Indian Academy of Pediatrics (IAP) Advisory Committee on Vaccines and Immunization Practices (ACVIP): Recommended Immunization Schedule (2023) and Update on Immunization for Children Aged 0 Through 18 Years

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ABSTRACT

Justification: In view of new developments in vaccinology and the availability of new vaccines, there is a need to revise/review the existing immunization recommendations.

Process: The Advisory Committee on Vaccines and Immunization Practices (ACVIP) of Indian Academy of Pediatrics (IAP) had a physical meeting on March 25, 2023, at Vaccicon, Kolkata, followed by online meetings to discuss the updates and new recommendations. Opinion of each member was sought on the various recommendations and updates, following which an evidence-based consensus was reached. The contents were finalized on September 8, 2023, during the National Conference of Pediatric - Infectious Diseases (NCPID) at Aurangabad. An online meeting of all members was held on November 15, 2023 and the recommendations were finalized.

Objectives: To review and revise the IAP immunization recommendations of 2020-21 and issue recommendations on existing and new vaccines.

Recommendations: The major changes include recommendation of HPV vaccine for boys; a 2-dose schedule of 9vHPV for boys and girls aged 9-14 y; a dose of Td vaccine at 16-18 y; guidance for injectable polio vaccine (IPV) for those patients who are changing from National Immunization Program to IAP schedule.

Keywords: *Boys, Guidelines, 9vHPV, Td vaccine*

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The Advisory Committee on Vaccines and Immunization Practices of the Indian Academy of Pediatrics (IAP-ACVIP) met on March 25, 2023 in Kolkata, West Bengal, and September 8, 2023 at the National Conference of Pediatric - Infectious Diseases (NCPID), Aurangabad, Maharashtra. ACVIP members who attended the meeting are listed in *Annexure I*. The aim of the meeting was to discuss and debate the recent developments in the field of vaccinology, to issue the relevant recommendations based on them, and to revise the existing IAP immunization timetable. This document presents the consensus recommendations, arrived at after detailed literature review, debates and discussions, held during the first physical meeting and subsequent meetings held online (dIAP or Zoom platform) and physically.

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PROCESS

The process for issuing recommendations included a review of the recent published literature including standard indexed journals, vaccine trials, recommendations of reputed international bodies like Advisory Committee on Immunization Practices (ACVIP), Centre

for Disease Control and Prevention (CDC), and World Health Organi-zation (WHO) as well as unpublished data from vaccine manufacturers. Data generated by studies done in India was specifically looked at and available local information was given preference. The summary of the key updates of ACVIP 2023 recommendations is given in **Box I**.

RECOMMENDATIONS

The IAP-ACVIP recommendations for vaccine for routine use are presented in **Table I** and **Fig. 1**. The recommendations about the newly introduced vaccines are summarized in **Box II**.

1. Td (Tetanus, Diphtheria) Vaccine

Additional Dose of Td at 16-18 y

The National Immunisation Program (NIP) schedule recommends a Tetanus-Diphtheria (Td) booster at 16 years of age and the IAP-ACVIP schedule recommends a final booster of the Tetanus, Diphtheria, Pertussis (Tdap) vaccine at 10 years of age, followed by Td every 10 years [1,2].

Diphtheria surveillance data from Kerala (2016) found that the majority of the diphtheria cases were in the age group 18-45 y (38%; 198/526), followed by the age groups 10-18 y (31%; 161/526), and 5-10 y (18%) [3]. In north Maharashtra, the age groups of 5-9 y and 10-14 y represented 33.3% (42/126) and 23.8% (30/126) of the total diphtheria cases, respectively [4]. In a serosurvey done in 2,400 school children aged 6-17 y, studying in the various government schools in Hyderabad, only 56% and 64% had protective levels of IgG antibodies against diphtheria and tetanus respectively [5]. These studies suggest a lack of protective antibodies in a significant proportion of older adolescents and adults and a poor uptake of Td beyond 10 y of age.

Box I Key Updates and Major Changes in Recommendations for IAP Immunization Timetable 2023

Td Vaccine

- A dose of Td vaccine is recommended at 16-18 years.

Injectable Polio Vaccine (IPV)

- A child, who has received 3 doses of fIPV at 6w-14w-9 mo, does not need an additional dose of IM-IPV. However, the child should receive a 2nd booster of IM-IPV at 4-6 y.

HPV vaccines

- HPV vaccines are recommended for boys
- For girls and boys 9-14 y, 9vHPV is recommended in a 2-dose schedule of 0-6 mo

New Vaccines

- Inactivated TZ84 strain of Hepatitis A vaccine marketed by BE Limited and Abott India Limited
- Quadrivalent HPV vaccine of Serum Institute of India Private Limited
- 14 valent pneumococcal conjugate vaccine of BE Limited
- MMR vaccine with Hoshino strain of Mumps of Zydus Lifesciences Limited
- Whole cell pertussis containing hexavalent vaccine of Serum Institute of India Private Limited
- Recombinant Zoster vaccine of GlaxoSmithKline

Studies have demonstrated persistence of diphtheria antibodies in > 95% of adolescents at 5 y and 10 y following a Tdap dose at 10 y of age. Nearly all participants had tetanus antibodies (≥ 0.1 IU/mL) throughout the study, however, the protection against pertussis was variable. Anti-pertussis toxin antibodies declined to pre-vaccination levels approximately 5 y post-vaccination; antibodies to filamentous hemagglutinin, pertactin and fimbrae waned at 5 y and 10 y but remained several-fold higher than pre-vaccination levels [6,7]. A Tdap vaccine administered at 10-12 y will provide protection against tetanus and diphtheria for approximately 10 y [8]. These results support the recommendations that one Tdap booster should be administered to all persons and Td boosters every 10 y thereafter between 11-64 y of age.

Adolescents rarely visit the doctor unless they have a medical health condition. Estimates of receipt of clinical preventive services among adolescents, is suboptimal in developed countries [9] and very low in low- and middle-income countries. In a study done in rural West Bengal, it was reported that only 29.4% adolescents had utilised adolescent reproductive and sexual health services at least once during adolescence [10]. This may explain the poor uptake of adolescent boosters and the consequent higher incidence of diphtheria and tetanus in older adolescents and adults.

