PRESIDENT'S PAGE

Goodbye Switch and Imminent Polio Victory

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The battle against polio will turn over a new leaf with the health ministry of Government of India (GoI) deciding to switch over to bivalent oral polio vaccine (bOPV) from the presently administered trivalent oral polio vaccine (tOPV) from April 25, 2016. After the switch date, only bOPV will be used both in Routine Immunization (RI) as well as polio campaigns. After switch date, remaining tOPV will be removed from cold chain and disposed off as per National Switch Plan [1].

Ideally, injectable polio vaccine (IPV) should be introduced 6 months prior to the switch as per the SAGE recommendation [2]. The GoI has introduced a single dose of IPV in RI schedules of six states since last November. IPV is given in addition to the existing oral polio vaccine (OPV) doses and does not replace any OPV doses. Many questions are likely to crop up in the mind of a pediatrician – the rationale behind the switch from tOPV to bOPV; the rationale behind a single dose of IPV; the current non-availability of IPV in private sector; the guidelines for polio immunization of infants after April 1 till IPV becomes available; whether IPV will be available to the private practitioners who have been using it for a few years now for all their patients; whether the private sector use only bOPV without IPV; will there be no IPV available in the private market as all will be used by the Government health services; can additional IPV supplies be mobilized from global resources to meet India shortfalls so that IPV can be introduced in all states before the switch; should India defer the switch until IPV is introduced in all states; should India implement the switch in April 2016 without introducing IPV in six low risk states, and if so, what are the possible risk and mitigation strategies; what is the rationale for intradermal IPV?

Let us review the situation.

The availability of two effective vaccines against poliomyelitis for the past five decades has ensured remarkable decline in the global burden of disease. The vaccines were developed in the USA during the 1950s, first the IPV by Jonas Salk, and later the live attenuated OPV by Albert Sabin. The Global Polio Eradication Initiative (GPEI) was launched in 1988 using OPV as the eradication tool and employing a four pronged strategy comprising high routine immunization coverage, supplementary immunization activities (SIAs)/pulse immunization, acute flaccid paralysis (AFP) surveillance and mop-up immunization. The cases of polio have drastically reduced from 350,000 in 1988 to 72 in 2015. As on date, Pakistan and Afghanistan are the only countries that have not succeeded in eliminating wild poliovirus transmission and cases. Wild virus type 2 has not been isolated since 1999. It exists only in tOPV and in laboratories.

Two new monovalent polio vaccines – mOPV Type 1 and type 3 – were licensed since 2005, and used to enhance the impact of SIAs in the key remaining reservoirs of wild polio. While mOPVs have provided the GPEI with much more potent tools for rapidly building population immunity, optimizing the balance of mOPVs proved much more difficult than originally anticipated, leading to alternating outbreaks of type 1 and 3 poliovirus in certain settings, and promoting the fast track development of a completely new bOPV in 2010. With intelligent use of mOPVs and bOPV, last case of wild poliovirus was reported from India in January 2011. WHO removed India from list of polio endemic countries in February 2012 [3].

Control of paralytic polio has been possible because of OPV. However, a rare but serious adverse effect associated with OPV is Vaccine Associated Paralytic Poliomyelitis (VAPP). These are the cases of AFP which have residual weakness 60 days after the onset of paralysis, and from whose stool samples, only vaccine-related poliovirus is isolated. VAPP may occur in the vaccine recipient (recipient VAPP, occurring within 4-40 days of receiving OPV) or contact of the vaccine recipient (contact VAPP). Another major problem with the use of OPV is the emergence of vaccine-derived polio virus (VDPV). These viruses arise due to mutation

and recombination in the human gut, and are 1-15% divergent from the parent vaccine virus. These viruses are neurovirulent and are transmissible and capable of causing outbreaks. They have been classified into three groups: circulating VDPV (cVDPV) – VDPV with evidence of virus circulation in the population causing two or more paralytic cases; VDPV in the immunodeficient person (iVDPV); and VDPV of ambiguous origin (aVDPV). Thousands of people got afflicted with VAPP and around 600 with type 2 cVDPV because of the continued use of OPV since 1999 [4]. Since 2006, majority of cVDPV cases are due to type 2. Recognition of VDPVs is the primary reason why synchronous discontinuation of OPV use globally and continuing to vaccinate against polio with IPV is mandatory in the post-polio eradication scenario.

