Indian Academy of Pediatrics (IAP) Advisory Committee on Vaccines and Immunization Practices (ACVIP): Recommended Immunization Schedule (2020-21) and Update on Immunization for Children Aged 0 Through 18 Years

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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:** Advisory Committee on Vaccines and Immunization Practices (ACVIP) of Indian Academy of Pediatrics (IAP) had a physical meeting in March, 2020 followed by online meetings (September-October, 2020), 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. **Objectives:** To review and revise the IAP recommendations for 2020-21 and issue recommendations on existing and new vaccines. **Recommendations**: The major changes include recommendation of a booster dose of injectable polio vaccine (IPV) at 4-6 years for children who have received the initial IPV doses as per the ACVIP/IAP schedule, re-emphasis on the importance of IPV in the primary immunization schedule, preferred timing of second dose of varicella vaccine at 3-6 months after the first dose, and uniform dosing recommendation of 0.5 mL (15 µg HA) for inactivated influenza vaccines.

Keywords: *Guidelines, Inactivated polio vaccine, Pneumococcal vaccine, Rabies vaccine, Varicella vaccine.*

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The Advisory Committee on vaccines and Immunization Practices (ACVIP) of the Indian Academy of Pediatrics met on 7 March, 2020, in Kolkata. ACVIP members and invitees who attended the meeting are listed in **Annexure I**. The aim of the meeting was to discuss and debate recent developments in the field of vaccinology, to issue the relevant recommendations based on them, and to revise IAP Immunization Timetable for the year 2020-21. 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 platform), in view of the prevailing corona virus disease 19 (Covid-19) pandemic and inability to have physical meetings.

PROCESS

The process for issuing recommendations included review of recent published literature including standard indexed journals, vaccine trials, recommendations of reputed international bodies like Advisory Committee on Immunization Practices, Center for Disease Control and Prevention (CDC), USA, World Health Organization (WHO) and 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 2020-2021 recommendations is given in **Box I**.

RECOMMENDATIONS

The ACVIP-IAP recommendations for the year

Box I Key Updates and Major Changes in Recommendations for IAP Immunization Timetable 2020/21

Polio immunization

- A booster of the injectable polio vaccine (IPV) is recommended at 4-6 years.
- The importance of IPV in the immunization schedule is re-emphasized.

Inactivated influenza vaccines

- A uniform dosing of 15 mcg (0.5 mL) of inactivated influenza vaccines is recommended for all children older than 6 months.

Varicella vaccine

- The second dose of varicella vaccine should preferably be administered 3-6 months after the first dose.

New vaccines introduction

- DTaP/IPV combination vaccine: Tetraxim
- Quadrivalent conjugate meningococcal vaccine: Menveo
- Monoclonal antibody cocktail for post exposure prophylaxis of rabies: Twinrab
- Conjugate (CRM 197) typhoid vaccine: Typhi BEV
- 10-valent pneumococcal conjugate vaccine: Pneumosil

2020-21 are being given in **Table I** and **Fig. 1**. The recommendations about the newly introduced vaccines are summarized in **Box II** and vaccines for high risk children are summarized in **Box III**.

Booster Dose of Injectable Polio Vaccine (IPV)

The last case of wild polio virus (WPV) in India was reported on 13 January, 2011 and on 27 March, 2014, India along with the rest of Southeast Asia was declared polio-free [1]. It needs to be emphasized that until worldwide polio eradication is achieved, cases of imported WPV from endemic neighboring countries or cases of circulating vaccine derived poliovirus (cVDPV), remains a real threat unless population immunity is maintained by vaccinating children adequately in their early years of life. Outbreaks of cVDPVs have occurred in countries which have been polio free for several years [2]. In the absence of inapparent infection, universal vaccination of infants and children is the only way to establish and maintain population immunity against polio. In 2018, the ACVIP had recommended an all IPV schedule at 6-10-14 weeks followed by an IPV booster at 15-18 months, and the recommendation for the OPV booster at 4-6 years was dropped [3]. A birth dose of OPV continues to be recommended.

IPV is immunogenic in an EPI schedule (6-10-14 weeks), but the titers achieved and the seroconversion rates are reported to be lower, compared with vaccination of infants at older ages (2-4-6 months) [4]. Studies examining the long-term persistence of antibodies following IPV vaccination, have shown persistence of antibodies only up to the school-entry age, with the highest titers observed with the 3+1 schedule [4], as all IPV using countries recommend a school age booster [5]. A pre-school booster resulted in SPR rising to 100% for

Box II IAP-ACVIP Recommendations on Newer Vaccines

- Approves the use of Menveo vaccine in the 2-55 years age group. It reiterates the use of this vaccine only in special situations, as published before [45].
- Approves the use of Typhibev vaccine for age >6 months and up to 45 years as single dose. There is no recommendation for a booster dose.
- Recommends the use of rabies mAbs over RIGs in the management of category 3 bites. Human monoclonal rabies antibody (Rabishield) and murine cocktail monoclonal rabies antibodies (Twinrab), both are available in India and approved for the post-exposure management of suspected rabies exposure.
- Approves the use of Tetraxim for the second booster of DPT/IPV at 4-6 years of age.
- Approves the use of Pneumosil till 2 years of age in a 3+1 schedule, with the booster administered between 12-18 months.
- In the absence of studies in the 2-5 years age group, the ACVIP does not presently recommend the use of Pneumosil beyond 2 years of age.