A booster of Td at 16-18 y will ensure assured protection against diphtheria and tetanus for the next 10 y. Replacement of the decennial Td by Tdap is not a cost-effective intervention [11], since the protective efficacy of Tdap administered in early adolescence, against pertussis does not last for more than 2-3 y. The reduction in pertussis disease burden attributable to the routine use of a second dose of Tdap, would therefore be limited [12]. However, if there is an increased risk of pertussis in a healthcare setting evident by documented or suspected healthcare-associated transmission of pertussis, revaccination of healthcare personnel with Tdap may be considered [13].

IAP-ACVIP Recommendation

- The IAP-ACVIP recommends a dose of Td vaccine between 16-18 y.

Table I IAP-ACVIP Immunization Timetable 2023: Vaccines for Routine Use

Age	*Vaccine*	*Comments*
Birth	BCG, OPV, Hepatitis B-1	BCG before discharge; OPV as soon as possible after birth; Hepatitis B should be administered within 24 hours of birth
6 wk	DTwP/DTaP-1, IPV-1, Hib-1, Hep B-2, Rotavirus-1, PCV-1	DTwP or DTaP may be administered in primary immunization; IPV: 6wk-10wk-14wk is the recommended schedule. If IPV, as part of a hexavalent combination vaccine, is unaffordable, the infant should be sent to a government facility for primary immunization as per UIP schedule.
10 wk	DTwP/DTaP-2, IPV-2, Hib-2, Hep B-3, Rotavirus-2, PCV-2	RV1 (GSK): 2 -dose schedule; all other rotavirus brands: 3-dose schedule
14 wk	DTwP/DTaP-3, IPV-3, Hib-3, Hep B-4, Rotavirus-3, PCV-3	An additional 4th dose of Hep B vaccine is safe and is permitted as a component of a combination vaccine
6 mo	Influenza (IIV)-1	Uniform dose of 0.5 mL ≥ 6 mo
7 mo	Influenza (IIV)-2	To be repeated every year, in pre-monsoon period, till 5 y of age
6-9 mo	Typhoid conjugate vaccine	There is no recommendation for a booster dose
9 mo	MMR-1	
12 mo	Hepatitis A vaccine	Single dose for live attenuated vaccine
15 mo	MMR-2, Varicella-1, PCV-Booster	
16-18 mo	DTwP/DTaP-B1, Hib-B1, IPV-B1	
18-19 mo	Hepatitis A-2, Varicella-2	Only for inactivated hepatitis A vaccine
4-6 y	DTwP/DTaP-B2, IPV-B2, MMR-3	
9-14 y	HPV	2 doses: 0-6 mo
10 y	Tdap	Tdap is to be administered even if it has been administered earlier (as DTP-B2)
15-18 y	HPV	3 doses; 0-2-6 mo (if not administered earlier)
16-18 y	Td	

Age in completed wk/mo/y. BCG: Bacillus calmette guerin; DTwP: Diphtheria, tetanus, and whole-cell pertussis; DTaP: Diphtheria, tetanus, and acellular pertussis; HepB: Hepatitis B; Hib B: Hemophilus influenzae B; MMR: Measles mumps rubella; OPV: Oral poliovirus vaccines; PCV: Pneumococcal conjugate vaccine; RVI: Monovalent rotavirus vaccine

2. Human Papilloma Virus (HPV) Vaccine

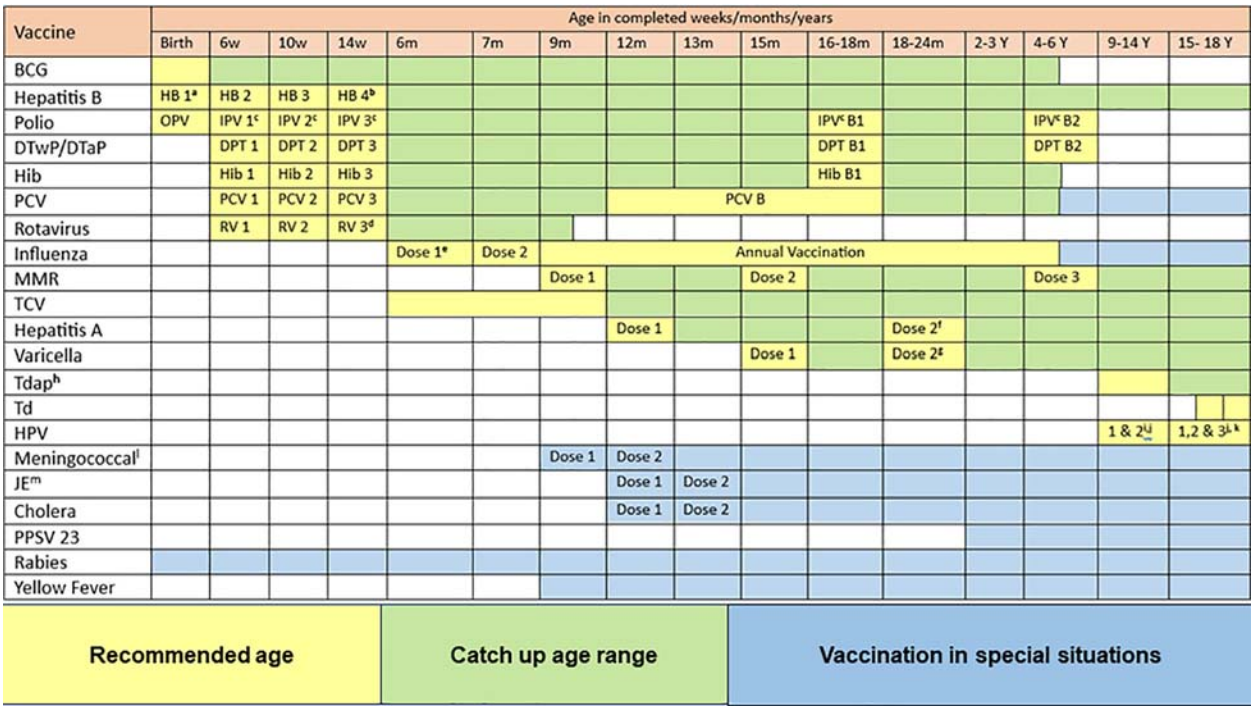
2-dose Recommendations for Girls and Boys Aged 9-14 y

All Human Papilloma Virus (HPV) vaccines were originally licensed and marketed using a 3-dose vaccination schedule. A 2-dose schedule was approved, based on demonstration of noninferiority of the immune response in the 9-14 y age group, when compared to young adult women in whom efficacy has been proven. A 2-dose schedule for 9-valent HPV *vaccine* (*9vHPV*) for 9-14 y was approved by USA CDC, European Medical Agency, Canada in 2016 and is currently approved in around 80 countries across the globe, including Australia, France, Germany, UK, USA as well as in Asian countries like, Singapore, Malaysia, Taiwan, Thailand and Vietnam.

