India's Preparedness for Introduction of IPV and Switch from tOPV to bOPV

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Global Polio Eradication and Endgame Strategic Plan 2013-18 calls for the ultimate withdrawal of oral polio vaccines (OPV) from all immunization programs across the world. The phased globally synchronized withdrawal would begin with type 2 serotype in 2016 through a switch from trivalent OPV (tOPV) to bivalent OPV (bOPV) and is associated with small but real risk of Vaccine Derived Polio Virus (VDPV) outbreaks. To mitigate this risk, efforts across the world, including India, are underway that comprise of Inactivated Polio Vaccine (IPV) introduction, containment of type 2 wild and vaccine strains, securing bOPV supplies, and surveillance and response protocols for any outbreaks after switch. Switch implementation in India is particularly challenging as country has one of the largest cold chain system in world with – 27000 cold chain points from where tOPV will be exchanged with bOPV and disposed in short time frame as any use/ storage of tOPV beyond switch will jeopardize the global polio eradication.

Keywords: *Endgame strategy, Global Polio eradication, Routine immunization.*

Global Polio Eradication and Endgame Strategic Plan 2013-18 calls for the ultimate withdrawal of oral polio vaccines (OPV) from all immunization programs across the world. The phased globally synchronized withdrawal would begin with type 2 serotype in 2016 through a switch from trivalent OPV (tOPV) to bivalent OPV (bOPV) and is associated with small but real risk of Vaccine Derived Polio Virus (VDPV) outbreaks. To mitigate this risk, efforts across the world, including India, are underway that comprise of Inactivated Polio Vaccine (IPV) introduction, containment of type 2 wild and vaccine strains, securing bOPV supplies, and surveillance and response protocols for any outbreak after switch. Switch implementation in India is particularly challenging as the country has one of the largest cold chain system in world with ~ 27000 cold chain points from where tOPV will be exchanged with bOPV and disposed in short time frame as any use/storage of tOPV beyond switch will jeopardize the global polio eradication.

Global polio eradication is now in the final phase, with wild poliovirus (WPV) type 1 limited to only Pakistan and Afghanistan since August 2014 with record low cases ever in 2015, WPV type 2 eradicated globally and no WPV type 3 since November 2012. The reality of a world free of polio has never been so close. This success is largely attributable to the widespread use of OPV in routine immunization (RI) and in mass campaigns globally [1].

Sabin poliovirus strains in OPV replicate in the intestine of the vaccinated and rarely mutate to cause paralysis in the recipient or close contacts (known as Vaccine-Associated Paralytic Polio, VAPP) or mutate to regain both the neurovirulence and transmissibility characteristics of WPV (circulating Vaccine Derived Polio Virus, cVDPV) causing outbreaks [2]. In 1999, overall risk of VAPP in India was estimated to be 1 case per 4.6 million OPV doses. The type 2 virus in tOPV is estimated to cause 100–200 cases of VAPP annually, accounting for ~26-31% of all VAPP cases [3].

During 2011-2015, almost 90% of globally reported cVDPV cases (204/230) were associated with the type 2 component of tOPV [1]. Similarly, out of the total 44 cases of cVDPVs in India since 2009, 41 are due to type 2 Sabin viruses (i.e. >90%) [4]. VDPVs can establish endemic and epidemic transmission; they are therefore incompatible with polio eradication [1].

As WPV nears eradication, the risks of OPV i.e. instances of VAPP and VDPV surpass the number of cases caused by WPV [5]. Moreover, the type 2 component of tOPV has been found to interfere with the immune response to types 1 and 3, a concern for achieving global eradication as type 1 WPV is still in circulation [5, 6]. Since WPV type 2 has been eradicated globally and majority of cVDPVs and nearly one third of VAPP are caused by type 2 Sabin strains, the risks associated with the use of type 2 component of tOPV (OPV2) now outweigh its benefits [7]. This necessitates

the withdrawal of the type 2 component of tOPV through a globally synchronized switch from tOPV to bOPV – that is, all tOPV use must stop and residual stocks worldwide should be destroyed as soon as operationally feasible. Once remaining serotypes (type 1 and 3) of WPV are eradicated, complete OPV cessation will be required to achieve final goal of global polio eradication [7, 8].