Box III IAP Recommended Vaccines for High-risk Children

Vaccines

1. Meningococcal vaccine
2. Japanese Encephalitis (JE) vaccines
3. Oral Cholera vaccine
4. Rabies vaccine
5. Yellow fever vaccine
6. Pneumococcal Polysaccharide vaccine (PPSV 23)

High-risk conditions

1. Congenital or acquired immunodeficiency (including HIV infection, immunosuppressive therapy, radiation)
2. Chronic cardiac conditions
3. Chronic pulmonary conditions (including asthma if treated with prolonged high-dose oral corticosteroids),
4. Chronic systemic diseases: Renal (including nephrotic syndrome), hematological, hepatic diseases, diabetes mellitus
5. Functional/ anatomic asplenia/hyposplenia
6. Cerebrospinal fluid leaks, cochlear implants; for pneumococcal infections

Specific high-risk groups

1. Children having pets in home: Rabies vaccine
2. JE endemic areas: Japanese encephalitis vaccine
3. During outbreaks: Oral cholera vaccine
4. For travelers Rabies vaccine, meningococcal vaccine, yellow fever vaccine

Table I IAP Immunization Timetable 2020/21: IAP Recommended Vaccines for Routine Use

Age	*Vaccine*	*Comments*
Birth	BCG OPV Hepatitis B-1 (BD)	BCG: before discharge OPV: as soon as possible after birth Hep B should be administered within 24 hours of birth
6 week	DTwP/DTaP-1 IPV-1 Hib-1 Hep B-2 Rotavirus-1 PCV-1	DTwP or DTaP may be administered in primary immunization IPV: 6-10-14 weeks is the recommended schedule. If IPV, as part of a hexavalent combination vaccine, is unaffordable, the infant should be sent to a government facility for primary immunization as per UIP schedule.
10 week	DTwP/DTaP-2 IPV-2 Hib-2 Hep B-3 Rotavirus-2 PCV-2	RV1: 2 -dose schedule; all other rotavirus brands: 3-dose schedule
14 week	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 month	Influenza (IIV)-1	Uniform dose of 0.5 ml for DCGI approved brands
7 month	Influenza (IIV)-2	To be repeated every year, in pre-monsoon period, till 5 y of age
6-9 month	Typhoid conjugate vaccine	As of available data, there is no recommendation for a booster dose
9 month	MMR -1	
12 month	Hepatitis A	Single dose for live attenuated vaccine
15 month	MMR-2, Varicella -1, PCV booster	
16-18 month	DTwP/DTaP-B1, Hib-B1, IPV-B1	
18-19 month	Hep A-2,Varicella-2	Only for inactivated Hep A vaccine
4-6 year	DTwP/DTaP-B2, IPV-B2, MMR-3	
10-12 year	Tdap, HPV	Tdap is to be administered even if it has been administered earlier (as DTP-B2) HPV: 2 doses at 6 mo interval between 9-14 y; 3 doses: from 15 y or immunocompromised of any age (0-1-6 mo for HPV2, 0-2-6 mo for HPV4)

Age in completed weeks/months/years.

all 3 serotypes and GMTs rising 32-fold to 55-fold for the 3 serotypes [6,7]. Following a pre-school booster, almost 100% SPR and high antibody titers persist for at least 5 years [8].

In the absence of a booster at 4-6 years, the seroprotection rates (SPR) against PV 1 and PV2 had fallen to 91% and 91.2% compared to a SPR of 100% in those who had received a school entry booster at 4-6 years [9]. There is low scientific evidence for ≥80% long-term (>5-10 years) persistence of protective antibodies following ≥3-4 doses of IPV before school age [10]. There are no studies regarding the long-term persistence of antibodies with the EPI schedule of 6-10-14 weeks or 2 doses of fractional doses intradermal IPV [4].

Some studies have suggested an inverse correlation between circulating levels of preexisting homotypic antibodies and excretion of poliovirus types 1, 2, and 3 following the administration of trivalent OPV, indicating better mucosal immunity with higher serum antibody titers [11]. There are no conclusive studies to demonstrate that the booster response occurs sufficiently rapidly to prevent re-infection or paralytic disease and that it is as effective as pre-existing immunity [12]. It has been recommended that "a minimal position

would be to recommend four to five doses of an IPV-containing vaccine with the last one administered at school-entry age" [4].

In a country like India, where risk of importation of polio virus (wild and cVDPV) is high, ACVIP re-emphasizes the use of OPV during national and subnational pulse polio days for all children. At this stage, these additional OPV doses in IPV primed children, will help in augmenting their gut immunity, which could be crucial for preventing circulation of polio virus.

ACVIP Recommendation

- A booster dose of IPV at 4-6 years of age for children who have received the initial IPV doses as per the ACVIP/IAP schedule.
- In case of non-availability of standalone IPV, this dose can be administered as a combination with DPT vaccines.

IPV in the Primary Immunization Schedule

In April 2016, a synchronous global switch was implemented from trivalent OPV (tOPV) to bivalent OPV (bOPV) in routine immunization programs. Simultaneously, IPV was introduced in the routine Immunization in all OPV-only using countries. Introduction of IPV was a risk mitigation strategy to overcome the risk associated with this switch. The switch was preceded by high quality SIAs with tOPV, to raise population immunity against type 2 PV [13]. Modelling studies done prior to the switch suggested that the risk of cVDPV would not last beyond a year and a half of the switch [14].

