months;
  - Vi-PS (polysaccharide) vaccines: 2 years
- Vaccination schedule:
  Typhoid conjugate vaccines (Vi-PS):
  Typbar-TCV®: Single dose at 9-12 through 23 months followed by a booster at 2 years of age
  Pedatyph® : Single dose at 9-12 through 23 months followed by a booster at 2 years of age
  Vi-PS (polysaccharide) vaccines: Single dose at 2 years; revaccination every 3 years;
- Currently, two typhoid conjugate vaccines, Typbar-TCV® and PedaTyph® are available in Indian market;
- An interval of at least 4 weeks with the MMR vaccine should be maintained while administering Typbar-TCV® and PedaTyph® vaccines
- 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. However, typhoid conjugate vaccine should be preferred over un-conjugated Vi- PS vaccine

Catch-up vaccination:

- Recommended throughout the adolescent period, i.e. up to 18 years of age

14. Influenza vaccine

Routine vaccination:

- *Minimum age:*
    - 6 months for trivalent inactivated influenza vaccine (IIV)
    - 2 years for live, attenuated influenza vaccine (LAIV)
- IIV: Recommended only for the vaccination of persons with certain high-risk conditions.
- LAIV: Recommended for only healthy children aged 2-18 years.
- For most healthy children aged 2 through 18 years, either LAIV or IIV may be used.
- LAIV should NOT be administered to following category of children:
    - Who have experienced severe allergic reactions to LAIV, any of its components, or to a previous dose of any other influenza vaccine;
    - Children 2 through 17 years receiving aspirin or aspirin-containing products;
    - Children with immunodeficiency;
    - Children 2 through 4 years of age with asthma or who had wheezing in the past 12 months;
    - Children who have taken influenza antiviral medications in the previous 48 hours
    - Children who have experienced severe allergic reactions to LAIV, any of its components

- IIV: 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.
- LAIV: 2- 9 years: One or two doses as per the ACVIP annual recommendations; 9 years and above: single dose
- *Dosage*:
- IIV : aged 6–35 months 0.25 ml; 3 years and above: 0.5 ml
- LAIV: see product insert of the available formulation

- For the 2016-17 season, since the A (H3N2) and B flu viruses have drifted, a child who has received two doses of influenza vaccine (IIV or LAIV) should receive one dose, and those who have received one dose in previous season should receive two doses of new formulation at least 4 week apart. The two doses need not have been received during the same season or consecutive seasons.

- 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 IIVs in the country contain the 'Swine flu' or 'A (H1N1)' antigen; no need to vaccinate separately.
- LAIV: Not recommended for children with chronic medical conditions
- ACVIP does not endorse the superiority of LAIV over the IIV. There is not adequate data is not available from the country to recommend discontinuation of LAIV use in healthy individuals contrary to recent CDC ACIP recommendations.
- Best time to vaccinate:
    - As soon as the new vaccine is released and available in the market
    - Just before the onset of rainy season.
    - Some regions may consider vaccination just prior to onset of winters based on local epidemiology data

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 (inactivated 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 till 18 years of age
- 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:**
  - Minimum age: 8 months;
  - Two dose schedule, first dose at 9 months along with measles vaccine and second at 16 to 18 months along with DTP booster
  - Not available in private market for office use
- **Inactivated cell culture derived SA-14-14-2 (JEEV® by BE India) :**

  - Minimum age: 1 year (US-FDA: 2 months)
  - Primary immunization schedule: 2 doses of 0.25ml each administered intramuscularly on days 0 and 28 for children aged ≥1 to ≤3 years
  - 2 doses of 0.5 ml for children >3years and adults aged ≥18 years
  - Need of boosters still undetermined
- **Inactivated Vero cell culture-derived Kolar strain, 821564XY, JE vaccine (JENVAC® by Bharat Biotech)**
  - Minimum age: 1 year
  - Primary immunization schedule: 2 doses of 0.5 ml each administered intramuscularly at 4 weeks interval
  - Need of boosters still undetermined.