SWITCH PLANNING AND RISK MITIGATION MEASURES

The Polio Endgame Strategic Plan 2013-2018 outlines strategies and timelines for the eradication of both wild and vaccine polioviruses. Objective 2 of plan deals with IPV introduction, OPV2 withdrawal and RI strengthening and provides global guidance for the switch [2]. Strategic Advisory Group of Experts (SAGE) for Immunization to World Health Organization (WHO) has identified five prerequisites to track progress toward switch preparedness. These prerequisites include introduction of at least one dose of IPV; access to bOPV licensed for RI; implementation of surveillance and response protocols for type 2 poliovirus; completion of poliovirus containment activities and verification of global eradication of WPV type 2 [9]. In October 2015, SAGE reviewed these preparations for switch and concluded that the world is ready for the switch during the low season of polio transmission in April 2016. Moreover, SAGE reaffirmed that to prevent the emergence of cVDPVs; the switch must be globally synchronized in all OPV using countries between two weeks window from 17 April and 1 May 2016 [10, 11]. Accordingly, India has decided National Switch date as 25th April, 2016. Findings from a dry run conducted in May 2015 in Assam and Uttar Pradesh to field test and pilot the switch in country has suggested that switch is operationally feasible in country. Country's preparation for OPV2 withdrawal as per SAGE criteria and other operational aspects of switch has been summarized in ***Table* I.**

Despite careful planning and effective implementation, the endgame is not risk-free. OPV2 withdrawal is associated with short term risk of circulating VDPV type 2 (cVDPV2s) outbreak because of silent transmission resulting from replication and mutation of type 2 vaccine virus in gut of recently immunized children. This risk is greatest in the first 6-12 months after cessation and declines with time as vaccine viruses are unlikely to circulate longer than a few months after OPV cessation [12]. Studies in Cuba, Indonesia and New Zealand have demonstrated that polioviruses were not detectable in environmental or stool samples 2-3 months after last OPV use and suggest that VDPV is unlikely to establish circulation in situations with high population immunity [8,12,13].

The long-term risks after OPV2 cessation would be mainly related to reintroduction of type 2 poliovirus from stocks stored in research facilities, manufacturing sites, and diagnostic laboratories [8,12,13]. These stocks are expected to be destroyed or contained in designated essential facilities, as specified in the current draft of the WHO Global Action Plan to Minimize Poliovirus Facility-associated Risk (known as GAP-III). Implementation of GAP-III is considered an important measure to reduce the emergence of cVDPV2s after the switch [8,14].

The risk of cVDPV outbreaks is largely related to low population immunity against particular serotype. A cross-sectional serologic assessment of immunity to poliovirus in traditional high risk areas of India in 2014 revealed that overall seroprevalence for Bihar, Madhya Pradesh and Mumbai were 97.3%, 97.9% and 86.9% for poliovirus types 1, 2 and 3, respectively. The study also concluded that areas with low RI coverage and urban migratory clusters have also achieved high levels of population immunity against all three poliovirus types [15]. According to WHO-UNICEF estimates on immunization, 2014 revision, OPV-3 coverage is 82% in India [16]. Further, no cVDPV outbreak has been reported in country since 2010 [4]. These findings suggest that country is maintaining high level of population immunity conducive to rapid decay of type 2 Sabin virus after switch and to prevent cVDPV emergences.

Boosting immunity to type 2 polioviruses preceding the switch with high-quality tOPV supplemental immunization activities (SIAs) is the cornerstone to reduce the likelihood of cVDPV2 emergence following the switch [1,10,11]. India has already done two nationwide mass campaigns in January and February, 2016. An additional SIA using tOPV and Mission Indradhanush round (MI, see later in this article) has been planned in April, 2016 in high risk areas. These campaigns in the backdrop of high seroprevalance will help to prepare the country to prevent cVDPV2 emergence or spread after the switch.

IPV Introduction in India as a Risk Mitigation Measure

To prepare for the switch, SAGE recommended in 2012 that at least one dose of IPV to be introduced into RI schedule in all OPV using countries [9]. Adding a dose of IPV in RI might decrease incidence of overall VAPP due to all three serotypes by as much as 80-90%. The