With a massive surge in requirements for IPV, a shortage resulted. According to the data published by the WHO, global coverage with one dose of IPV was about 50% in 2016, 60% in 2017, and only 72% in 2018 [15]. Thus, population immunity against PV type 2 has decreased, with resultant increase in cVDPV cases/outbreaks [16,17]. In 2017, there were two countries with cVDPV2 outbreaks with 96 cases; whereas, as of 13 October, 2020, worldwide there were 449 cases of cVDPV2 [18]. This data suggests that India is not free from the risks of cVDPV. In fact, India comes under the category of countries at high risk for cVDPV. Moreover, India has a long border with Pakistan, a country which is still endemic for WPW type 1. There is an imperative need to maintain population immunity against type 2 PV, which can only be achieved by administering IPV either in the IAP schedule or 2 doses of fractional dose intradermal IPV at 6 weeks and 14 weeks or a single dose of full-dose intramuscular IPV at 14 weeks. No child born after the switch should be left unprotected against type 2 PV.

ACVIP Recommendation

- No child should be administered only pentavalent vaccine and bOPV in infancy without IPV (two doses of fractional dose intradermal IPV at 6 weeks and 14 weeks or a single dose of full-dose intramuscular IPV/ hexavalent combination at 14 weeks). If hexavalent vaccines are unaffordable/unavailable, the infant must be referred to a government healthcare facility for the primary immunization as per UIP schedule.
- Infants and young children, born after the switch (25 April, 2016), who have not received IPV in any schedule, should receive at least one dose of an IPV/ IPV combination vaccine, intramuscularly, at the earliest opportunity.

Uniform Dosing for Inactivated Influenza Vaccines

Since the 1970s, when whole virion vaccines were in use, the standard-dose of IIVs in children less than 3 years of age has been 7.5 mcg per antigen, which is half the dose, given to older children and adults. As higher dose increased the reactogenicity, the lower dose was adopted to reduce reactogenicity and febrile convulsions observed with the whole virus vaccines that were in use at that time [19]. However, the immune response in young children was very variable, especially against the B strains in the vaccine. This was particularly significant in children younger than 3 years of age, who were vaccine-naïve [20]. Higher dose of 0.5 mL (15µg) in the 6-23 months age group is expected to result in higher levels of post vaccination HI antibody titer, which may result in increased efficacy [21]. Since, the complications of influenza are much higher in infants, studies were done to evaluate the safety, immunogenicity and superiority of full dose (0.5 ml; 15 µg) in the age group of 6-35 months to have uniform dosage recommendations in all age groups.

Studies have generally shown comparable reactogenicity and non-inferior immunogenicity with the full dose, in comparison with the half dose, in children 6-35 months of age [22-25]. Statistically superior immunogenicity was seen only in infants between 6-11 months of age, for H3N2 and B/Yamagata and not for H1N1 [25]. Superior GMTs were demonstrated against both vaccine B strains in children 6-17 months of age and unprimed children 6-35 months of age [24].

In children 6-35 months of age, the quadrivalent vaccine in a dose of 0.5 ml, demonstrated an efficacy of 63% (97·5% CI 52-72) against moderate-severe influenza, in a season when there was a 68% mismatch between the vaccine strains and the strains isolated in the study [25].

Several countries including USA, Finland, Australia,

UK, New Zealand and Canada have adopted a uniform dosage schedule for all age groups.

ACVIP Recommendation

- ACVIP endorses the use of a uniform dosing schedule of inactivated influenza vaccines (15 µg/0.5 mL) for all children older than 6 months.

So far, two brands, Influvac Tetra (Abbott) and Fluarix Tetra (Glaxo Smithkline) have received DCGI approval for this uniform dosage recommendation [26,27]. ACVIP endorses a dose of 0.5 mL per dose in children older than 6 months for these brands. Uniform dosage recommendations shall be extended to other brands also, once they get approval from the licensing authority (DCGI) in India. Till then, the manufacturer's age specific recommendations regarding dosage may be followed.

Second Dose of Varicella Vaccine

The timing of the second dose would depend on the relative contributions of primary and secondary vaccine failure to the incidence of breakthrough varicella. Primary vaccine failure could be defined as the failure to seroconvert or the failure to mount a protective immune response after vaccination despite seroconversion, whereas secondary vaccine failure is the gradual waning of immunity over time. Primary vaccine failure will favor an early second dose (few months after dose 1), whereas secondary vaccine failure will favor a delayed second dose (few years after dose 1).

Studies examining the immunological response to the second dose given after 6 weeks and given after 4-5 years have shown that the SPR (>5 U/mL by gpELIZA) are similar with both schedules, while the GMTs are higher with the longer interval schedule. However, the mean Stimulation Index (SI), which is a marker of the CMI is superior when the second dose is administered at 4-5 years [28,29]. Increases of GMTs by > 10-fold is observed following the second dose, irrespective of the interval between doses [30,31]. This is not seen with other viral vaccines. Such large increases suggest an inadequate priming and that the second dose is for completing the immune response initiated by the first dose.

Persistence of antibody in children after 1 dose of varicella vaccine has been demonstrated in both short-term and long-term follow-up studies [32-34], for periods as long as 9-20 years, with titers rising during the period of follow-up [32,34], indicating an absence of waning of antibody titers with time especially when there are occasions for natural boosting, thus suggesting a primary vaccine failure rather than waning immunity.

The highest incidence rate of breakthrough varicella was seen in the first 4-5 years after vaccination [35]. Vaccine effectiveness dropped from 97% in the first year post-vaccination to 86% in the second year and then remained stable till 8 years [36]. In a study from China, effectiveness was also shown to drop after the first year and then remain stable over the next 5 years [37]. These patterns are seen in primary vaccine failure, rather than waning immunity.