Catch up vaccination:

- All susceptible children up to 18 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):
  - 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.
- 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:*
  - MTCVs are recommended for all category II and III bites.
  - *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.
  - *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
  - Rabies immunoglobin (RIG) along with rabies vaccines are recommended in all category III bites.

  - Equine rabies immunoglobin (ERIG) (dose 40 U/kg) can be used if human rabies immunoglobin is not available;
- *Pre -exposure prophylaxis:*
  - 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).
  - 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 is not required during re-exposure therapy.

TABLE I IAP IMMUNIZATION TIMETABLE 2016

I. IAP recommended vaccines for routine use

Age (completed weeks/months/years)	Vaccines	Comments
Birth	BCG OPV 0 Hep-B 1	Administer these vaccines to all newborns before hospital discharge
6 weeks	DTwP 1 IPV 1 Hep-B 2 Hib 1 Rotavirus 1 PCV 1	**DTP:** • DTaP vaccine/combinations should preferably be avoided for the primary series • DTaP vaccine/combinations should be preferred in certain specific circumstances/conditions only • 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 **Polio:** • All doses of IPV may be replaced with OPV if administration of the former is unfeasible • Additional doses of OPV on all supplementary

		immunization activities (SIAs) • Two doses of IPV instead of 3 for primary series if started at 8 weeks, and 8 weeks interval between the doses • No child should leave the facility without polio immunization (IPV or OPV), if indicated by the schedule • See footnotes under figure titled IAP recommended immunization schedule (with range) for recommendations on intradermal IPV **Rotavirus:** • 2 doses of RV1 and 3 doses of RV5 & RV 116E • RV1 should be employed in 10 & 14 week schedule, 10 & 14 week schedule of RV1 is found to be more immunogenic than 6 & 10 week schedule
10 weeks	DTwP 2 IPV 2 Hib 2 Rotavirus 2 PCV 2	**Rotavirus:** If RV1 is chosen, the first dose should be given at 10 weeks
14 weeks	DTwP 3 IPV 3 Hib 3 Rotavirus 3	**Rotavirus:** • Only 2 doses of RV1 are recommended. • If RV1 is chosen, the 2nd dose should be given at 14 weeks

	PCV 3	
6 months	OPV 1 Hep-B 3	**Hepatitis-B:** 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.
9 months	OPV 2 MMR-1	**MMR:** • Measles-containing vaccine ideally should not be administered before completing 270 days or 9 months of life; • The 2nd dose must follow in 2nd year of life; • 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; either can be used • An interval of at least 4 weeks with the MMR vaccine should be maintained while administering this vaccine
12 months	Hep-A 1	**Hepatitis A:** • Single dose for live attenuated H2-strain Hep-A vaccine • Two doses for all inactivated Hep-A vaccines are recommended
15 months	MMR 2 Varicella 1 PCV booster	**MMR:** • The 2nd dose must follow in 2nd year of life • However, it can be given at anytime 4-8 weeks after the 1st dose

		Varicella: The risk of breakthrough varicella is lower if given 15 months onwards
16 to 18 months	DTwP B1/DTaP B1 IPV B1 Hib B1	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. **DTP:** • 1st & 2nd boosters should preferably be of DTwP • Considering a higher reactogenicity of DTwP, DTaP can be considered for the boosters
18 months	Hep-A 2	**Hepatitis A:** 2nd dose for inactivated vaccines only
2 years	Booster of Typhoid Conjugate Vaccine	• A booster dose of Typhoid conjugate vaccine (TCV), if primary dose is given at 9-12 months • A dose of Typhoid Vi-polysaccharide (Vi-PS) vaccine can be given if conjugate vaccine is not available or feasible; • Revaccination every 3 years with Vi-polysaccharide vaccine • Typhoid conjugate vaccine should be preferred over Vi- PS vaccine
4 to 6 years	DTwP B2/DTaP B2 OPV 3 Varicella 2 MMR 3	**Varicella:** the 2nd dose can be given at anytime 3 months after the 1st dose. **MMR:** the 3rd dose is recommended at 4-6 years of age.

