The Need and Potential of Inactivated Poliovirus Vaccine

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As the polio endgame progresses, the world will increasingly rely on inactivated polio vaccine (IPV) for protection against polio (wild and vaccine-related) and for risk mitigation during the phased removal of oral polio vaccine (OPV). IPV has already been introduced in most countries and strategies are underway to ensure the remaining OPV-only using countries succeed in introducing IPV in light of operational challenges. Questions remain as to the ideal dosing schedule for IPV in developing countries as well as the length of time for IPV to be administered beyond certification of eradication of wild polioviruses and total OPV withdrawal. IPV policies will likely evolve and new technologies will become available to meet unforeseen needs during this historical and unprecedented public health endeavor. Pediatricians in India have a crucial role to play in this global effort by supporting the overall polio eradication strategy and ensuring that all targeted children in India receive IPV.

Keywords: *Polio eradication, Vaccine associated paralytic poliomyelitis, Vaccine-derived poliovirus*.

Global polio eradication efforts continue to achieve results. Of the three types, wild poliovirus type 2 (WPV2) was eradicated in 1999 and certified in 2012 by the Global Commission for the Certification of the Eradication of Poliomyelitis [1]. No wild poliovirus type 3 (WPV3) has been detected anywhere in the world for over three years, since November 2012 [2]. So, it is likely that WPV3 has also been eradicated; however, the Certification Commission will have to scrutinize all information before making a final declaration. India interrupted all WPV transmission in 2011 after which the South East Asia Region was certified as having eliminated WPV in 2014, a major milestone in the eradication trajectory [3]. In 2015, wild poliovirus type 1 (WPV1) continued to circulate only in Pakistan and Afghanistan, but with only 74 polio cases, the lowest in history [2]. Both countries are inching towards interrupting WPV1 transmission.

These successes were achieved using oral poliovirus vaccine (OPV) containing live attenuated polioviruses – trivalent (tOPV with types 1, 2 and 3), monovalent (mOPV with type 1 or 3) and bivalent (bOPV with types 1 and 3). However, the vaccine (Sabin) genotypes of polioviruses can regain neurovirulence and very rarely cause vaccine-associated paralytic polio (VAPP) either in the vaccinated child or in a close contact [4]. Where OPV coverage is sub-optimal, Sabin genotypes can spread among non-immune children, leading to rare lineages of vaccine-derived polioviruses (VDPVs) that have regained both the neurovirulence and transmissibility characteristics of WPV. Circulating VDPVs (cVDPVs) can cause polio outbreaks [4]. Since 2000, more than 600 persons have been paralyzed in outbreaks caused by type 2 cVDPVs [5].

For a polio-free world, not only WPVs but also VAPP and cVDPVs must be stopped from occurring. Discontinuing OPV inoculation will prevent VAPP, but the resultant immunity gap in the community will constitute a risk for the emergence of cVDPVs and polio outbreaks, a setback we cannot accept [6]. The major reason cVDPVs can be generated after OPV is stopped is if some places have stocks of OPV and continue to use the vaccine. These areas can serve as reservoirs to infect completely unvaccinated populations which will foster vaccine virus transmission and regaining of the wild virus phenotype causing outbreaks. This can happen if OPV is the only vaccine to be used to prevent polio. But as noted below, there is another tool to prevent polio, the inactivated polio vaccine (IPV).

In 2013, the World Health Organization (WHO) unveiled the 'Polio Eradication and Endgame Strategic Plan 2013-2018', in which the term 'eradication' addresses WPVs and 'endgame' addresses VAPP and VDPVs [7]. The tool for mitigation of risks related to withdrawing OPV is IPV, consisting of killed polioviruses. India pioneered advocacy for IPV to complete and conclude eradication [8,9]. The endgame is a new strategy for completion of polio eradication – rid the world of polio due either to WPV or vaccine viruses. According to the strategic plan, global endgame

interventions and WPV eradication interventions in Pakistan and Afghanistan will run concurrently [7].

In recent years, countries using OPV had an estimated 300-500 cases of VAPP annually with 26-31% of all VAPP cases caused by Sabin type 2 virus [10]. The majority of VAPP in contacts of vaccinated children is due to Sabin type 2 [11]. Of all cases of polio due to cVDPVs, nearly 90 percent were due to Sabin 2 serotype [5]. Therefore, the global need to stop all Sabin 2 related polio, VAPP and cVDPVs, is extremely urgent. The beginning of the endgame will have two components – introduction of IPV universally in all countries currently using OPV exclusively, and globally synchronized withdrawal of Sabin type 2 from all OPV [7]. The latter was achieved through a switch from tOPV to bOPV which took place in April 2016. Eventually, after eradication of WPVs 1 and 3, bOPV will be discontinued and all countries will use IPV exclusively, until further decisions are made. Polio eradication saves money through productivity increases of individuals saved from paralytic polio [12].