A single retrospective study has demonstrated an increasing incidence and severity over 10 years [38]. Some outbreak studies, which do not represent the entire population, have suggested waning immunity as a cause of vaccine failure [39].

Globally, as of end 2018, about 36 countries had included the varicella vaccine in their NIPs, about 23 have introduced a 2-dose schedule [40]. Approximately half of these 23 have preferred the shorter interval between doses.

Generally, there is more robust evidence for a primary vaccine failure following 1 dose of varicella vaccine and very limited evidence for secondary vaccine failure. A short interval between 2 doses of the varicella vaccine might be preferable to reduce breakthrough varicella, especially in countries with poor coverage and where the wild-type virus circulates predominantly. In India, in the bigger cities, 2-3 years is the usual entry age for pre-school. This may result in breakthrough varicella before the receipt of a delayed second dose. In India, varicella vaccine is not in the NIP and is recommended only by the IAP and the overall uptake is low and exposure to varicella following 1 dose may give rise to breakthrough varicella. Since the aim of varicella vaccination, in office practice, is the best possible protection for the individual child, an earlier second dose will be beneficial over a delayed second dose.

ACVIP Recommendation

- The second dose of varicella vaccine should be preferably administered 3-6 months after the first dose.

New Vaccines

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

Quadrivalent Conjugated Meningococcal Vaccine

The quadrivalent conjugate meningococcal vaccine, Menveo (Glaxo SmithKline) has been licensed by the Drug Controller General of India (DCGI). Menveo contains *N. meningitidis* serogroup A, C, Y, and W-135

Vaccine	Age in completed weeks/months/years															
	Birth	6w	10w	14w	6m	7m	9m	12m	13m	15m	16-18m	18-24m	2-3 Y	4-6 Y	9-14 Y	15- 18 Y
BCG																
Hepatitis B	HB 1[a]	HB 2	HB 3	HB 4[b]												
Polio	OPV	IPV 1[c]	IPV 2[c]	IPV 3[c]							IPV[c]B1			IPV[c]B2		
DTwP/DTaP		DPT 1	DPT 2	DPT 3							DPT B1			DPT B2		
Hib		Hib 1	Hib 2	Hib 3							Hib B1					
PCV		PCV 1	PCV 2	PCV 3				PCV B								
Rotavirus		RV 1	RV 2	RV 3[d]												
Influenza					Dose 1[e]	Dose 2	Annual Vaccination									
MMR							Dose 1			Dose 2				Dose 3		
TCV																
Hepatitis A								Dose 1				Dose 2[f]				
Varicella										Dose 1		Dose 2[g]				
Tdap[h]/Td																
HPV															1 & 2[j]	1, 2 & 3[j]
Meningococcal[k]							Dose 1	Dose 2								
JE								Dose 1	Dose 2							
Cholera								Dose 1	Dose 2							
PPSV 23																
Rabies																
Yellow Fever																

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

(a)To be given within 24 h after birth. When this is missed, it can be administered at first contact with health facility; (b) An extra dose of Hepatitis B vaccine is permitted as part of a combination vaccine when use of this combination vaccine is necessary; (c) IPV can be given as part of a combination vaccine; (d) 3rd dose of Rota vaccine is not necessary for RV1; (e) Influenza vaccine should be started after 6 mo of age, 2 doses 4 wks 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; after the age of 5y, this vaccine is recommended in the high-risk group only; (f) Single dose is to be given for the live attenuated Hepatitis A vaccine. The inactivated vaccine needs two doses; (g) 2nd dose of Varicella vaccine should be given 3-6 mo of age after dose 1. However, it can be administered anytime 3 mo after dose 1 or at 4-6 y; (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, irrespective of previous Tdap administration. If Tdap is unavailable/unaffordable, it can be substituted with Td; (i) Before 14 completed years, HPV vaccines are recommended as a 2-dose schedule, 6 mo apart; (j) From 15th y onwards and the immunocompromised subjects at all ages, HPV vaccines are recommended as a 3-dose schedule, 0-1-6 (HPV2) or 0-2-6 (HPV4); (k) Menactra is approved in a 2-dose schedule between 9-23 mo. Minimum interval between two doses should be 3 mo. Menveo is recommended as a single dose schedule after 2 y of age.

Fig. 1 ACVIP recommendations 2020-21.

oligosaccharides conjugated individually to *Corynebacterium diphtheriae* CRM197 protein. Each dose of vaccine contains 10 µg MenA oligosaccharide; 5 µg of each of MenC, MenY, and MenW- 135 oligosaccharides; and 32.7 to 64.1 µg of CRM197 protein [41].

In general, in pooled cohort of 2–10 years and 11-18 years age group, non-inferiority of MENVEO to MenACWY-DT (Menactra-Sanofi Pasteur Inc)was demonstrated for all serogroups. Persistence of antibodies were demonstrated in children and adolescents up to 5 years post-vaccination. Menveo demonstrated a favorable tolerability profile in all the age groups [42,43].

In the Indian licensure study, 72%, 95%, 94%, and 90% of subjects achieved a post-vaccination hSBA >8, for serogroups A, C, W, and Y, respectively, which were similar across all the 3 age groups [4]. Post-vaccination GMTs showed increases of 17-fold against serogroup A, 42-fold against serogroup C, 7-fold against serogroup W, and 15-fold against serogroup Y, compared to pre-vaccination GMTs. Post-vaccination GMTs were generally somewhat higher with increasing age. The vaccine was well tolerated with no safety concerns [44]. This vaccine is recommen-ded for use only in special situations, as published before [45].