If we stop giving type 2 in OPV, VAPP due to type 2 will stop, but, the risk of VDPV2 emergence will increase. Currently, high population immunity created by high and repeated coverage of tOPV is preventing its emergence. As we stop type 2 vaccine, the risk of VDPV will increase unless high population immunity is sustained using IPV. This is the rationale of the end game strategy of introduction of IPV followed by globally synchronous tOPV to bOPV switch, six or more months later. As wild poliovirus types 1 and 3 have not yet been globally eradicated, the phased withdrawal of OPV antigens will begin with a shift from tOPV (containing types 1, 2 and 3) to bivalent OPV (bOPV, containing types 1 and 3). bOPV is safe and more immunogenic to types 1 and 3 than is tOPV [5].\

As India has fully interrupted the wild poliovirus transmission, and has been declared a polio-free country by the WHO, the time to withdraw OPV is approaching fast, considering the risk of VAPP and VDPV associated with continuation of OPV in post-eradication scenario. The process of gradual withdrawal of OPV synchronously from all over the world without exposing children to the risk of wild or vaccine-derived polio is the greatest concern to the GPEI.

IPV FOR **I**MMINENT **P**OLIO **V**ICTORY

Let us see the rationale behind the decision to employ only a single dose of IPV. It is only an interim arrangement owing mainly to the limited availability of IPV globally. One dose of IPV will induce an immunity base to poliovirus type 2, and strengthen immunity against types 1 and 3. The immunity base offered by IPV would be expected to greatly reduce the consequences of poliovirus type 2 exposure (in terms of paralytic disease), post-switch. In case of a post-switch outbreak due to type 2 polio virus, a second dose of polio vaccine (monovalent type 2 OPV or IPV) should rapidly close any remaining immunity gaps.

Evidence in favor of single dose of IPV

There is good amount of evidence to support 'one-dose IPV' recommendation to prevent paralytic polio in those exposed to cVDPV2 or wild poliovirus type 2. A case control study from Senegal demonstrated that one dose of IPV was 36% effective against paralytic polio caused by wild poliovirus type 1 [6]. One dose of IPV induces seroconversion of 32-63% against type 2 poliovirus. In a recent study from Cuba, seroconversion was higher when IPV was administered at 4 months of age (63%) compared to 32-39% in earlier studies where IPV was given at 6-8 weeks of age [7,8]. More importantly, among those who did not seroconvert (37%), 98% had a priming response to a subsequent dose of IPV – that is, they developed significant antibody responses within 7 days of subsequent exposure to IPV [8].

IPV closes the immunity gap against type 2 poliovirus. A study from Cote d'Ivore demonstrated that, previously tOPV-vaccinated infants who were seronegative, had seroconversion rates against type 2 poliovirus of 100% after one dose of IPV *versus* 53% after tOPV [9]. Similarly, in India, previously OPV-vaccinated infants who were seronegative to type 2 poliovirus had seroconversion rates against type 2 of 100% after IPV [10]. In India, type 2 is responsible for around 40% of all cases of VAPP and majority of them occur after four months of age. Thus the single dose of IPV given at 14 weeks would not only prevent all cases of VAPP caused by type 2, but will also significantly reduce the overall tally of VAPP. A recent study from India demonstrated that giving IPV to children with multiple previous doses of OPV substantially boosts intestinal immunity and decreases excretion prevalence after challenge with bOPV [11].

Furthermore, it is expected that prior receipt of IPV should contribute to curtailing transmission of poliovirus in the setting of an outbreak since it also reduces the duration of shedding and the amount of virus in the stool [11,12]. In India, a single IPV dose in children aged 6-11 months, 5 years, and 10 years of age who received multiple prior OPV doses reduced excretion prevalence by 54-72% (type 1) and 51-81% (type 3) after a challenge with bOPV [11,12].

In summary, administration of one dose of IPV would boost humoral and mucosal immunity in children already immune from OPV, provide protection against VAPP, and facilitate outbreak control with mOPV, should polioviruses be reintroduced.

Recently, the SAGE reviewed progress on these readiness indicators [4,13]. All high risk countries are on track for introducing IPV. Current shortage of IPV is due to the technical challenges encountered in the rapid scale-up of IPV production required to meet the timeline. Supply shortages will delay introduction by a few months in some low-risk countries but are unlikely to increase the short-term risk of cVDPV2. Experts feel that "the benefits of withdrawing OPV2 outweigh the risks, hence the decision to proceed with the global switch from tOPV to bOPV between April 17 and May 1, 2016. Furthermore, OPV2 withdrawal should be synchronized worldwide. A prolonged staggered withdrawal would pose a risk of continuous generation of cVDPV2s and potential exportation of these viruses to regions or countries with susceptible children born after the switch. Withdrawal of OPV2 during the seasonally low-transmission month of April further reduces the risk of type 2 polio outbreaks [14]."