10 to 12 years	Tdap/Td HPV	**Tdap:** is preferred to Td followed by Td every 10 years **HPV:** • Only 2 doses of either of the two HPV vaccines 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. • For 3 dose schedule, the doses can be administered at 0, 1-2 (depending on brand) 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), liver disease and diabetes mellitus
- 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.

For details see footnotes under figure titled 'IAP recommended immunization schedule (with range)'

TABLE II GEOMETRIC MEAN TITER (GMTS)S OF IGG VI-POLYSACCHARIDE ANTIBODY AT BASELINE, 6 WEEKS AND 12 MONTHS POST VACCINATION IN A SUBGROUP EVALUATION OF IMMUNOGENICITY FOR PEDATYPH®.

Anti-Vi IgG of children receiving 1& 2 doses Vi-TT (in ELISA units)#				
Age/Time	**N**	Pre-injection	6 weeks*	12 months**
0.5-2 Years	4	1 (1,1)	36 (6.9, 194)	17 (4.8, 57)
>2-5 Years	9	1.2 (0.8, 1.8)	46.8 (28.7, 76.4)	12.4 (8.8, 17.3)
> 5 Years	49	2.1 (1.7,2.6)	30.7 (25.3, 37.2)	14.4 (11.7, 17.7)
All ages	62	1.8 (1.5, 2.2)	32 (27, 39)	14 (12, 17)

**6 weeks post vaccination IgG Vi polysaccharide Antibody GMT (95% CI) EU/ml (after one dose); **12 months post vaccination IgG Vi polysaccharide Antibody GMT (95% CI) EU/ml (after two doses); P-values: <0.001 on comparing Vi-IgG values after one and two doses with the baseline levels (drawn from the data contained in the reference number 5). #Anti-Vi IgG measurements expressed in ELISA units based on a human anti-Vi reference (Lot No PUN/TYP/01) for S. typhi containing 118ELISA units/ml. The ELISA units are not calibrated against NIH Human anti-Vi IgG reference or EU mentioned in NIH publications.*

TABLE III GEOMETRIC MEAN TITER OF ANTI-VI IMMUNOGLOBULIN G ANTIBODIES* AT BASELINE AND AT 42 DAYS, 540 DAYS, 720 DAYS AND AT 1095 (3 YEARS) IN AN 'UNBOOSTERED' SUBGROUP FOLLOWING THE ADMINISTRATION OF A SINGLE DOSE OF TYPBAR-TCV® OR TYPBAR®.

		Day 0	**Day 42**	**Day 540**	**Day 720**	**Day 1095**
Open Label Trial (6mo-2 yrs)	**Typbar-TCV**					
	No. of subjects	307	307	122	220	33
	GMT EU/ml (95% CI)	9.5 (9,10)	1937.4 (1785,2103)	58.7 (49, 71)	48.7 (43,56)	58.4(37, 98)
	Fold change		205	6.2	5.2	16.7
Controlled Trial (2-45 yrs)	**Typbar-TCV**					
	No. of subjects	332	332	212	243	60
	GMT EU/ml (95% CI)	10.4 (9.6,11.3)	1292.5 (1153,1449)	92.8 (81, 106)	81.7 (73,92)	81.9 (45, 151)
	Fold change		124	8.9	7.8	17.5
	Typbar					
	No. of subjects	305	305	194	197	124
	GMT EU/ml (95% CI)	11.6 (10.5,12.9)	411.1 (359,471)	51.7 (39, 91)	45.8 (40,53)	31.5 (26, 49)
	Fold change		35	4.4	3.8	2.7

**Anti-Vi IgG antibodies were assessed by enzyme-linked immunosorbent assay (ELISA) using the VaccZyme commercial kit [2]. GMTs: Geometric mean titers; SC: seroconversion;*

TABLE IV GEOMETRIC MEAN TITER OF ANTI-VI IMMUNOGLOBULIN G ANTIBODIES* AND SEROCONVERSION (>4 FOLDS FROM THE BASELINE) IN THE 'UN-BOOSTERED' SUB-GROUP OF CHILDREN AT 2 AND 3 YEARS AND 'BOOSTERED' (BOOSTED AT 2 YEARS AFTER FIRST DOSE) SUBJECTS AT 3 YEARS (1 YEAR AFTER BOOSTER) FOLLOWING THE ADMINISTRATION OF A SINGLE DOSE OF TYPBAR-TCV® OR TYPBAR®.