9vHPV Vaccine Study: 2-dose Schedule Study

An open-label, noninferiority, immunogenicity trial was conducted to compare the seroconversion rates (SCR) and immunogenicity of 2 doses of 9vHPV in girls and boys aged 9-14 y as compared to 3 doses in adolescent girls and young women. Four weeks after the last dose, the SCR to each individual serotype, in the 2-dose cohort, was > 98%. The geometric mean titers (GMT) of HPV antibodies at 1 month after the last dose, for all the 9 HPV subtypes was higher in girls and boys who received 2 doses 6 months apart and in girls and boys who received 2 doses 12 months apart as compared with adolescent girls and young women who received 3 doses over 6 months. Noninferiority criteria for seroconversion rates were met for all 9 HPV types [14].

At follow up till 36 months, anti-HPV GMTs in girls and boys who received 2 doses were generally similar to or greater than GMTs in young women who had received 3 doses. Seropositive status was maintained across HPV types, in most boys and girls who received 2 doses and young women who received 3 doses till 2 to 2.5 y after the last dose [15]. In a follow up study of the 9vHPV vaccine, seropositivity rates remained > 90% through month 90 for



a. To be given within 24 h after birth. When this is missed, it can be administered at first contact with health facility. All stable preterm and LBW babies should be administered a birth dose and 3 more doses with pentavalent/hexavalent combination vaccines.
b. An extra dose of Hepatitis B vaccine is permitted as part of a combination vaccine when use of this combination vaccine is necessary.
c. IPV can be given as part of a combination vaccine.
d. 3rd dose of Rota vaccine is not necessary for RV1 (GSK).
e. Influenza vaccine should be started after 6 months, 2 doses 4 weeks apart, usually in the pre-monsoon period. At other times of the year, the most recent available strain should be used. Annual influenza vaccination should be continued, for all, till 5 y of age. For those at high risk of Influenza related complications, annual vaccination should be continued till 18 years and beyond.
f. Single dose is to be given for the live attenuated Hepatitis A vaccine. The inactivated vaccine needs two doses.
g. 2nd dose of Varicella vaccine should be given 3-6 mo after dose 1. In catch up schedule, in those >12 years of age, the 2nd dose is to be given after 4 weeks.
h. Tdap should not be administered as the second booster of DPT at 4-6 y. For delayed 2nd booster, Tdap can be given after 7 y of age. A dose of Tdap is necessary at 10-12 y. If a dose of Tdap was administered at more than or equal to 9 y of age, the adolescent Tdap is not necessary. If Tdap is unavailable/unaffordable, it can be substituted with Td.
i. From 9-14 years, HPV vaccines are recommended as a 2-dose schedule, 6 months apart.
j. 9vHPV-Gardasil-9 is approved for boys between 9-14 years of age and females between 9-26 years of age. HPV4-SII is recommended for females and males between 9-26 years of age. Gardasil 4 is licensed till 45 years of age only for females.
k. From 15 y onwards and in immunocompromised subjects at all ages, HPV vaccines are recommended as a 3-dose schedule, 0-2-6 months.
l. Menactra is approved in a 2-dose schedule between 9-23 mo. Minimum interval between two doses should be 3 mo. Menveo is recommended as a single dose schedule after 2 y of age. For those with ongoing exposure to meningococci, boosters are recommended every 5 years.
m. In endemic areas

Fig. 1 IAP-ACVIP Recommendations 2023

each of the 9vHPV vaccine types. No cases of vaccine related high-grade intraepithelial neoplasia or genital warts were observed in the per-protocol population based on a maximum follow-up of 8.2 y (median 7.6 y) post-dose 3 [16].

Gender-neutral Vaccination: Need for HPV Vaccination for Males

Infection with the high-risk HPVs, principally serotype 16 and 18, is the cause of almost all cervical cancers in women. However, oropharyngeal cancer (including tonsils and base of tongue), anal and penile cancers are also HPV-associated cancers and impose a significant burden in males as well. It is estimated that HPV is the causal agent in 5% of all human cancers with HPV16 predominating. Apart from cervical cancers, the other HPV-associated cancers are not amenable to screening and are increasing in both males and females and usually detected at a late stage.

The aim of any vaccination program is to halt transmission of the pathogens and prevent all associated diseases. Gender neutral vaccination (GNV) will also prevent non-cervical HPV-associated diseases that have

Box II IAP-ACVIP Recommendations on Newer Vaccines

4vHPV: Cervavac

Schedule for Cervavac:

- 9-14 years of age (boys and girls): Two-dose schedule (0.5 mL at 0 and 6 months). The interval between the 1st and 2nd dose should not be <5 months.
- 15-26 years of age (females and males) and immunocompromised: 3-dose (0.5 mL at 0, 2, and 6 months) schedule. The second dose should be administered at least 1 month after the first dose and the third dose should be administered at least 3 months after the second dose.

Inactivated TZ84 strain Hepatitis A vaccines: Hapibev and Havshield

- This vaccine is recommended for the prevention of Hepatitis A in children ≥ 12 months of age in a 2-dose schedule of 0-6 months.

14 valent pneumococcal conjugate vaccine of BE Limited: PneuBEvax 14

- This vaccine is recommended for the primary immunization, for the prevention of invasive pneumococcal disease caused by pneumococcal serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F, in a 6w-10w-14w schedule. This vaccine is presently not recommended for the booster dose in the 2nd year of life.

MMR vaccine with Hoshino strain of Mumps: ZyvacMMR

- There is immunogenicity and safety data available in children between 15-18 months only, so this vaccine is recommended in children between 15-18 months.

Whole cell pertussis containing hexavalent vaccine: Hexasiil

- This vaccine is recommended for primary immunization against diphtheria, tetanus, pertussis, Hepatitis, Poliomyelitis and Hemophilus influenzae type B infections, in infants in a 6wk-10wk-14wk schedule.

Recombinant Zoster vaccine: Shingrix

- This vaccine is recommended in all immunocompetent adults aged ≥ 50 years, irrespective of prior receipt of varicella vaccine or zoster vaccine live (ZVL).

serious morbidity in males as well. GNV programs have been found to be cost-effective interventions [17]. GNV will reduce transmission, impart herd immunity, facilitate the eradication of HPV and protect boys from infection. Girls only vaccination programs will not lead to eradication.

