

## **Introduction of Inactivated Poliovirus Vaccine in National Immunization Program and Polio Endgame Strategy**

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The World Health Organization declared India – among other 10 countries in South East Region – as 'polio-free' in 2014. Since then, the Government of India (GoI) has scaled up its initiatives against polio endgame which targets virus eradication and sequential withdrawal of type 2 virus from oral polio vaccine (OPV). However, prior to choosing the switch from trivalent OPV (t-OPV) to bivalent OPV (b-OPV), it was suggested to include inactivated poliovirus vaccine (IPV) in the national immunization schedule to protect vaccine naïve population against type 2 poliovirus. The GoI declared introduction of single dose of intramuscular IPV at 14 weeks since October 2015. In addition, anticipating the scarcity of IPV at present in India, GoI also recommended two intradermal doses of IPV in few states since April 2016. This review discusses the programmatic implications of these strategies along with recommendations by the Advisory Committee on Vaccines and Immunization Practices of Indian Academy of Pediatrics (IAP-ACVIP) on polio endgame strategy.

**Keywords:** *Eradication, Global polio eradication initiative, oral poliovirus vaccine, Poliomyelitis, Prevention.*

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**I**n January 2013, the Global Polio Eradication Initiative (GPEI) launched the Polio Eradication and Endgame Strategic Plan 2013-2018, which was developed with an approach to tackle both wild and vaccine virus eradication in parallel rather than sequential manner [1]. In the November 2013 meeting, the Strategic Advisory Group of Experts (SAGE) on immunization recommended a global, coordinated withdrawal of the type 2 component of trivalent oral polio vaccine (tOPV) from immunization programmes by April 2016. For countries which use only tOPV in their routine infant immunization programmes, this will require switching from tOPV to bOPV (containing only types 1 and 3) for that purpose [2]. Prior to this switch, SAGE recommends that all countries introduce at least one dose of inactivated poliovirus vaccine (IPV) into their infant immunization schedules as a risk mitigation measure by providing immunity in case a type 2 poliovirus re-emerges or is reintroduced [2]. Initially, the plan stresses the need to introduce IPV at least 6 months in advance to the proposed switch date in order to provide adequate time to enhance population immunity against type 2 [1]. SAGE recommends that one dose of IPV should be administered at or after 14 weeks of age through routine immunization (RI), in addition to the 3-4 doses of OPV. The group also offers flexibility to countries to consider alternative schedules (*e.g.* earlier IPV administration)

based on local conditions; for example, documented risk of vaccine-associated paralytic poliomyelitis (VAPP) prior to 4 months of age [2].

Three main risks are identified following type 2 poliovirus removal. These include immediate time-limited risk of circulating vaccine-derived poliovirus type 2 (cVDPV2) emergence; medium- and long-term risks of type 2 poliovirus re-introduction from a vaccine manufacturing site, research facility, diagnostic laboratory or a bioterrorism event; and spread of virus from rare immune-deficient individuals who are chronically infected with OPV2 [3]. All these risks have the potential to cause substantial polio outbreaks or even re-establishment of polio virus transmission in polio-free regions.

### **GOVERNMENT OF INDIA INITIATIVES**

Following SAGE recommendations and GPEI directives, the Government of India (GoI) has taken following decisions regarding polio immunization during implementation of endgame strategies in India:

- Introduction of at least single dose of intramuscular IPV (IM-IPV) administration at 14 weeks or first contact afterwards in the RI along with 3rd dose of DTP in 6 states *viz* Bihar, Uttar Pradesh, Madhya Pradesh, Gujarat, Punjab and Assam [4];

- Nationally coordinated switch from tOPV to bOPV all over the country on 25th April 2016 associated with cessation of use, withdrawal, destruction and validation of all available tOPV stocks from all over the country [5].
- Introduction of fractional dose (0.1 mL) intradermal IPV (ID-fIPV) at 6 and 14 weeks in Orissa, Andhra Pradesh, Telangana, Tamil Nadu, Kerala, Karnataka, Maharashtra and Puducherry from April, 2016 [6]. This change in approach from single-dose intramuscular IPV to fractional-dose intradermal IPV is mainly due to scarcity of IPV.

**PERSPECTIVES OF ADVISORY COMMITTEE OF VACCINES AND IMMUNIZATION PRACTICES (ACVIP) OF INDIAN ACADEMY OF PAEDIATRICS (IAP)**

*Role of IPV in raising population immunity against type 2 poliovirus before the ‘switch’*

The GPEI has recommended introduction of IPV in RI well-before (*i.e.* six months prior) to the proposed ‘switch’ in order to raise population immunity against type 2 [1]. The committee has reviewed the practical aspects of this decision and concludes that the impact of IPV would not be significant in raising population immunity against type 2 virus before the ‘switch’. There are many states that have not yet introduced IPV in their immunization schedules. On the other hand, there is no data regarding the coverage of single dose of IPV from the Indian states that have already introduced the vaccine. The ‘population immunity’ is a product of IPV immunogenicity and coverage. Hence, the immunity provided by tOPV, through RI and supplementary immunization activities (SIAs) would ultimately determine the population immunity against type 2 poliovirus prior to proposed global switch to bOPV from tOPV. The committee believes that a high performance round with tOPV would have benefitted more than IPV introduction to raise population immunity against type 2 before the switch. In recent trials, tOPV is found to be more immunogenic than IPV against type 2 poliovirus [7].