In the context of an IPV shortage, there is a suggestion of using fractional doses (one-fifth of the full IPV dose) via the intradermal (ID) route – two fractional doses of IPV (ID-fIPV) administered at 6 weeks and 14 weeks (the "prime-boost" model) as an alternative to the intramuscular injection of one full dose of IPV in the high performing states. This would possibly make IPV available for many eligible infants because of cost saving. However, it is programmatically more demanding. The logistic implications also need to be considered. It will also be necessary to conduct cross sectional sero-surveys and prospective cohort studies to understand the immunogenicity and protection provided by the two fractional doses in the Indian setting .

ID-IPV will be utilized in eight Indian states (Tamilnadu, Kerala, Andhra Pradesh, Telangana, Karnataka, Odisha, Maharashtra and Puducchery) from April 2016. In six Indian states (Bihar, Uttar Pradesh, Madhya Pradesh, Gujarat, Punjab and Assam), single intramuscular dose of IPV will be given. The previous study done in Moradabad on ID-IPV did not provide adequate seroconversion against type 2 poliovirus, but at that time jet injectors were used. This time GoI is planning to use BCG syringes as a study in Bangladesh has documented adequate seroconversion (81%) following two doses. We need to study all aspects before issuing any recommendation on acceptance of ID-IPV as a reliable mode of providing adequate sero-protection to a vaccinee.

So far, Indian Academy of Pediatrics (IAP) has not approved/recommended ID-IPV in private sector. IAP Advisory Committee on Vaccines and Immunization Practices (ACVIP) maintains that for RI, at least two-doses of IPV starting from at least 8 weeks of age and maintaining an interval of at least 8 weeks between them are necessary to provide/accord adequate immune protection against all types of polioviruses. Considering the extraordinary situation in context of extreme shortage of IPV and the urgent need of providing immunity against type 2 poliovirus, the committee is willing to provisionally accept immune-protection accorded by two ID-fIPV doses given at 6 and 14-week of age against type 2 polioviruses, provided another full dose of intramuscular IPV is offered at least 8 week interval of the second dose of ID-fIPV.

Another concern is the vaccine scarcity. It is because of failure of the existing IPV production sites in industrialized countries to scale up production of IPV in their manufacturing units as was expected and as promised by the vaccine manufacturers to the Government. The situation may take some time (probably few months) for improvement.

It is not true that IPV will only be available for use in public sector. One can practice the alternate two-dose schedule where two doses of IPV are given with an interval of two months, starting at 8 weeks of age, if IPV is available in private market. If no IPV is available, then we will have to use only the bOPV.

So, let us be clear about certain facts:

1. In view of the global polio eradication scene, use of live polio vaccine in the community needs to be stopped.
2. The first step in this will be omitting type 2 vaccine virus from OPV as there is no wild poliovirus type 2 since 1999.
3. We are expecting that IPV will take care of cVDPV due to type 2 poliovirus.
4. Currently, supply of IPV is not adequate, especially in the developing world.
5. Whenever available, IPV should be administered according to IAP schedule. Until such time. tOPV/ bOPV, depending on availability, will have to be used as primary polio vaccine.

After smallpox, poliomyelitis is the second viral disease targeted for global eradication. No doubt, it is heartening to see the polio virus getting extinct and becoming historical because of the sustained efforts over years. In 1985, I had undertaken a campaign 'Goodbye Polio', with the help of medical students of the BJ Medical College in Pune. Many innovative ideas were implemented, like taking postmen's help to find out the

drop-outs, and using computers to enlist the slum dwelling infants. Looking back to the efforts which started 30 years ago, I feel that the time has come to strive hard if we want to be the proud witnesses of polio being eradicated in the second decade of 21st century.

It is essential for every IAPian to think seriously of his/her social responsibility. The goal of polio eradication cannot be achieved by the government alone. It requires participation of each and every member of our Academy. Some members take 'how am I concerned?' attitude. Some members are unaware of national programs, while some do not take these programs seriously. If the IPV crunch in private sector continues, one should not hesitate in sending patients to the public health facility to get IPV. If everyone contributes own bit, we can easily give the last punch to throw out the unwelcome guest.

Let us start working hard at individual and local area level. Together we can contribute maximum share as IAP organization – quantitatively and qualitatively. Let us resolve – 'Mission of each IAPian… polio eradication.'

***P**erseverance, **O**pting switch to bOPV, **L**ooking out for cVDPVand use of **I**PV will make virus **O**bsolete .*

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