Global/India Burden of Oropharyngeal Cancers (OPC)

Globally, head and neck cancers are the sixth most common cancer and one of the most common cancers in India [18]. The annual crude incidence rate per 100,000 in India has been reported as 2.4 in males and 0.52 in females. In India, in 2020, there were an estimated 17,175 new cases of OPC in males and 3,442 in females, with 10,367 deaths in males and 2,066 in females [19]. The contribution of HPV to squamous cell carcinoma of head and neck has been rising and presently stands at 47.7% overall and up to 72.2% in oropharyngeal cancers. As compared to HPV-negative head and neck cancers, HPV positive head and neck cancers tend to affect patients who are younger, consume less or no alcohol, and do not smoke. They are generally diagnosed at a higher stage and may have distant metastasis at diagnosis. They have a reasonably good response to the treatment [20].

A systematic review from India showed the prevalence of HPV in head and neck cancers ranging from 0-86.6% in India. The broad range resulted from the heterogeneity of the data. Data from 3,847 patients of head and neck cancer patients showed that 1,110 patients were HPV positive, implying a cumulative prevalence of HPV positive head and neck cancers in India around 28.85%. There was no difference in treatment outcome among HPV positive and HPV negative cancer patients [21].

Global/India Burden of Anal Cancers

HPV related cancers also include anal cancers with approximately 90% of anal cancers being related to HPV. In the meta-analysis study carried out by De SanjoseÌ et al in 2019, HPV16 was present in 80.7% of anal cancers [22]. Worldwide, in 2020, there were an estimated 29,159 cases of anal cancer in women with an age-standardized rate (ASR) of 0.58/100,000 and 21,706 cases of anal cancer in men with an ASR of 0.49/100,000. There were an estimated 9,877 deaths in women and 9,416 deaths in men [23].

Estimated figures for India were, 3,111 cases in males and 2,341 in females, with an estimated 1,560 deaths in males and 1,216 deaths in females [19]. In a study done from two major cities in India, the prevalence of anal HPV was 95% (95% CI 91%-97%) in men who have sex with men (MSM) [24]. Among the women living with HIV from India, the anal HPV prevalence was 14.3% and high-risk HPV prevalence was 9.2% [23].

Global/India Burden of Penile Cancers

Worldwide, in 2020, there were an estimated 36,068 cases of penile cancers (PeCa), with 13,211 deaths [18]. The estimated burden in India was 10,677 cases and 4,760 deaths, with an estimated age-standardized incidence of 0.84 cases per 100 000 person-years (95% CI: 0.79-0.89) [19]. In a single centre analysis of 40 cases from India, the overall prevalence of HPV in PeCa was 42.5% as compared to 20% in controls. Among the subtypes, the most common subtype was HPV 16 noted in 33.3% of cases,

followed by HPV 18 in 29.2% of cases [25].

HPV immunization in Male Population

Above mentioned data support the use of HPV vaccines in males. To date, 125 countries have introduced HPV vaccine in their national immunization program for girls, and 47 countries also recommend HPV vaccination for boys [26].

IAP-ACVIP Recommendation

- Due to the significant burden of HPV related cancers and other conditions, the IAP-ACVIP recommends the use of HPV vaccines in boys.
- All currently licensed HPV vaccines, including 9vHPV vaccines have excellent safety profiles and are highly efficacious, or have met immune bridging standards in both male and female. 9v HPV Vaccine is recommended in a 2-dose schedule with an interval of six months, for boys and girls between 9 to 14 y. This schedule also has cost-saving and programmatic advantages that may facilitate high coverage. The 3-dose schedule of the 9vHPV vaccine is recommended for females, when the schedule is initiated after 15 years of age.

3. Injectable Polio Vaccine

Guidance on Changeover from NIP to IAP Schedule

The IAP-ACVIP recommends five doses of full-dose (0.5 mL) intramuscular (IM) inactivated polio vaccine (IPV), including three primary doses at 6wk, 10wk and 14wk and two booster doses at 16-18 mo and 4-6 y [1]. The National Immunization Programme (NIP) recommends 3 doses of fractional-dose (0.1 mL) inactivated polio vaccine (fIPV) at 6 wk-14wk-9mo given intradermally (ID), along with bivalent oral polio vaccine (bOPV), 2 drops, at 6w-10w-14w and 16-18 mo [27].

It is not uncommon for a changeover from the NIP to the IAP schedule after 6 months of age as the NIP does not provide for many of the vaccines recommended by IAP for infants beyond 6 months of age. For this reason, guidance is being issued regarding use of IPV in children shifting from the NIP to the IAP schedule.

Following 2 doses of fIPV at 6wk-14wk, the IAP-ACVIP recommended an additional dose of full dose IM-IPV at least 8 wk after the last dose of fIPV [28]. This recommendation was made as 2 doses of fIPV at 6wk-14wk resulted in seroconversion of 82-85% against type 2. It was expected that an additional dose of IM-IPV will increase the seroconversion rates to a much higher level. The NIP now recommends 3 doses of fIPV at 6wk-14wk-9mo, with the 9 mo dose being a booster dose [27]. There is no substantial difference in seroconversion rates between 2 and 3 doses of ID fIPV, and 2 and 3 doses of full-dose IM-IPV, although the full dose gives higher titres of antibodies for poliovirus type 1, 2, and 3 [29].

A 2-dose schedule of IPV at 14w and 36w resulted in seroconversion rates of 96%, 98% and 85%, for serotypes 1, 2 and 3 respectively, by the intradermal route and 99%, 99% and 97% by the IM route [30]. Hence, any additional benefit from an additional dose of IM-IPV, will be of marginal benefit only. Two doses of fIPV administered at 14wk and 36wk resulted in higher seroconversion rates compared to an earlier schedule of 6wk and 14wk, for all serotypes: fIPV 96%, 98%, 85% (14 wk and 36 wk); 83%, 84%, 83% (6 wk and 14 wk) [30,31].

IAP-ACVIP Recommendations for IPV

- For infants who have received the 3-dose fIPV as per the NIP, an additional dose of IM-IPV is not necessary at 16-18 mo.
- A booster of IM-IPV is recommended at 4-6 y. The rationale for a booster at 4-6 y has been published earlier [1].