ROLE OF IPV IN THE ENDGAME

The introduction of IPV in OPV-using countries started in 2015 in a staggered manner and will continue in 2016 and beyond until every country has IPV in their national immunization program. IPV is highly efficacious and very safe – no serious adverse events have been attributed to IPV [13,14]. Two or three doses, given at appropriate age intervals, are sufficient for ~100% antibody response to the three types of polioviruses, with quite high titers [15-17]. Higher titers and seroconversion rates are obtained when IPV is given after maternal antibody wanes and with intervals of over 8 weeks [15-17]. One dose induces seroconversion in 19-41% for type 1; 32-63% for type 2; and 28-54% for type 3 [18]. The remaining children are immunologically primed so that a second dose results in a rapid anamnestic response in <7 days [19].

Effective mucosal immunity to protect against WPV infection may be needed at the pharyngeal and intestinal levels. IPV induces pharyngeal immunity similar to that of OPV, but much less intestinal immunity [15,20]. On the other hand, in OPV-immunized children, a dose of IPV boosts both humoral and intestinal immunity several-fold higher than a dose of OPV [15,20]. This is the basis for the endgame recommendation to give one dose of IPV at the time of the third dose of OPV, at age 14 weeks or more. There is no restriction intended as one dose only, as the document calls for 'at least one dose'.

Thus, IPV will mitigate the risk of cVDPV2 emergence after the tOPV-bOPV switch and will also enhance immunity against types 1 and 3 that should protect Indian children in case of virus re-introduction from any source – importation or laboratory breach. In case of an outbreak of cVDPV2, a dose of IPV will rapidly boost immunity in primed children. Furthermore, IPV-primed children will mount quicker and higher humoral antibody response to a dose of mOPV2 than in exclusively OPV-inoculated children [21]. These are the advantages of introducing IPV, even if the coverage may not be as high as desired.

For an outbreak response by way of 'mop-up' vaccination, OPV has been the vaccine of choice for ease of inoculation, but IPV used in campaign mode in the future will offer additional benefits. The greatest risk of re-introduction of live vaccine virus type 2 or cVDPV type 2 will be within one or two years after the switch [22]. IPV avoids the risk of re-seeding vaccine virus type 2 that will be inherent in mOPV2 given in campaigns. The age cohorts already given OPV doses will be rapidly boosted with both humoral and intestinal immunity, helping in interruption of transmission. Children born after the switch would either have received IPV or had not received it due to incomplete coverage – both groups will benefit from a dose of IPV as described above.

India has begun giving IPV in some States in November 2015 and will continue until the entire country is covered. One dose of IPV is given intramuscularly in the right thigh (for easy recall by mothers), while pentavalent vaccine is given on the left thigh, in the same sitting. When India rolls out pneumococcal conjugate vaccine (PCV), expected in the near future, IPV will be given in the right and pentavalent and PCV in the left thigh with >2.5 cm gap. The safety and effectiveness of giving two, three or four injected vaccines in one clinic visit is supported by good evidence [23-25].

The introduction of IPV in all OPV using countries has resulted in demand greater than supply; this is hopefully a very short term problem. Such shortage has resulted in two reactions – one, some countries have chosen to delay introduction or stagger in-country coverage expansion and second, countries are considering giving fractional doses of IPV intradermally (ID). The excellent immunogenicity of ID fractional (one-fifth) dose of IPV was documented in pioneering research in India, confirmed by many recent studies [19,26,27]. A single ID fractional dose at age 14 weeks may not induce as good an immune response as one full intramuscular dose. However, two ID fractional doses given at 6 and 14 weeks induce comparable seroconversion to one intramuscular full dose at 14

weeks; surprisingly, the antibody titers after two doses were much higher than one full dose [28]. Recently, the Government of India has decided to use available IPV in this ID fractional two-dose schedule in selected States – even though such use is at present off-label (Haldar P, personal communication) [29]. This policy was decided upon as an interim measure to tide over the shortage of supply and the 2 ID fractional IPV doses will be given in lieu of one full intramuscular dose.

SHORT-MEDIUM AND LONG-TERM IPV USE

Endgame activities are expected to take place until 2018 and beyond. During this period all OPV using countries will give bOPV according to the usual schedule under the Expanded Program on Immunization (EPI) and at least one dose of IPV to all children. Several countries have decided to offer more than one full intramuscular dose; India has not considered this option as yet. All children who reach 14 weeks of age after the tOPV-bOPV switch will not receive any Sabin type 2 vaccine virus at all. The question if they should get more than one dose of IPV also has not been considered in India. Following the switch, we anticipate a few instances of VDPV2 emergence arising out of chains of transmission that may begin by vaccine virus transmission from those who got Sabin 2 vaccine virus, to those who did not get it. The probability, frequency and time sequence of such cVDPV2 emergences are unknown since the world has not had any experience with this unique situation.