Typhoid Conjugate Vaccine

Typhibev (Biological E vaccines) is a typhoid conjugate vaccine where the source of the Vi antigen is *C. frenundii*, which is in conformity with WHO specifications. Each dose of 0.5 ml contains Typhoid Vi Polysaccharide (produced from C. Freundii sensu lato 3056): 25 µg conjugated to 16.7 µg to 100 µg of CRM197 [46].

A multicentric phase II/III study showed that seroconversion (anti-Vi IgG >2 ug/ml) was obtained in 99% subjects (95%CI: 97.06, 99.79) in Typhibev compared to 99.4% in comparator group Typbar-TCV (Bharat Biolech India Limited). Non inferiority was established with comparator TCV. Anti Vi IgG >4.3 ug/ml (criteria defined for having sustained protection for at least 4 years) also fulfilled predefined non inferiority criteria. The side effects profile was comparable with the comparator vaccine [47].

Typhibev was licensed for use in India by DCGI in February, 2020; approved for those aged older than 6 months to 45 years, to be given in 0.5 mL single dose, intramuscular injection [46].

Monoclonal Antibody Cocktail for Post Exposure Prophylaxis Of Rabies

In the 2018-19 recommendations, the ACVIP, strongly endorsed the use of monoclonal antibodies (mAbs) for rabies post-exposure prophylaxis (PEP) [3,48]. Twinrab (Zydus Vaxxicare) is the second rabies mAb to receive DCGI approval. Twinrab is a combination of two murine anti-rabies mAb, docaravimab (62-71-3) and miromavimab (M777-16-3). The two mAbs individually bind to and neutralize both rabies and rabies-like virus strains isolated from canine, human, and bovine sources, preventing their entry into the neighboring cells [49].

In a phase 3, randomized study, comparing anti-rabies monoclonal antibody cocktail (Twinrab) against Human Rabies Immunoglobulin (HRIG), the GMTs of the antibodies induced with Twinrab were shown to be non-inferior to the antibodies induced with HRIG, with no statistically significant difference in the two groups and a similar adverse effect profile was seen in the two groups [50].

The recommended dose of Twinrab is 40 IU/kg of body weight. Twinrab is indicated for post exposure prophylaxis in individuals with suspected rabies exposure. Twinrab must always be used in combination with rabies vaccine as part of post-exposure prophylaxis in line with the recommendation of WHO [3,48].

DTaP/IPV Combination Vaccine

Tetraxim (Sanofi Pasteur) is a fully liquid, DTaP/IPV combination vaccine to be administered by intramuscular route. Each 0.5 ml dose contains: Diphtheria toxoid (≥30 IU), Tetanus toxoid (≥40 IU), *Bordetella pertussis* antigens: pertussis toxoid and filamentous haemagglutinin (25 µg each), inactivated poliomyelitis virus (type 1: 40 D antigen Units (DU), type 2:8 DU, type 3:32 DU [51].

In a review done over 619 subjects in five clinical studies, it was found the DTaP-IPV combination vaccine was highly immunogenic [52]. Tetraxim booster at 4-6 years of age has been shown to be associated with strong anamnestic responses to all antigens [6] and has been shown to be as immunogenic as DTwP-IPV when given as a school-entry booster [7]. The vaccine induced seroprotective titers (>0.01IU/mL) against diphtheria and tetanus, persist till at least 5 years after the pre-school booster [8].

10-Valent Pneumococcal Conjugate Vaccine

Pneumosil (Previously SIIPL-PCV) (Serum Institute of India Pvt Ltd Pneumococcal Conjugate Vaccine) is a pneumococcal polysaccharide conjugate vaccine that has been pre-qualified for use by WHO on 18 December, 2019 [53]. This is the third pre-qualified PCV vaccine after Prevenar-13 (Pfizer) and Synflorix (GSK vaccines).

Pneumosil is a pneumococcal polysaccharide

conjugate vaccine containing saccharides of the capsular antigens of *Streptococcus pneumoniae* serotypes 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, and 23F, conjugated using CDAP (1-cyano-4-dimethylamino pyridinium tetrafluoroborate chemistry) and chemically activated. Each dose of 0.5 ml vaccine contains 2 µg each of serotypes 1, 5, 9V, 14, 19A, 19F, 23F, 7F, 6A and 4 µg of serotype 6B conjugated to non-toxic diphtheria CRM197 carrier protein: 19-48 mcg [53]. It is available as a ready to use vial containing vaccine in liquid form with a vaccine vial monitor [54].

In the phase 1/2 study done in Gambia, in infants, seroprotection rates (SPR) of >90% was observed for all serotypes with PCV 13 following the primary immunization, whereas SPR of > 90% was observed for all serotypes except serotypes 6A and 6B, following SIIPL-PCV. Serotype-specific IgG GMCs estimates after the primary series were above 1 mg/mL for all serotypes following both vaccines. The serotype-specific OPA GMTs following the primary series were comparable for the two vaccines for six (1, 5, 6B, 14, 19F, and 23F) of 10 serotypes, while the responses were lower following SIIPL-PCV^{TM} for the remaining 4 serotypes [55].