NEW VACCINES

The newly introduced vaccine products are detailed below and the IAP-ACVIP recommendations for these are given in **Box II**.

i) 9vHPV

The 9-valent HPV (9vHPV) vaccine contains serotypes 6, 11, 16, 18, 31, 33, 45, 52 and 58. Each 0.5-mL dose contains the L1 protein of~30 µg of HPV Type 6, ~40 µg of HPV Type 11, ~60 µg of HPV Type16, ~40 µg of HPV Type 18, ~20 µg of HPV Type 31, ~20 µg of HPV Type33, ~20 µg of HPV Type 45, ~20 µg of HPV Type 52, and ~20 µg of HPV Type 58. Each 0.5 mL dose of the vaccine also contains approximately 500 µg of aluminium (provided as AAHS), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 µg of polysorbate 80, 35 µg of sodium borate, <7 µg yeast protein, and water for injection. The product does not contain any preservative or antibiotics.

Route of administration: Intramuscular (IM)

Storage: The vaccine is stored between +2° to +8°C and should not be frozen. Any frozen vaccine should be discarded. The vaccine should be protected from light.

Clinical studies: The phase III efficacy trial consisted of a cohort of 14,000 females aged 16-26 y, in which the efficacy of 9vHPV was compared to 4vHPV for the prevention of ≥ CIN2, vulvar intraepithelial neoplasia

(VIN) grade 2 or 3, and vaginal intraepithelial neoplasia (VaIN) grade 2 or 3 caused by HPV 31, 33, 45, 52, or 58 [32]. The results are shown in **Table II**. The immunogenicity of 9vHPV to 6, 11, 16 and 18 was noninferior to that of 4vHPV. This was used to infer efficacy of 9vHPV against 6, 11, 16 and 18. In the 9vHPV group, the GMTs of antibodies against 6, 11, 16 and 18 was noninferior to that of 4vHPV and >99% seroconverted against all 9 serotypes.

In an immune bridging trial comparing 9vHPV in 2,400 females and males aged 9-15 y with 400 females aged 16-26 y, > 99% seroconverted against all 9vHPV serotypes. The GMTs in the 9-15 y cohort was significantly higher than the 16-26 y cohort [14].

In a cohort of 600 adolescent females aged 9-15 y comparing 4vHPV and 9vHPV, the seroconversion rate (SCR) was 100% in both groups and the GMTs were noninferior in the 9HPV group as compared to the 4vHPV group. SCR was > 99% and GMTs were noninferior in males aged 16 through 26 y compared with females of the same age group [33].

Concomitant administration of 9vHPV with Tdap and the meningococcal conjugate vaccine did not interfere with the immunogenicity against all 9 HPV serotypes [32]. In the safety analysis, most adverse events were injection site-related pain, swelling, and erythema that were mild to moderate in intensity. The safety profiles were similar in 4vHPV and 9vHPV vaccines. Among females aged 9 through 26 y, the local reactogenicity with 9HPV was more than that observed with 4vHPV [32].

IAP-ACVIP Recommendations for 9vHPV

- Females and males aged 9-14 y: 2 doses at an interval of 6 to 12 months.
- Females 15-26 y: 3-dose schedule of 0-2mo-6mo
- 3-dose schedule in immunocompromised in both age groups.

ii) 4vHPV New

This new 4-valent HPV (4vHPV) vaccine is produced from *Hansenula polymorpha*. Each dose of 0.5 mL contains the L1 protein of HPV type 6 ≥ 20 µg, HPV type 11 ≥ 40 µg, HPV type 16 ≥ 40 µg, HPV type 18 L1 ≥ 20 µg, Al^{3+} ≤ 1.25 mg.

Indications: In females 9-26 y of age for the prevention of the following diseases caused by HPV serotypes included in the vaccine: cervical, vulvar, vaginal, and anal cancer caused by HPV types 16 and 18, genital warts (condyloma acuminata) caused by HPV types 6 and 11, cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma in situ (AIS), and CIN grade 1 caused by types 6, 11, 16, and 18, VaIN grades 2 and 3, VIN grades 2 and 3, and anal intraepithelial neoplasia (AIN) grades 1, 2, and 3.

In males 9-26 y of age for the prevention of the following diseases caused by HPV types included in the vaccine: Anal cancer caused by HPV types 16 and 18, genital warts (condyloma acuminata) caused by HPV types 6 and 11, AIN grades 1, 2, and 3 caused by 6, 11, 16, and 18.

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

Clinical studies: The phase 2/3 study, participants were divided in 2 cohorts. The cohort 1 consisted of 350 males and 349 females aged 9 to 14 y who received two doses of new 4vHPV vaccine six months apart and 338 females received the existing 4vHPV vaccine. Cohort 2 consisted of males and females age 15 to 26 y who received 3 doses in a 0-2mo-6mo schedule. In this cohort, 381 males and 411 females received the new 4vHPV vaccine and 378 females received the three doses of existing 4vHPV vaccine [34].

The primary objective of the study was to demonstrate immunogenic noninferiority of the new 4vHPV vaccine (Cervavac) to the existing 4vHPV (Gardasil-4), one month after the last dose i.e., at 7 months. In the cohorts of 9-14 years age, Geometric Mean Fold Rise (GMFR) for all 4 serotypes was > 1000-fold. In the same cohorts, noninferiority was demonstrated for high risk (oncogenic) HPV types as lower bound of GMT ratio (CI was above

Table II 9vHPV Vaccine Efficacy Data

Endpoint related serotypes	*Endpoint*	*VE (%)*	*(95% CI)*
HPV 31, 33, 45, 52, 58	≥ CIN2, VIN2/3, VaIN2/3	96.7	(80.9-99.8)
	≥ CIN2	96.3	(79.5- 99.8)
	6-month persistent infection	96.0	(94.4-97.2)

VE: Vaccine efficacy, HPV: Human papilloma virus, CIN: Cervical intraepithelial neoplasia, VIN: Vulvar intraepithelial neoplasia, VaIN: Vaginal intraepithelial neoplasia; 9vHPV: 9-valent human papilloma virus

0.5). Post-vaccination, at 7-month time point (1 month after the last dose), a 100% seroconversion was reported across all four vaccine types (serotypes 6, 11, 16, and 18) in initially seronegative populations. The GMT ratios observed between the new 4vHPV vaccine (Cervavac) to the existing 4vHPV (Gardasil-4), in 9-14 years age group are shown in **Table III** [34]. The new 4vHPV was found to be noninferior to the comparator vaccine in 15-26 years as well (unpublished data; Personal communication).

Safety profile: Most of the adverse effects reported were predominantly mild to moderate in intensity and recovered completely. No vaccine related SAE or solicited reactogenicity with severity of Grade 3 or more was reported. Overall incidence of AEs with the newer HPV was similar to that observed with the comparator vaccine.