TABLE 1 STATUS OF FIVE PREREQUISITES AND KEY OPERATIONAL ASPECTS FOR THE SWITCH FROM TRIVALENT OPV TO BIVALENT OPV

Prerequisite as per SAGE	*Country's Status*
1. Introduction of at least 1 dose of IPV into the RI program.	*a*) 6 States introduced single full dose IPV (at 14 weeks of age) from 30th November,2015, 22 States/UTs expected to start IPV around 1st April, 2016 *b*) 8 States/UT expected to introduce 2 f-IPV schedule at 6 and 14 weeks in April, 2016.
2. bOPV licensed for use in RI and SIAs	*a*) bOPV is in use in country since 2010 in SIAs and is licensed for use in both RI and SIAs.
3. Implementation of surveillance (AFP, ES) and response protocols (EPRP) for type 2 poliovirus to detect and interrupt any cVDPV2 transmission that may take place after the switch.	*a*) AFP rate and adequate stool rate was 10.81 and 86% respectively in 2015 which is in conformation with the current international standards. *b*) At present there are 23 ES sites in 6 states across the country [19]. Expansion planned to additional sites in Hyderabad and Mumbai in 2016. *c*) EPRP is in place and revised regularly. Simulation exercises were conducted in 12 states from 2013-15 and planned in remaining states in 2016-17. *d*) Global stockpile of mOPV type 2 for cVDPV2 outbreaks post switch is being maintained and will be made available to country as required.
4. Completion of Phase 1 containment activities including an inventory of all facilities holding infectious WPV materials and implementation of measures to ensure safe handling of residual type 2 materials (As per GAP-III)	*a*) As part of Phase –I (preparation for poliovirus type 2 containment) and Phase IIa (Containment of WPV2) activities, all unneeded WPV2 materials have been destroyed. Needed materials have been transferred to National Institute of Virology, Pune (Designated Essential Facility). *b*) A National Biosafety Assessment Board has been constituted comprising of experts from fields like virology, epidemiology, public health, bio-safety and NRA and has been trained by WHO. Board Members will validate the quality of containment in country. *c*) Phase-II b (Containment of Sabin type 2 polioviruses-(will begin within 3 months of switch)
5. Verification of WPV2 global eradication	*a*) Global certification of eradication of WPV2 has been done on 20th September, 2015
Operational aspect	*Country's status*
1. Establishment of management structure for operationalization of switch	*a*) National Switch Plan finalized and funding secured for switch. *b*) Immunization Division at MoHFW coordinating activities at national level. Partners (WHO and UNICEF) providing technical support to the GoI *c*) State Task Force and District Task Force for Immunization coordinating activities at state and district level
2. Minimizing tOPV wastage after switch while avoiding stock-outs and securing bOPV supplies.	*a*) A high level meeting at MoHFW held in December, 2015 with officials from NRA, professional bodies, vaccine testing lab, suppliers and partners. *b*) Supply orders of tOPV have been cancelled beyond February, 16. Procurement for bOPV done and suppliers have been informed. *c*) A web based tool and eVIN is being used to update inventory of polio vaccines from ~ 27,000 cold chain points across the country. *d*) NRA of India is developing mechanism to control supplies in private sector in view of switch date. *e*) Professional bodies, local municipal bodies, other Ministries and Departments (Coal, Power, Petroleum and Natural gas, Defence, Civil Aviation, Railways, Home Affairs) have been taken into loop for ensuring switch in all health facilities
3. Trainings and IEC plan	*a*) National level workshop has been done and cascaded trainings are being done at all levels *b*) IEC material have been developed for both private and public sector by UNICEF with technical assistance from WHO
4. Validation of Switch	*a*) National Certification Committee for Polio Eradication has been entrusted with the task of Switch Validation. *b*) Switch monitors have been identified who will verify both public and private sector

AFP: Acute Flaccid Paralysis, ES: environmental Surveillance, MoHFW: Ministry of Health and Family Welfare ,NRA: National Regulatory Authority, IEC: Information, Education and Communication.

introduction of one dose of IPV led to the elimination of VAPP in Hungary [3]. Unlike OPV, immune response to IPV does not vary significantly between industrialized and tropical developing country settings [5]. Studies suggest that a single dose of IPV will effectively close immunity gaps to all 3 poliovirus serotypes in previously tOPV-vaccinated children. To test the same in India scenario, a recent study in India assessed a schedule with bOPV (at birth, 6 and 10 weeks) followed by the co-administration of bOPV and IPV (at 14 weeks) which resulted in excellent seroconversion rates (nearly 98-99% to poliovirus type 1 and 3, and 69%–78% to type 2). Intestinal mucosal immunity is required to interrupt the transmission of poliovirus. Two recent studies in India found that in infants and children with a history of multiple doses of OPV, a single dose of IPV boosted intestinal mucosal immunity and reduced the prevalence of excretion after an OPV challenge by 38%–76%, compared to no polio vaccination. Studies also indicate that IPV is more effective in boosting intestinal mucosal immunity than OPV among OPV-immunized individuals [1]. Child malnutrition is a significant health problem in India (as per NFHS-4 data, 34 % children under 5 years are underweight) and a recent trial in Pakistan demonstrated that single simultaneous administration of IPV and bOPV achieved high seroconversion rate for type 2 in malnourished (84%) as well as normal children (100%) [8].