A significant booster response (except for type 5) was noted with both vaccines in children primed at 6-10-14 weeks with the SIIPL-PCV and the comparator vaccines. The magnitude of the booster response was higher for 1, 6B, 9V, 19A, and 23F with SIIPL-PCV, while it was higher for 5, 19A and 19F with PCV 13. The OPA GMTs following the booster vaccination in toddlers were generally comparable with both vaccines [55].

In comparison with Synflorix, both vaccines elicited a significant booster immune response for all 10 serotypes except serotype 5, while the OPA GMTs showed a booster response for all 10 serotypes. Persistence of antibodies was seen for all serotypes till 1 year of follow up [56].

The DCGI has approved it for active immunization against invasive disease and pneumonia caused by *Streptococcus pneumoniae* serotypes 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F and 23F in infants from 6 weeks of age group for three dose regimen (dosing schedule: 6, 10 and 14 weeks) [57]. The WHO has approved it for active immunization against invasive disease, pneumonia and acute otitis media caused by *Streptococcus pneumoniae* serotypes 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F and 23F, till the age of 2 years [58].

Competing interests: Representatives of a few vaccine manufacturing companies also presented their data in the consultative meetings. None were involved in formulating the recommendations. *Funding*: None. The first physical meeting was held during Vaccicon 2020 at Kolkata. The organizers provided the premises for the meeting. Indian Academy of Pediatrics provided the online platform for subsequent online meetings.

REFERENCES

1. GPEI-How India Eradicated Polio [Internet]. [cited 2020 Nov 23]. Available from: *https://polioeradication.org/news-post/how-india-eradicated-polio-challenges-and-lessons-learned/*
2. Chard AN, Datta SD, Tallis G, et al. Progress Toward Polio Eradication - Worldwide, January 2018-March 2020. MMWR Morb Mortal Wkly Rep. 2020 26;69:784-9.
3. Balasubramanian S, Shah A, Pemde HK, et al. Indian Academy of Pediatrics (IAP) Advisory Committee on Vaccines and Immunization Practices (ACVIP) Recommended Immunization Schedule (2018-19) and Update on Immunization for Children Aged 0 Through 18 Years. Indian Pediatr. 2018;55:1066-74.
4. Emmanuel Vidor. Polio vaccines- Inactivated. *In:* Plotkin SA, Offit PA, Orenstein WA, Edwards KM editors. Plotkin's Vaccines. 7th ed. Philadelphia: Elsevier; 2018. p.841-65.
5. Rennels MB. Need for polio boosters after age two years. Vaccine. 2009;27:179-80.
6. Mallet E, Matisse N, Mathieu N, et al. Antibody persistence against diphtheria, tetanus, pertussis, poliomyelitis and Haemophilus influenzae type b (Hib) in 5-6-year-old children after primary vaccination and first booster with a pentavalent combined acellular pertussis vaccine: immunogenicity and tolerance of a tetravalent combined acellular pertussis vaccine given as a second booster. Vaccine. 2004;22:1415-22.
7. Langue J, Matisse N, Pacoret P, et al. Persistence of antibodies at 5-6 years of age for children who had received a primary series vaccination with a pentavalent wholecell pertussis vaccine and a first booster with a pentavalent acellular pertussis vaccine: immunogenicity and tolerance of second booster with a tetravalent acellular vaccine at 5-6 years of age. Vaccine. 2004 Mar 29;22(11-12):1406-14.
8. John T, Voysey M, Yu LM, et al. Immunogenicity of a low-dose diphtheria, tetanus and acellular pertussis combination vaccine with either inactivated or oral polio vaccine compared to standard-dose diphtheria, tetanus, acellular pertussis when used as a pre-school booster in UK children: A 5-year follow-up of a randomised controlled study. Vaccine. 2015;33:4579-85.
9. Zinke M, Disselhoff J, DTP a-HBV-IPV-110 and -111 study groups, Gartner B, Jacquet J-M. Immunological persistence in 4-6 and 7-9 year olds previously vaccinated in infancy with hexavalent DTPa-HBV-IPV/Hib. Hum Vaccin. 2010;6:189-93.
10. Persistence of protective antibodies following immunization with IPV. Accessed on October 27, 2020. Available at *https://www.who.int/immunization/polio_grad_duration_protection pdf?ua=1#:~:text=High%20scientific%20evidence%20for%20%E2%89%A5,%2D%E2%80%90%204%20doses%20of%20OPV.&text=of%20OPV%20in%2067%20children,all%20three%20types%20of%20poliovirus*
11. Glezen WP, McCollough RH, Lamb GA, Chin TD. Quantitative relationship of preexisting homotypic antibodies to excretion of poliovirus types 1, 2, and 3 following the feeding of trivalent attenuated poliovirus vaccine. Am J Epidemiol. 1969;90:146-56.
12. Abbink F, Buisman AM, Doornbos G, Woldman J, Kimman TG, Conyn-van Spaendonck MAE. Poliovirus-specific memory immunity in seronegative elderly people does not protect against virus excretion. J Infect Dis. 2005;191:990-9.
13. Meeting of the Strategic Advisory Group of Experts on immunization, October 2015 – conclusions and recommendations. Releve Epidemiol Hebd. 2015;90:681-99.
14. Thompson KM, Duintjer Tebbens RJ. Modeling the dynamics