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

IAP-ACVIP Recommendations for the new 4vHPV

- IAP-ACVIP strongly recommends the use of HPV vaccines.
- 9-14 y of age (boys and girls): Two-dose schedule (0.5 mL at 0 and 6 mo). The interval between the 1st and 2nd dose should not be < 5 mo.
- 15-26 y of age (females and males): 3-dose (0.5 mL at 0-2 mo-6mo) schedule. The second dose should be administered at least 1 month after the first dose and the third dose should be administered at least 3 months after the second dose.
- Not licensed beyond 26 y.

iii) Inactivated Hepatitis A vaccines: TZ84 strain

These vaccines are inactivated Hepatitis A vaccines derived from the TZ84 strain of Chinese origin. Healive (Sinovac) the original vaccine derived from the same strain, is a WHO prequalified vaccine. Vaccine bulk of Healive is imported and then fill-finished in Indian units to produce the vaccine.

Table III Comparison Between the new 4vHPV Vaccine and the Quadrivalent HPV Vaccine in 9-14 years of age

Serotype	*GMT ratio in Girls (98·75% CI)*	*GMT ratio in Boys (98·75% CI)*
HPV 6	0·95 (0·83-1·08)	0·90 (0·78-1·03)
HPV11	0·69 (0·61-0·78)	0·62 (0·54-0·71)
HPV 16	0·88 (0·76-1·01)	0·76 (0·65-0·88)
HPV 18	1·26 (1·09-1·46)	1·05 (0·91-1·22)

Composition: Each 0.5ml dose which is in a pre-filled syringe contains: Inactivated HAV antigen (TZ84): 250 u, aluminium hydroxide: 0.175 ~ 0.31 mg qs, disodium hydrogen phosphate: qs, sodium chloride: 4.5 mg, sodium dihydrogen phosphate: qs, water for injection: qs to 0.5 ml [35]. It is produced in human diploid cells.

Storage: The vaccine should be stored at +2°C to + 8°C and should not be frozen. Vaccine, if frozen should be discarded.

Shelf life: 3 y

Dosage and schedule: The vaccine is to be administered in a 2-dose schedule. The 1st dose should be administered after 12 months of age and the second dose is to be given 6 months later (i.e., 0, 6 months schedule). The vaccine is for intramuscular injection.

Clinical phase 3 study in India: In a phase 3 study done in India, 2 doses of the TZ84 strain vaccine, with inactivated Hepatitis A vaccine (HM175 strain) vaccine, as a comparator, administered IM 6 months apart, in two age cohorts (1-7 and 8-15 y), resulted in 100% seroconversion at day 210 following vaccination in both the groups. 75.54% subjects in the TZ84 group and 73.93% in the inactivated Hepatitis A vaccine (HM175 strain) group achieved > 4-fold increase in anti-HAV IgG antibodies concentration at day 210 from baseline, which were similar. A similar trend was also observed for TZ84 vaccine and inactivated Hepatitis A vaccine (HM175 strain) groups in the age subsets of 1-7 y (85.47% vs. 82.46%) and 8-15 y (65.52% vs. 65.83%). The GMC of anti-HAV IgG antibodies (mIU/mL) at day 210 was significantly higher in the TZ84 vaccine group compared with the inactivated Hepatitis A vaccine (HM175 strain) [40139.65 (95% CI: 32889.82, 48987.55) vs 18167.84 (95% CI: 14451.70, 22839.550] [36]. Overall, 11.35% of recipients reported any adverse effects (AEs); 10.77% in the TZ84 vaccine group and 11.92% in the inactivated Hepatitis A vaccine (HM175 strain) group. The majority of AEs were mild in severity. Injection site pain was the most common AE (reported in > 5% of subjects) in both TZ84 strain vaccine and inactivated Hepatitis A vaccine (HM175 strain) groups. The majority of AEs (89/93; 95.70%) were reported within 7 days of vaccination [36].

IAP-ACVIP Recommendations on New Inactivated Hepatitis A Vaccines

- These vaccines derived from TZ84 strain are recommended in children aged ≥ 12 mo, in a 2-dose schedule of 0-6mo.

iv) 14-valent Pneumococcal Polysaccharide Conjugate Vaccine

Composition: Each dose of 0.5 mL of this vaccine contains 3 µg *Pneumococcal* polysaccharide serotype 1, 2.2 µg each of *Pneumococcal* polysaccharide serotypes 3, 4, 5, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F, and 4.4 µg of *Pneumococcal* polysaccharide serotype 6B. It is adsorbed onto aluminium phosphate. The polysaccharides are conjugated to 20-50 µg of CRM197 [37].

Indications: It is indicated for the prevention of invasive pneumococcal disease caused by pneumococcal serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F from 6 weeks of age onwards.

Schedule: Primary immunization in a 6w-10w-14w schedule.

Contraindications: Known hypersensitivity to previous dose of vaccine or known hypersensitivity to any component of the vaccine.

Storage: At +2°C - +8°C. The vaccine should not be frozen. Any frozen vaccine should be discarded.

Clinical studies: A single blind randomized active-controlled phase 3 study to evaluate immunogenicity, safety, and tolerability of BE's 14-valent pneumococcal polysaccharide conjugate vaccine was administered to 6-8-week-old healthy Indian infants in a 3-dose (6 wk-10 wk-14 wk) primary dosing schedule, 0.5 mL per dose, intramuscularly. The comparator vaccine was PCV-13. A total of 1290 (645 in test vaccine arm, 645 in comparator arm) infants were enrolled from 15 sites across India. The primary end point was to demonstrate noninferiority of BE-PCV14 to PCV-13 in terms of proportion of subjects seroconverted (anti-PnCPS IgG titres ≥ 0.35 µg/mL) for the 12 common serotypes at day 86. BE-PCV 14 demonstrated noninferiority with PCV 13 with respect to proportion of subjects who seroconverted with anti-PnCPS IgG titres ≥ 0.35 µg/mL, on day 86 for the 12 common serotypes (unpublished data taken from product insert) [37].