These findings form the technical rationale that IPV will help protect against paralytic polio from type 2 polioviruses should cVDPV2s emerge, facilitate responses to any cVDPV2 outbreaks after the switch to bOPV through priming effect, will aid in eradicating WPV by boosting immunity to types 1 and 3 polioviruses and is likely to be effective in Indian setting [5,8]. It is imperative to mention that use of IPV is not primarily meant to prevent emergences of cVPDV2s but to mitigate the risk of paralytic disease occurrence and spread in case of any outbreak. [8,17]. In view of these evidences and as per SAGE 2012 recommendations, Government of India decided to introduce IPV in country [18].

Almost all countries using only OPV at the start of 2013 had committed to introduce IPV before the end of 2015 and ~90 including India have already introduced IPV as of 1st February, 2016 [19]. Rapid IPV introduction across many countries, introduction of IPV in SIA of endemic countries, requirement of maintaining a stockpile of IPV for post switch VDPV emergences and global constraints to scale up the production has led to worldwide shortages of IPV [19]. In view of IPV supply shortages, phase-wise introduction of IPV was planned in the country. In the first phase, IPV has been introduced in 6 States in India on 30th November, 2015. IPV was planned to be introduced in remaining states in April, 2016. However, due to continued global shortages and amidst the evidence from Cuba and Bangladesh indicating that the "prime-boost" effect of 2 fractional doses (1/5th of full IPV dose) at 6 and 14 weeks offer better protection than a single full dose, the Indian Expert Advisory Group for polio eradication in February, 2016 recommended GoI to go for fractional dose IPV (f-IPV) introduction in selected States/UTs [1, 20]. Accordingly, GoI has now planned for f-IPV introduction in 8 States/UTs in April, 2016. Remaining 22 States/UTs are expected to introduce single full dose IPV from 1st April, 2016. As the country has high level of population immunity against all three types of polioviruses (to prevent emergence of cVDPV2s), phased introduction of IPV is not an impediment to OPV2 withdrawal [8].

India has also planned to conduct operational and immunogenicity studies in States with f-IPV introduction to further decide on the continuation and/or expansion of the use of f-IPV in the country. Other operational aspects

BOX 1 OPERATIONAL ASPECTS OF IPV INTRODUCTION

A. *Minimizing IPV wastage*

a) Open vial policy is applicable for IPV

b) 5 dose presentation to States/UTs with predominantly hilly or hard to reach areas

c) Message that Shake test is not applicable has been incorporated in Operational guidelines and training package

B. *Route and dose considerations*

a) Site for IPV will be anterolateral aspect of right thigh (for single full dose) or right upper arm (for fractional doses). This will help in easy recall of IPV administration in case MCP card is not available.

b) 1 full dose (0.5 ml intramuscular) at 14 weeks or 2 Fractional doses (0.1 mL intradermal each dose) at 6 & 14 weeks.

C. *Recording and reporting tools*

a) HMIS, MCTS and MCP cards are being modified to incorporate IPV

b) Monitoring formats have been modified to capture data on IPV introduction

D. *Trainings and communication:*

a) National level training has been done. Cascaded training going on in States/UTs where IPV to be introduced

b) IEC material and plan has been prepared

HMIS:Health Management Information System, MCTS: Mother and Children Tracking System, MCP: Mother and Child Protection card.

of IPV introduction such as minimizing vaccine wastage, route and dose considerations, recording and reporting tools, trainings and communications are outlined in ***Box* 1**.

Strengthening Routine Immunization

Strengthening the RI system that distributes and administers IPV will help to maximize the impact of IPV use. Though mass polio campaigns achieve high coverage, Universal Immunization Programme fully immunizes only about 65.3% of children [21]. In order to address this gap, Mission Indradhanush was launched on 25th December, 2014 which aims to rapidly increase immunization coverage in the country to >90% by 2020. Two phases of MI have already been completed in 2015 where nearly 20 lakh children were fully immunized. Phase-3 of MI will start from 7th April, 2016, which not only will help in boosting type 2 immunity before switch but also in increasing IPV coverage.

CONCLUSION

IPV introduction and tOPV to bOPV switch is a landmark public health endeavor which will build a positive legacy. India is not only prepared to make it a safe venture but also taking a leadership e.g., fractional dose introduction of IPV has never been done in any country's programme, and India was the first country in world to conduct dry run for switch. Country is utilizing the opportunity of switch to develop and test novel mechanisms in vaccine and logistic supply chain. Endeavor of polio endgame has refuelled liaison with Ministries/departments other than health and National regulatory authorities, for conducting switch in a risk free manner, which would also lay foundation for the eventual global cessation of all OPV.

Contributors: PH: substantial contribution to design conceptual framework of article, revising it critically for important intellectual content and analysis of collected data; Concept and design of article, drafting the article, revision of article and compilation, collation and analysis of collected data.
Funding: None; *Competing interest*: None stated.

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