of oral poliovirus vaccine cessation. J Infect Dis. 2014;210 Suppl 1:S475-484.
15. UNICEF, WHO. Progress and Challenges with Achieving Universal Immunization Coverage [Internet]. [cited 2020 Oct 30]. Available from: *https://www.who.int/publications/m/item/progress-and-challenges-with-achievinguniversalimmunization coverage*
16. Huyen DTT, Mach O, Thanh Trung N, et al. Rapid Disappearance of Poliovirus Type 2 (PV2) Immunity in Young Children Following Withdrawal of Oral PV2-Containing Vaccine in Vietnam. J Infect Dis. 2019; 220:386-91.
17. Yan D, Wang D, Zhang Y, et al. Implication of a High Risk of Type 2 Vaccine-Derived Poliovirus Emergence and Transmission after the Switch from tOPV to bOPV. J Infect Dis. 2020; jiaa386.
18. GPEI-Circulating vaccine-derived poliovirus [Internet]. [cited 2020 Oct 30]. Available from: *https://polioeradication.org/polio-today/polio-now/this-week/circulating-vaccine-derived-poliovirus/*
19. Wright PF, Dolin R, La Montagne JR. From the National Institute of Allergy and Infectious Diseases of the National Institutes of Health, the Center for Disease Control, and the Bureau of Biologics of the Food and Drug Administration. Summary of clinical trials of influenza vaccines–II. J Infect Dis. 1976; 134:633–8.
20. Walter EB, Rajagopal S, Zhu Y, Neuzil KM, Fairchok MP, Englund JA. Trivalent inactivated influenza vaccine (TIV) immunogenicity in children 6 through 23 months of age: do children of all ages respond equally? Vaccine. 2010; 28:4376-83.
21. Black S, Nicolay U, Vesikari T, et al. Hemagglutination inhibition antibody titers as a correlate of protection for inactivated influenza vaccines in children. Pediatr Infect Dis J. 2011;30: 1081-5.
22. Skowronski DM, Hottes TS, Chong M, et al. Randomized controlled trial of dose response to influenza vaccine in children aged 6 to 23 months. Pediatrics. 2011;128:e276-289.
23. Jain VK, Domachowske JB, Wang L, et al. Time to Change Dosing of Inactivated Quadrivalent Influenza Vaccine in Young Children: Evidence From a Phase III, Randomized, Controlled Trial. J Pediatr Infect Dis Soc. 2017;6:9-19.
24. Robertson CA, Mercer M, Selmani A, Klein NP, Jeanfreau R, Greenberg DP. Safety and Immunogenicity of a Full-dose, Split-virion, Inactivated, Quadrivalent Influenza Vaccine in Healthy Children 6-35 Months of Age: A Randomized Controlled Clinical Trial. Pediatr Infect Dis J. 2019;38:323–8.
25. Claeys C, Zaman K, Dbaibo G, et al. Prevention of vaccine-matched and mismatched influenza in children aged 6-35 months: a multinational randomised trial across five influenza seasons. Lancet Child Adolesc Health. 2018;2:338-49.
26. Influvac Tetra 2020/2021 Product Information. Accessed on October 27, 2020. Available at: *https://www.mylan.ca/-/media/mylanca/documents/english/product-pdf/influvac-tetra-pm-en.pdf?la=en-ca*
27. FLUARIX-TETRA 2020/2021 North. Product information. Assessed on October 27,2020. Available at *https://india-pharma.gsk.com/media/850622/fluarix-tetra.pdf*
28. Watson B, Rothstein E, Bernstein H, et al. Safety and cellular and humoral immune responses of a booster dose of varicella vaccine 6 years after primary immunization. J Infect Dis. 1995; 172:217-9.
29. Nader S, Bergen R, Sharp M, Arvin AM. Age-related differences in cell-mediated immunity to varicella-zoster virus among children and adults immunized with live attenuated varicella vaccine. J Infect Dis. 1995;171:13-7.
30. Kuter B, Matthews H, Shinefield H, et al. Ten year follow-up of healthy children who received one or two injections of varicella vaccine. Pediatr Infect Dis J. 2004;23:132-7.
31. Ngai AL, Staehle BO, Kuter BJ, et al. Safety and immuno-genicity of one vs. two injections of Oka/Merck varicella vaccine in healthy children. Pediatr Infect Dis J. 1996;15:49-54.
32. Shinefield H, Black S, Digilio L, et al. Evaluation of a quadrivalent measles, mumps, rubella and varicella vaccine in healthy children. Pediatr Infect Dis J. 2005;24:665-9.
33. Johnson CE, Stancin T, Fattlar D, Rome LP, Kumar ML. A long-term prospective study of varicella vaccine in healthy children. Pediatrics. 1997;100:761-6.
34. Asano Y, Nagai T, Miyata T, et al. Long-term protective immunity of recipients of the OKA strain of live varicella vaccine. Pediatrics. 1985;75:667-71.
35. Baxter R, Ray P, Tran TN, et al. Long-term effectiveness of varicella vaccine: a 14-Year, prospective cohort study. Pediatrics. 2013;131:e1389-1396.
36. Vázquez M, LaRussa PS, Gershon AA, et al. Effectiveness over time of varicella vaccine. JAMA. 2004;291:851-5.
37. Fu C, Wang M, Liang J, Xu J, Wang C, Bialek S. The effectiveness of varicella vaccine in China. Pediatr Infect Dis J. 2010;29:690-3.
38. Chaves SS, Gargiullo P, Zhang JX, et al. Loss of vaccine-induced immunity to varicella over time. N Engl J Med. 2007;356: 1121-9.
39. Bayer O, Heininger U, Heiligensetzer C, von Kries R. Metaanalysis of vaccine effectiveness in varicella outbreaks. Vaccine. 2007; 25:6655-60.
40. Varela FH, Pinto LA, Scotta MC. Global impact of varicella vaccination programs. Hum Vaccines Immunother. 2019;15: 645-57.
41. Menveo product monogram. Accessed on July 21 2020. Available at *https://india-pharma.gsk.com/media/870843/menveo. pdf*
42. Halperin SA, Gupta A, Jeanfreau R, et al. Comparison of the safety and immunogenicity of an investigational and a licensed quadrivalent meningococcal conjugate vaccine in children 2-10 years of age. Vaccine. 2010;28:7865-72.
43. Jackson LA, Baxter R, Reisinger K, et al. Phase III comparison of an investigational quadrivalent meningococcal conjugate vaccine with the licensed meningococcal ACWY conjugate vaccine in adolescents. Clin Infect Dis Off Publ Infect Dis Soc Am. 2009;49:e1-10.
44. Lalwani S, Agarkhedkar S, Gogtay N, et al. Safety and immunogenicity of an investigational meningococcal ACWY conjugate vaccine (MenACWY-CRM) in healthy Indian subjects aged 2 to 75 years. Int J Infect Dis IJID Off Publ Int Soc Infect Dis. 2015;38:36-42.
45. Vashishtha VM, Choudhury P, Kalra A, et al. Indian Academy of Pediatrics (IAP) recommended immunization schedule for children aged 0 through 18 years–India, 2014 and updates on immunization. Indian Pediatr. 2014;51:785-800.
46. Typhibev Product Insert. Accessed on October 27, 2020. Available from: *https://www.biologicale.com/pdf/Product_VB_International_Marketing.pdf*
47. Siddalingaiah N, Tuluva T, Turaga K, et al. A multicentre single blind randomised controlled phase-II/III study to evaluate immunogenicity and safety of single intramuscular dose of biological e's vi-capsular polysaccharide-CRM197 conjugate typhoid vaccine in healthy infants, children and adults in comparison with a licensed comparator. IAP ResRCHcon 2020 Abstracts. Indian J Pediatr. 2020; 87:974-88.
48. World Health Organization null. Rabies vaccines: WHO position paper, April 2018 - Recommendations. Vaccine. 2018;36:5500-3.
49. Twinrab. Package Insert. Accessed on October 27, 2020. Available from: *https://twinrab.com/*
50. Kansagra K, Parmar D, Mendiratta SK, et al. A phase 3,