For serotypes 22F and 33F (which are not part of PCV-13) seroconversion rate of the BE-PCV-14 group were compared with the lowest performing serotype in the PCV-13 group (ie, serotype 3). Comparison of the GMC titers and GMC ratios between BE-PCV-14 and PCV-13, showed was noninferiority of BE-PCV-14 to PCV-13 for all shared serotypes and against 2 unique serotypes (22F and 33F). Comparison of opsonophagocytosis assay (OPA) (proportion of subjects with OPA ≥ 1:8 lower limit of quantitation) and OPA GMT, showed was noninferiority of BE-PCV-14 to PCV-13 for all the 12 shared serotypes. The proportion of subjects with OPA ≥ 1:8, was 98.2% for ST 22F and 96.5% for ST 33F. 27% of subjects in the BE-PCV-14 group and 28% of subjects in the PCV 13 group showed adverse effects. In a safety and immunogenicity study in 12-23 months toddlers (phase 2), the SCR in the BE-PCV-14 group, were noninferior to the PCV 13 group [37].

IAP-ACVIP Recommendations on 14v Pneumococcal Polysaccharide Conjugate Vaccine

- IAP/ACVIP recommends the 14v Pneumococcal Polysaccharide Conjugate Vaccine for the prevention of invasive pneumococcal disease caused by pneumococcal serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F, in a 6wk-10wk-14wk schedule.
- This vaccine is presently not recommended for the booster dose in the 2nd year of life due to lack of adequate data.

v) Whole cell Pertussis (wP) containing Hexavalent Vaccine

This is a fully liquid vaccine which contains diphtheria and tetanus toxoids, pertussis (whole cell), hepatitis B (rDNA), poliomyelitis (inactivated) and Hemophilus influenzae type B conjugate vaccine.

Each 0.5 ml dose of this vaccine contains: diphtheria toxoid: ≥ 30 IU, tetanus toxoid: ≥ 40 IU, B. pertussis (whole cell): ≥ 4 IU, HBsAg (rDNA): 15 µg, Inactivated polio vaccine (Salk): Type 1: 40 DU, Type 2:8 DU, Type 3:32 DU, Hib PRP: 10 µg, conjugated to TT: 19-33 µg, Aluminium Phosphate ≤ 1.25 mg and 2-Phenoxyethanol 0.5%.

Indications: For the active immunization of infants beyond six weeks of age against diphtheria, tetanus pertussis, hepatitis B, poliomyelitis and invasive disease caused by *Hemophilus influenzae* type B. It is recommended for primary immunization, in a three-dose scheduled at 6wk-10 wk-14 wk.

Contraindications: Moderate to severe hypersensitivity reaction occurring after the previous administration of any dose of DPT containing vaccines. It is also contraindicated in those with known hypersensitivity to any of the vaccine constituents. It is also contraindicated in infants who developed an acute encephalopathy of unknown etiology, within seven days of previous administration of DPT containing vaccine. Infants with a progressive neurological illness or uncontrolled seizures should not receive this vaccine. Acute moderate to severe illnesses are a precaution for administration of this vaccine [38].

Clinical study: In a noninferiority phase 3 clinical trial, wP containing hexavalent vaccine was compared to simultaneously administered wP containing pentavalent vaccine and Injectable Polio vaccine of the same

manufacturer. The noninferiority criteria for all antigens were ~10%. The GMC for all antigens in infants, were comparable and establishing the noninferiority of the new wP containing hexavalent vaccine compared to wP containing pentavalent vaccine and Injectable Polio vaccine of the same manufacturer. No significant difference was reported in the incidence of local and systemic AEs [Unpublished data].

A phase 2 study done in toddlers to compare the safety, reactogenicity and immunogenicity of the new wP containing hexavalent vaccine compared to wP containing pentavalent vaccine and Injectable Polio vaccine of the same manufacturer administered simultaneously, showed noninferiority in seroconversion rates [Unpublished data].

IAP-ACVIP Recommendations on wP Containing Hexavalent Vaccine

- This vaccine is recommended for primary immunization against diphtheria, tetanus, pertussis, hepatitis, poliomyelitis and *Hemophilus influenzae* type B infections, in infants in a 6wk-10wk-14wk schedule. Sufficient data is not available regarding the use of this vaccine as a booster dose in the second year of life. IAP/ACVIP does not recommend this vaccine as a booster in the second year of life.

vi) Measles Mumps and Rubella (MMR) Vaccine Containing Hoshino Strain of Mumps

This is a live attenuated vaccine which consists of Edmonston Zagreb strain of measles virus propagated in human diploid cells, Hoshino strain of mumps virus propagated in chick fibroblast cells and RA27/3 strain of rubella virus propagated in human diploid cells. This is a freeze-dried vaccine (0.5 mL) vial, which comes with sterile water for injection, and is to be reconstituted before use [39].

Strength: Each dose of 0.5 mL of this vaccine contains not less than 1000 CCID50 live attenuated measles virus (*Edmonston zagreb* strain) propagated on human diploid cells, 5000 CCID50 live attenuated mumps virus (*Hoshino* Strain) propagated on chick fibroblast cells and 1000 CCID50 live attenuated rubella virus (RA27/3 Strain) propagated on human diploid cells.

Clinical indication: Indicated for active immunization against measles, mumps and rubella.

Contraindications: Subjects with moderate to severe allergic reaction to previous dose of the vaccine or known hypersensitivity to any other component of the vaccine, pregnancy. Pregnancy should be avoided for 1 month following vaccination, Moderate to severe immunosuppression due to drugs, radiation, advanced leukemia or lymphoma, serious malignant disease or some congenital disorders of immunity.

Clinical studies: The phase 2 study was done in 123 healthy children 15-18 months of age, who were administered a single dose of the Hoshino strain Measles Mumps and Rubella (MMR) vaccine from either the single-dose or the multi-dose formulations. The SCR for anti-measles and anti-mumps antibodies was 100% while that for anti-rubella antibodies was 98.9% after the MMR vaccination. Even in those seropositive prior to vaccination, SCR were 100% for measles and mumps and 99.1% for rubella. The GMT of anti-measles, anti-mumps and anti-rubella antibodies was 3154.0 mIU/mL, 90.6 EU/mL and 141.7 IU/mL, respectively. The vaccine was well tolerated, with 21.8% reporting some adverse event. The most common adverse event reported during the study was fever in 19 subjects (15.4%) followed by rash and rhinorrhoea in five subjects (4.1%) each [40].

The phase III clinical trial, conducted on 328 children of either sex, aged 15-18 months, was a noninferiority trial with the existing Indian MMR vaccine as the comparator vaccine. The seropositivity rates for measles was 100.0% in both groups, 94.5% vs. 94.0% for mumps and 95.5% vs. 91.0% for rubella [41].