Parameters	**Unboostered**		**Boostered at 3 years (boosted after 2 yrs of 1st dose)**
	At 2 years	**At 3 years**	
Open label (6mo-2 yrs)			
GMTs (95% CI)	48.7 (43,56)	58.4 (37, 98)	302.68 (255, 359) 5folds
SC (>4 folds)	59.5%	72.7%	92.4 %
Controlled trial (Typbar-TCV) (2-45 yrs)			
GMTs (95% CI)	81.7 (73,92)	81.9 (45, 151)	287.09 (232,356) 3.5 folds
SC (>4 folds)	74.1%	83.6%	90.2%
Controlled trial (Typbar) (2-45 yrs)			
GMTs (95% CI)	45.8 (40,53)	31.5 (26, 49)	249.34 (156,398)
SC (>4 folds)	53.5%	38.7%	71.8 %

**Anti-Vi IgG antibodies were assessed by enzyme-linked immunosorbent assay (ELISA) using the VaccZyme commercial kit [2]. GMTs: Geometric mean titers; SC: seroconversion;*

TABLE V Comparative Analysis of available Varicella Vaccine Brands in India: Composition, process of development, stability and cost.

Brand name ®	Manufacturer/ Marketer	Composition (Vaccine formulation)						Process of development		Stability (Shelf life at 2-8°C)	Cost (Rs)
		Strain	Quantity of antigen	Preservative	Stabilizer	Antibiotic	Other	Adherence to GMP	Other		
VARIPED	Merck Sharp & Dohme (MSD) Pharmaceuticals Pvt. Ltd	Oka/Merck varicella	Minimum of 1350 PFU	None	MSG 0.36 mg, Sucrose, & hydrolyzed Gelatin 8.9 mg	Neomycin (traces)	Sodium Phosphate & Potassium Phosphate as pH regulators; Bovine calf serum & trace residual components of MRC 5 cells	Yes,	USFDA & European Medicines Agency approved	24 months	1690
VARILRIX	GlaxoSmithKline (GSK) Vaccines	Oka/GSK strain	Not less than $10^{3.3}$ PFU	None	Anhydrous lactose, Sorbitol, Mannitol, Amino acids	Neomycin (traces)	Human serum albumin	Yes	European Medicines Agency approved	24 months	1560
BIOVAC-V	Manufactured by Changchun Changsheng Life Sciences, China marketed in India by M/s Wockhardt India Ltd	Oka strain (VR 795 Varicella Oka strain)	2511 PFU	Fucose 17.5mg	MSG 3.0 mg, Sorbierite 2.5 mg	None	Dextran & L-Arginine	-	Approved by State Food and Drugs Administration, China	24 months	1699
VARIVAX	Changchun Institute of biological products, China marketed in India by M/s VHB life Scinces Ltd	Oka strain	Not less than 2000 PFU	None	MSG 0.7 mg, Gelatin 2.1 mg, Dextran, Sucrose	Neomycin (traces)	Mannitol as a humectant, Human Albumin, Sodium Orthophosphate & Potassium Phosphate	-	No information	24 months	1690

NEXIPOX	Changchun BCTH Biotech (Baiko), China marketed in India by M/s Novo Medi Sciences Pvt Ltd	Oka strain (VR 795 Varicella Oka strain)	≥2000PFU	Human Albumin 5mg	Trehalose 10mg, Sucrose , Dextran	Neomycin (traces)	Human Albumin, Bovine calf serum, Mannitol as a humectant.	-	Certificate of GMP from People's Republic of China	36 months	2259

PFU=Plaque forming units; MSG= Monosodium L glutamate;

TABLE VI COMPARATIVE ANALYSIS OF AVAILABLE VARICELLA VACCINE BRANDS IN INDIA: CLINICAL DATA ON IMMUNOGENICITY, EFFICACY, EFFECTIVENESS AND SAFETY