Mathematical modeling using best assumptions predict the highest risk of cVDPV2 emergence to exist during the 6-12 months post-switch [22]. Others, notably one of us (TJJ), suspect that the probability of detection of cVDPV2 may be higher during the 12 to 24 month-period 6 months after the switch. This risk may likely end about three years after the last large scale inoculation of Sabin 2 vaccine virus. If containment of all laboratory-held viruses is not perfect, release from a laboratory could constitute a possible risk. Once such a situation occurred in India, during 2002-2003, when circulation of a WPV2 strain with genetic sequences not seen in humans for a long time was identified [29]. IPV will serve as an 'insurance policy' against such contingencies.

Unfortunately, we do not have data on the durability of immunity induced by a single dose of IPV. All high income countries use IPV but they are liberal with doses, many giving 4-7 doses [30]. In low income countries, the recommendation regarding the number of doses is likely to change and evolve, particularly if we discover: (1) waning antibody over time; (2) priming alone is not protective; or (3) a higher proportion of seroconversion than provided by a single dose is necessary. Theoretically, two doses given at an interval of 4-6 months, with the first dose given after maternal antibody has waned, ought to provide long term immunity. This is based on the knowledge that long-lived memory and antibody-secreting plasma cells are elicited if the booster is delayed by 4-6 months [15]. Another inactivated picornavirus vaccine (hepavirus in hepatitis A vaccine), given as two doses 6 months apart, induces immunity that is anticipated to last life-long [31].

The endgame plan envisages the eradication of WPV1 shortly; thereafter the opportunity to discontinue even bOPV will present in the near future – expected in 2018-2020. The current global recommendation is to continue IPV for a period of at least 5 more years, after which decisions on continuation/discontinuation may be allowed for individual countries [7].

OPERATIONAL CHALLENGES TO IPV INTRODUCTION IN INDIA

Globally, the rapid introduction of a vaccine covering more than 100 nations is an unprecedented exercise and poses many challenges. Since 2013, over 90 countries have introduced IPV in their EPI schedule [32]. A dose of IPV is 5-fold or more expensive than a dose of OPV [33]. Thus, introduction of IPV can lead to financial stress for both individual countries and the Global Polio Eradication Initiative (GPEI). The Vaccine Alliance (GAVI) is assisting financially some 73 countries, including India [34,35].

IPV manufacturers also have been facing problems of rapid up-scaling of production [36]. The necessary quantities of IPV for all countries are not available; therefore, GPEI has classified countries on a scale of risk of cVDPV emergence and/or spread and proposed a schema for late introductions [6]. India is considered a high priority country, considering the population size, conditions of sanitation and hygiene, <90 per cent coverage of EPI vaccines and recurrent emergences of cVDPV in the recent past. At the same time, India is a potential large scale supplier of IPV, but production delays have affected the supply prospects. Under these circumstances, India will use an antigen-sparing approach in selected states, by way of two ID fractional doses (each 1/5 of a full dose), as stated earlier.

FUTURE PROSPECTS REGARDING POLIO IMMUNIZATION

The world is sailing in unchartered waters of global polio eradication and the endgame, but we do expect complete success in a few years. Obviously all countries will continue to use IPV for a number of years. Currently almost all IPV is made from laboratory maintained fully virulent WPVs, which demands an exceptionally secure

environment for fear of accidental release. Much research had been done on making IPV using Sabin attenuated vaccine strains, with far less serious consequences in case of any accidental release. Recently, Japan licensed such indigenously made Sabin IPV and currently it is the vaccine used in the national immunization program [37]. China has successfully manufactured and tested Sabin IPV [38]. Other manufacturers are actively exploring the shift from WPVs to vaccine viruses as vaccine raw material.

We referred to hepatitis A vaccine, which is adjuvanted with aluminium salt. The potential of antigen-sparing with use of adjuvant in IPV is being actively explored in several places [39]. Devices for needle-free inoculation of IPV intradermally, both injection devices and micro-needle patch are currently under rigorous testing; they will be very helpful for IPV given in campaign mode especially in outbreak response [39]. Recently, a monovalent IPV with type 2 antigen has been tested successfully; it will offer another intervention tool against any future outbreak of cVDPV 2 [39]. Combining IPV with other childhood injected vaccines is a method currently used in most high income countries. The usual preservative thimerosal cannot be used as it damages the immunogenic epitopes in IPV [40]. Therefore combinations should be preservative free or compatible with the alcoholic (phenoxy ethanol) preservative that is safe for IPV. These conditions are satisfactory when the pertussis component is acellular, but not killed whole cell pertussis vaccines. India and many low and middle income countries use thimerosal-containing pentavalent vaccine; hence we cannot expect a hexavalent vaccine with IPV any time soon. However one Indian manufacturer is in advanced stage of clinical trials with such a combination vaccine.

As with the effort to eliminate WPVs, navigating the endgame and securing total eradication of all polio is a test of political will, strategy adaptation, and cooperation across several fronts and agencies, including in public and private sectors. The pediatric professionals and the Indian Academy of Pediatrics will, we hope, continue to lead in this Himalayan task.

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