Among the subjects seronegative at baseline, the seroconversion rates for the test vaccine and the comparator vaccine were 100.0% & 100% for measles, 94.0% & 93.3% for mumps, and 95.1% & 91.5% for rubella. The GMT for anti- measles antibodies at the end of the study was significantly greater in the test vaccine group (2355.5 mIU/mL) than in the comparator group (1448.1 mIU/mL) ($P < 0.01$). There was no difference in the adverse event profile of the two groups ($P > 0.05$). Most of the adverse effects were classified as “mild’ in intensity [41].

The results of this phase III clinical trial show that the test vaccine was noninferior to the comparator MMR vaccine and both had comparable, mild adverse effects profile.

IAP-ACVIP Recommendations on Hoshino Strain MMR Vaccine

- Since the phase 2 and 3 trials for this vaccine were done in children in age range of 15-18 months, there is immunogenicity or safety data available only in this age group. IAP/ACVIP recommends this vaccine to be used in children 15 -18 months of age.

vii) Recombinant Zoster Vaccine

The recombinant zoster vaccine (RZV) contains the gE antigen of the Varicella Zoster Virus (VZV), which is

obtained by culturing genetically engineered Chinese Hamster Ovary cells, which carry a truncated gE gene, in media containing amino acids, with no albumin, antibiotics, or animal-derived proteins. The gE protein is purified by several chromatographic steps, formulated with excipients, filled into vials, and lyophilized.

Composition: Each 0.5-mL dose contains: 50 µg of the r-gE antigen, 50 µg of MPL and 50 µg of QS-21. The vaccine does not contain any preservative [42].

Storage: The vaccine should be stored at +2°to +8°C, protected from light and should be discarded if frozen. After reconstitution, the vaccine should be administered immediately or stored refrigerated between 2° and 8°C (36° and 46°F) for up to 6 hours prior to use.

Schedule: *The* schedule consists of 2 doses; the first dose is followed by the 2nd dose, 2-6 month later, by IM route.

Contraindications: Hypersensitivity to the active substances or to any of the excipients.

This can be administered simultaneously with unadjuvanted inactivated seasonal influenza vaccine, 23-valent pneumococcal polysaccharide vaccine (PPV23) or Tdap. The vaccines should be administered at different injection sites [42].

Clinical Phase 3 studies: The ZOE-50 study was done in adults > 50 y. In this study, the overall vaccine efficacy (VE), in those > 50 y was 97.2% (95% CI, 93.7 to 99.0; *P* < 0.001), with similar VE in age groups 50-59 y, 60-69 y and > 70 y [43,44]. The ZOE-70 study was done in adults >70 y. In this study, the overall VE observed was 89.8% (84.2-93.7), with VE of 90.0% (83.5-94.4) in 70-79 y and 89.1% (74.6-96.2) in those > 80 y. The VE at the end of the 1st year was 97% (88.8-99.7) with a sustained VE of 85.1% (64.4-94.9) at the end of 4 y [45]. The VE against post-herpetic neuralgia (PHN) was 88.8% (68.7-97.1) in adults > 70 y and 91.2% (75.9-97.7) in those > 50 y. When the data of ZOE 50 & 70 were pooled, overall, VE was 91.3% (86.8 to 94.5), with similar VE in the 70-79 and > 80 y age groups. The pooled VE against PHN was 88.8% (68.7 to 97.1) in those > 70 y and 91.2% (75.9 to 97.7) in those > 50 y [46]. In the long term follow up study over 10 y, the overall VE from 1 month post-dose 2 was 89.0% (85.6-91.3). At the end of year 1 it was 97.7% (93.1-99.5), at year 6, 88.5% (74.9-95.6) and year 10, 73.2% (46.9-87.6) [47].

Efficacy of this vaccine in the immunocompromised has also been studied. In patients who had undergone an autologous bone marrow transplant, the overall VE was 68.2% (55.5-77.9). In the 18-49 y age group, the VE was 71.8% (38.7-88.3) and in those > 50 y, 67.3% (52.6-77.9). VE against PHN was 89.3% (95% CI: [22.5; 99.8]). In adults with hematological malignancies, the VE was 87.2% (95% CI: 44.3-98.6) [48].

Good humoral and cell mediated immunity (CMI) has been demonstrated in subjects with solid tumours, recipients of solid organ transplant, HIV, rheumatoid arthritis, inflammatory bowel disease, other acquired immunodeficiencies and chronic medical conditions.

All solicited reports of injection-site reactions including grade 3, and of systemic reactions including grade 3 were much higher in the vaccine group as compared to the placebo. However, the rate of all serious adverse events, potential immune-mediated diseases and death were similar in the vaccine and placebo groups.

In USA, in 2017, the vaccine was approved for adults > 50 y [49] and in 2021, for those > 18 y, who are or will be at increased risk of Herpes Zoster due to immuno-deficiency or immunosuppression caused by known disease or therapy [50].

IAP-ACVIP Recommendations on Recombinant Zoster Vaccine (RZV)

- ACVIP recommends the recombinant Zoster vaccine, to all immunocompetent adults aged ≥ 50 y, irrespective of prior receipt of varicella vaccine or zoster vaccine live (ZVL).
- It should be administered intramuscularly in a 2-dose schedule, with the 2nd dose administered 2-6 months after the first dose.
- If the 2nd dose is administered at an interval of < 4 weeks, it is an invalid dose and should be repeated at least 4 weeks after the early dose.
- For those who have received ZVL, RZV may be offered at least 2 months after the ZVL dose.
- RZV is recommended to those with past history of HZ. It may be administered any time after clinical recovery.
- Presently, in India, this vaccine is not recommended for individuals before 50 y of age.

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ANNEXURE I

Members who attended the physical meeting in Kolkata (March 25, 2023): Indra Shekhar Rao, Srinivas G Kasi, Arun Wadhwa, B Rajsekhar, Rajendra Khadke, Sanjay Lalwani, Bhaskar Shenoy, Ananda Kesavan TM, Srinivas Kalyani, Chandra Mohan Kumar, Kripasindhu Chatterjee, Vineet Saxena, Upendra Kinjawadekar, Basavaraja GV. Shashi Kant Dhir could not attend the meeting.

Members who attended the physical meeting in Aurangabad: Indra Shekhar Rao, Srinivas G Kasi, Shashi Kant Dhir, B Rajsekhar, Rajendra Khadke, Sanjay Lalwani, Bhaskar Shenoy, Ananda Kesavan TM, Srinivas Kalyani, Chandra Mohan Kumar, Kripasindhu Chatterjee, Vineet Saxena, Upendra Kinjawadekar, Basavaraja GV. Arun Wadhwa could not attend the meeting.