*Single dose of intramuscular IPV at 14 weeks: Will it be effective?*

The ACVIP has also reviewed the decision to administer a single dose of IM-IPV at 14 weeks. It believes that the combined schedule of bOPV and IPV shall provide adequate protection against type 1 and 3 polioviruses; however, it is the protection against type 2 polioviruses, especially for the children born post-switch that should be the major concern. A single dose of IPV at 14 weeks may not provide adequate seroconversion, especially against

type 2 in the vaccinees. The committee reiterates its earlier recommendation that at least two doses of IPV – given at or after 8 weeks of age with 8 week interval – are mandatory to provide adequate seroprotection to all the three serotypes of poliovirus [8]. A recent systematic review conducted on immunogenicity and effectiveness of 1 or 2 doses of IPV vaccine has also reaffirmed ACVIP’s above recommendations. The review concludes that routine immunization with two full or fractional doses of IPV given after 10 weeks of age is likely to protect >80% of recipients against all types of polioviruses [9]. According to this review, one and two full doses of intramuscular IPV seroconverted 41% and 80% subjects, respectively, against serotype 2 [9]. The GPEI’s decision of introducing a single dose of IPV is based on a Cuban study [10] in which 63% of subjects seroconverted to a single dose when given at 4 months of age and among those who did not seroconvert (37%), 98% had a priming response to a subsequent dose of IPV [10]. However, there are certain issues that deserve attention. First, there is no incontrovertible proof of reasonably good seroconversion of single dose of IPV at 14 weeks. In the Cuban trial, the first dose of IPV was given at 4 months, not at 14 weeks. It is not yet clear whether immunological priming after a single dose of IPV is protective against paralytic disease. Another risk would be leaving children ‘unprotected’ against type 2 for first 3-4 months of life. Further, the coverage attained with 14-week IPV dose would be considerably less than at 6 weeks, considering the current ‘drop-out’ rates of DTP 3. A recent study from Bangladesh [7] revealed promising degree of priming with an early (6 week) dose of IPV. The cumulative effect of one dose given at 6 weeks (seroconversion and priming) was seen in 90.2% of subjects [7]. The committee opines that decisions having far reaching impact on global health should have broader evidence base; solely relying on few studies may prove perilous.

*Intradermal fractional doses of IPV at 6 and 14 weeks: IAPACVIP’s viewpoint*

The ACVIP has not yet approved the use of intradermal fractional-dose IPV (ID-fIPV) for office-practice. However, in wake of recent developments, the committee has reviewed all the available recent studies on immunogenicity and priming of ID-fIPV [7,10-14] (**Table I**). Most of these studies have reported lower immunogenicity of a one-fifth (*i.e.* 0.1 mL) ID-fIPV dose compared with full dose (*i.e.* 0.5 mL) IM-IPV. Also, the geometric mean titers (GMTs) of poliovirus-specific serum neutralizing antibodies were found significantly lower than full dose IM-IPV [7,10-14]. Seroconversion appears to be dependent on the age at administration of

**TABLE I** SEROCONVERSION AFTER TWO INTRADERMAL FRACTIONAL (1/5TH) DOSE OF INACTIVATED POLIOVIRUS VACCINE (ID-fIPV)

Reference	Place	Schedule (age at doses)	Age at which SC measured	Mode of delivery (of ID-fIPV)	Number of participants	SC by serotype* (%) (After 1st dose)			SC by serotype* (%) (After 2nd dose)		
						P1	P2	P3	P1	P2	P3
Nirmal, <i>et al.</i> 1998 [11]	India	6, 14 wks	18 wk	Needle & syringe	30	-	-	-	90	70	97
Resik, <i>et al.</i> 2010 [12]											
Cuba	6, 10 wks	10 and 14 wk	Biojector 2000	187	5	19	7	27	55	43	
Mohammed, <i>et al.</i> 2010 [13]	Oman	2 mo, 4 mo	4 and 6 mo	Biojector 2000	186	10	17				
	9	70	72								
Estívariz, <i>et al.</i> 2012 [14]**	India	6-9 mo	4 wks later	PharmaJet	Variable#	100#	59	36	-	-	-
Resik, <i>et al.</i> 2013 [10]	Cuba	4 mo, 8 mo	8 and 9 mo	Biojector 2000	157	17	47	15	94	98	93
Anand, <i>et al.</i> 2015 [7]	Bangladesh	6, 14 wks	14 and 18 wk	MicronJet 600	155	13	19	14	88	81	89