Brand name®	Immunogenicity data		Efficacy data		Effectiveness data		Population impact data	Safety data		Clinical experience/ usage	
	Indian trial	Publication in an Indexed journal	Efficacy studies	Publication in an Indexed journal	Effectiveness study/impact data	Publication in an Indexed journal		PMS trial	Publication	National	Worldwide
VARIPED	Yes	No (poster presentation only)	Yes	Yes	Yes	Yes (33 studies, 28 studies with 1 dose & 5 studies with 2 doses)	Yes (US, Canada, Germany, Spain, Australia, Taiwan)	Yes	Yes	Marketing approval received in India 2014	191 million doses used worldwide in 38 countries.
VARILRIX	Yes	Yes (MMRV trial in India)	Yes	Yes	Yes	Yes (13 studies, all with 1 dose)	Yes (Uruguay, Australia, Germany, Taiwan)	Yes	Yes	Marketing approval in 1998; Approx 4.98 million doses sold since launch	62.9 million doses used in over 90 countries since 1986
BIOVAC-V	Yes	Yes	No	No	Yes	Yes (2 studies)	No	Yes (Studies done in few districts of China)	No	Marketing approval in June 2014; Approx 1.9 million doses sold since launch	20.7 million doses used in China, Philippines, Pakistan, & Guatemala
VARIVAX	Yes	?	No	No		Yes (1 study)	No	?	?	Marketing approval in 2004; Approx 5.0 million doses sold since launch	No information
NEXIPOX	Yes	Yes (Studies published in Chinese	No	No	Yes	Yes (1 study)	No	Yes (studies done in few districts of	Yes (Studies published in Chinese	0.25 million doses sold since its approval in India	More than 90 million doses sold since 2008 in

		journals)						China)	journals)		Philippines, Macau, China

TABLE VII COMPARATIVE ANALYSIS OF AVAILABLE VARICELLA VACCINE BRANDS IN INDIA: ONE DOSE VARICELLA VACCINE EFFECTIVENESS (VE) ESTIMATES BY VARICELLA DISEASE SEVERITY, DURATION OF PROTECTION AND BREAKTHROUGH RATES. (ADAPTED FROM THE REFERENCE 30).

Brand name®	Manufacturer	All varicella		Combined moderate & severe varicella		Severe varicella		Duration of protection	Breakthrough rates (after single dose)
		No. estimates	Mean VE (range)	No. estimates	Mean VE (range)	No. estimates	Mean VE (range)		
VARIPED	MSD Pharmaceuticals Pvt. Ltd	28	81% (44%-100%)	18	96% (86%-100%)	11	99% (97%-100%)	Up to 10 years after vaccination	9-14%
VARILRIX	GSK	8	70% (20%-92%)	5	93% (80b%-100%)	3	100%	Unknown (7 years based on antibodies persistence)	5.06%
BIOVAC-V	Changchun Changsheng Life Sciences; China	2	80%	-		-	-	20 years after immunization*	-
VARIVAX	Changchun Institute of biological products, China	1	77%	-		-	-	-	-
NEXIPOX	Changchun BCTH Biotech (Baike), China	1	91%	-		-	-		0.01%

VE=Vaccine effectiveness; *Ref: http://www.cs-vaccine.com/en/cp_page.asp?id=329

ANNEXURE. II

Proforma for assessing a vaccine brand for granting IAP ACVIP accreditation *(Based on different attributes of a vaccine brand)*

Attributes	
Vaccine formulation (Appropriateness)	
Composition-Quantity of antigen	
Preservative	
Stabilizer	
Adjuvant	
Antibiotic/s	
Other	
Process of development	
Adherence to GMP	
Other	
Clinical data	
Immunogenicity data	
--Publication in indexed journal	
Efficacy data	
--Publication in indexed journal	
Effectiveness data	
--Publication in indexed journal	
Population based studies	
---Publication in indexed journal	
Other	
Safety data	
PMS trial/study	
---Publication in indexed journal	
Other	
Clinical experience/usage	
National	
Worldwide	

Other	
Standardization	
WHO Pre-Qualification	
US FDA approval	
Other (like EMA, local FDA, etc)	
Other parameters	