randomised, open-label, non-inferiority trial evaluating anti- rabies monoclonal antibody cocktail (TwinrabTM) against human rabies immunoglobulin (HRIG) [published online ahead of print, 2020 Jun 17]. Clin Infect Dis. 2020; ciaa779.
51. Tetraxim. Package Insert. Accessed on: October 27, 2020. Available from: *https://www.sanofi.in/-/media/Project/One-Sanofi-Web/Websites/Asia-Pacific/Sanofi-IN/Home/science-and-innovation/for-healthcare-professionals/product-information/Tetraxim-API.pdf?la=en*
52. Jacquet JM, Bégué P, Grimprel E, et al. Safety and immunogenicity of a combined DTPa-IPV vaccine administered as a booster from 4 years of age: a review. Vaccine. 2006;24:2440-8.
53. Ma C, Park JY, Montgomery EA, et al. A Comparative Clinicopathologic Study of Collagenous Gastritis in Children and Adults: The Same Disorder With Associated Immune-mediated Diseases. Am J Surg Pathol. 2015; 39:802-12.
54. Gavi-supported PCV profiles to support country decision making Pneumococcal and Rotavirus Working Group Gavi Secretariat and partners, July 2020. Accessed October 30,2020. Available at *https://www.gavi.org/sites/default/files/document/2020/Gavi-PCV-vaccines-profiles-july-2020.pdf*
55. Clarke E, Bashorun AO, Okoye M, et al. Safety and immunogenicity of a novel 10-valent pneumococcal conjugate vaccine candidate in adults, toddlers, and infants in The Gambia-Results of a phase 1/2 randomized, double-blinded, controlled trial. Vaccine. 2020;38: 399-410.
56. Phase 3 Study of 10-valent Pneumococcal Conjugate Vaccine (PNEUMOSIL) in Healthy Infants - Full Text View - ClinicalTrials.gov [Internet]. [cited 2020 Oct 25]. Available from: *https://clinicaltrials.gov/ct2/show/NCT03197376*
57. Pneumosil [DCGI Package insert].Mumbai, India: Serum Institute of India Pvt Ltd; 2020.
58. Pneumosil [WHO Package insert]. Mumbai, India: Serum Institute of India Pvt Ltd; 2020. Accessed on: October 27, 2020. Available from: *https://www.path.org/media-center/new-pneumococcal-vaccine-serum-institute-india-achieves-who-prequalification/*

ANNEXURE I

Members Who Attended the Physical Meeting in Kolkata (7 March, 2020)

(in alphabetical order)

Abhay K Shah, Bakul J Parekh, G V Basavaraja, Kripasindhu Chatterjee, S Balasubramanian, S Shivananda, Sanjay Marathe, Sanjay Srirampur, Shashi Kant Dhir, Srinivas Kalyani, Srinivas G Kasi, Sunil Agarwalla, Rohit Aggarwal (*Special invitee*).

Piyush Gupta and Sanjay Verma could not attend the meeting.

developing countries. There is also a lack precise knowledge on the disease among pediatricians. Other challenges include paucity of trained personnel to