SC: Seroconversion; ID-fIPV: Intradermal fractional dose IPV; \*Definition of seroconversion: 4-fold increase in serum neutralising antibodies over expected titre based on 28-30 day half-life of maternal antibodies, or a change from undetectable to detectable antibodies; \*\*In this study conducted in Moradabad, India, the enrolled subjects had already received multiple doses of OPV; #A single dose of fIPV was given to 6-9 mo old children. The above figure shows seroconversion of seronegative children. In type 1 group, only 1 child was seronegative; in type 2 and type 3 groups, 41 and 78 children were seronegative, respectively. In children who were type-1 seropositive, an increase of more than four times in antibody titre was detected 56% (9/16) subjects 28 days after they were given intradermal IPV.

the first dose and the interval between the doses. However, despite limited seroconversion with first dose, a considerable priming responses were observed even after one dose of ID-fIPV given at different ages [7,10]. In all of these studies, barring one [11], different types of needle-free devices (jet injectors or micro-needle based devices) were utilized to deliver ID dose of IPV. In the Indian study conducted in Vellore [11], needle and syringes were used to deliver ID-fIPV. In this study, the seroconversion against type 2 poliovirus after 4 weeks of 2nd dose at 14 weeks was 70% [11].

The recent recommendation of GPEI/GoI to use fractional dose IPV by ID route is based on the trial done in Bangladesh [7]. In this study, ID-fIPV failed the non-inferiority test (*i.e.* with a non-inferiority margin of 10% in seroconversion) when compared with full dose IM-IPV for all serotypes for seroconversion and priming observed with 1 or 2 doses. The seroconversion at 18 weeks following two doses of fIPV at 6 and 14 weeks was 80.9% whereas the corresponding rate for IM-IPV was 91% [7]. Further, the GoI intends to use standard BCG needle and syringe for intradermal administration of ID-fIPV whereas in the Bangladesh study, a microneedle based device (MicronJet 600) was used [7]. It would have been more appropriate to consider Vellore study [11] while recommending two-dose ID-fIPV schedule for eight states as in this study, needle and syringes instead of needle-free devices were used as GoI is now planning to utilize in field.

#### THE CURRENT SCENARIO AND THE NEW OBJECTIVES OF IAP-ACVIP RECOMMENDATIONS

With the introduction of single dose of intramuscular IPV in RI of six Indian states from November 2015, and GoI's proposed introduction of two doses of ID-fIPV in rest of the country from April 2016, there is a lot of confusion amongst pediatricians/IAP members regarding the exact IPV schedule for primary immunization. The scarcity of IPV, particularly in private market, has further aggravated the confusion. The IAP-ACVIP is recommending three doses of IPV, given intramuscularly at 6, 10, and 14 weeks or two doses at 8 and 16 weeks of age for primary immunization in its schedule [8].

The main objective of GoI's initiatives (described above) is to enhance population immunity against type 2 poliovirus just prior to proposed switch from t-OPV to b-OPV in April 2016 so that the risks associated with the complete removal of type 2 vaccine virus can be mitigated. The decision to employ only a single dose of IPV and two doses of intradermal IPV is only an interim arrangement owing mainly to the limited supply and availability of IPV. On the other hand, the main aim of existing IAP-ACVIP guidelines on polio immunization [8] is to provide almost

100% protection against VAPP along with the best possible humoral and mucosal protection against polioviruses to an individual child in office practice setting. Considering the recent initiatives taken by the GoI as described above, the ACVIP will have to add another objective, *i.e.* to provide protection against type 2 poliovirus to naive children born post-switch. IPV would be the only source of providing immunity against type 2 poliovirus to children after April 2016. Therefore, the focus would be protection against VAPP along with provision of protection against type 2 poliovirus by maximizing type 2 population immunity. Since the threat of cVDPV type 2 emergence would be greatest, at least for one year following tOPV to bOPV switch, the latter objective would need to override the former for the time being.

### RECOMMENDATIONS

In context to the GoI's initiatives regarding polio endgame strategy and the anticipated situation of shortage of IPV, there is an urgent need of providing immunity against type 2 poliovirus. It is thus imperative to provisionally follow the suggested schedule of two ID-fIPV doses given at 6 and 14 weeks of age against type 2 poliovirus. However, review of literature shows that intradermal mode of administration of IPV results in significantly lower seroconversion, priming and GMTs against all types of poliovirus than the full dose intramuscular IPV. There is a felt need to undertake more studies particularly with ID-fIPV for evaluating seroprotection, schedule and delivery through conventional BCG needles and syringes. Therefore, full dose of IM-IPV needs to be offered to children at least after 8 weeks interval of the second dose of ID-fIPV dose for enhanced and improved seroconversion/seroprotection. Similarly, for the recipients of single dose of IM-IPV at 14 weeks, another dose of IM-IPV should be offered at least 8 weeks after the first dose.

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**ANNEXURE**

**IAP Advisory Committee on Vaccines & Immunization Practices, 2016-17:** *Office-bearers:* Pramod Jog (Chairperson), Sachidanand S. Kamath (Chairperson), Anupam Sachdeva (Chairperson), Vipin M Vashishtha (Convener), Jaydeep Choudhary (Convener), Bakul J Parekh (IAP Coordinator); *Members:* Jeeson C Unni, Sangeeta Yadav, Sanjay Srirampur, Baldev Prajapati

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