

Polio Endgame: Information Gaps Related to Vaccines and Immunity

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Evidence generated through research studies has guided programmatic actions and fine-tuned strategies for the Global Polio Eradication Initiative (GPEI). However, many gaps still persist in the understanding of a risk-free implementation of the polio endgame. Immediate concerns relate to the introduction of inactivated polio vaccine (IPV) and switch from trivalent oral polio vaccine (tOPV) to bivalent oral polio vaccine (bOPV) in routine immunization schedule. A comprehensive understanding of mucosal immunity in populations and best response options against circulating vaccine derived poliovirus (cVDPV) outbreaks in post tOPV-bOPV switch is essential to mitigate the risks of wild and vaccine-derived poliovirus importations and emergence of cVDPVs in polio-free countries. A clearer picture is also needed on few operational issues, interference between polio vaccines and other EPI vaccines and products related to polio endgame. It is also extremely important to develop mechanisms to identify and manage long-term poliovirus excretors who may pose a risk of reintroduction into the population after global eradication of poliovirus.

Keywords: Eradication, Information gaps, Polio, tOPV-bOPV switch.

India used multiple innovative strategies and interventions to overcome technical and operational barriers during its journey towards polio eradication. Research played a pivotal role in identifying and overcoming many challenges by guiding programmatic actions and fine-tuning strategies. Analytical research studies and clinical trials led to a better understanding of the risk factors for poliovirus transmission and immunogenicity of available polio vaccines. Independent program evaluations through periodic seroprevalence surveys contributed to optimization of the use of different polio vaccines. Vaccine trials and epidemiological analysis have guided the development of polio endgame strategy [1].

India led many research studies to fill information gaps at various stages of the Global Polio Eradication Initiative (GPEI). Globally, a lot of efforts was undertaken in recent years to address the information/understanding gap which might impede the progress towards global eradication. However, many potential gaps still persist in the understanding of polio vaccination and immunity. As the polio program enters an uncertain phase of endgame strategy, it is extremely important to identify and address these gaps in information; for a predictable and risk-free progress towards a lasting world free of wild and vaccine polioviruses. A few issues pertaining to the switch from trivalent to bivalent oral polio vaccine (tOPV-bOPV), the introduction of inactivated polio vaccine (IPV) in routine immunization schedule, and the best response options against potential

circulating vaccine-derived poliovirus (cVDPV) outbreaks need immediate attention. Lack of comprehensive understanding of mucosal immunity in populations may affect mitigating the risks of poliovirus importations and emergence of cVDPVs in polio free countries. Further clarity is needed on some operational issues and vaccine interference due to co-administration of polio and other EPI vaccines. Lack of clarity on mechanisms to identify and manage long-term poliovirus excretors will be important for the polio program even after global eradication of poliovirus.

INFORMATION GAPS

tOPV-bOPV Switch and Sequential Sabinvirus Withdrawal

Continued use of tOPV, despite global eradication of type-2 poliovirus in 1999 is responsible for >95% of all cVDPV cases and approximately 30% of vaccine-associated paralytic poliomyelitis (VAPP) cases in the last few years [2]. Switching to bOPV from tOPV, besides eliminating the risk of type-2 VDPV and VAPP, will also provide an additional push to eradicate wild poliovirus (WPV) types 1 and 3 by virtue of superiority of bOPV over tOPV [3]. The 65th World Health Assembly endorsed the global switch from tOPV to bOPV in all OPV-using countries and the Strategic Group of Experts (SAGE) on immunization reaffirmed that the switch should be undertaken in April 2016. It has also been recommended that all OPV using countries should introduce at least one dose of IPV in their program as a

part of this switch process [4,5]. Many research studies have guided the OPV switch plan [6,7]. Yet, many questions relevant to the use of bOPV in combination with IPV at DPT3 in the routine immunization (RI) schedule still remain unanswered.

- (i) Just a couple of months prior to the switch, >200 million doses of tOPV would have been given to children in India immunized as a part of the National Immunization Days (NIDs). These vaccine strains (Sabin poliovirus) may continue to circulate in communities if immunity levels against type-2 poliovirus are low. Post tOPV-bOPV switch, an OPV2-naive birth cohort would develop and accumulate with time. This cohort would be deprived of mucosal immunity against type-2 poliovirus [6]. This will pose the risk of emergence of cVDPV2 post tOPV-bOPV switch from any circulating OPV2 strains from the pre-switch tOPV administered. The risk will be highest during the immediate post-switch period. Similar risk situations will be encountered for cVDPV1 and cVDPV3 when bOPV is finally removed from the program. Though no effective tool seems to be available presently against this extremely important risk associated with tOPV-bOPV switch, there are some efforts to develop combined IPV formulations with added mucosal adjuvant; the double mutant of a bacterial heat-labile toxin (dmLT). Though animal data suggest that vaccination with dmLT-IPV combination results in specific induction of mucosal immunity, further human trials are needed for development of these vaccines [8-10].
- (ii) Post tOPV-bOPV switch, type-2 OPV-naive birth-cohort will result in accumulating gap in mucosal immunity in the community. Simultaneously, type-2 OPV virus circulating in this cohort from the previous tOPV immunization may be emerging as VDPVs. A mathematical modelling is needed to estimate the 'breakeven' duration, after tOPV-bOPV switch, when the incremental gap in mucosal immunity in this birth cohort could lead to an outbreak of cVDPVs in the community. This understanding is extremely important to pre-empt all potential cVDPV2 outbreaks in future.
- (iii) Similar concern, as above, is applicable to mucosal immunity profile against type-1 and 3 polioviruses, of a similar cohort during bOPV withdrawal currently schedule for 2019-20. It is also worthwhile knowing the both humoral and mucosal immunogenicity against type-1 poliovirus when mOPV1 is given in EPI schedule to support the program to understand the risk associated with a

switch from bOPV to mOPV1 before withdrawal of all OPVs.

Introduction of IPV in Routine Immunization

In response to the World Health Assembly (WHA) declaration in 2012, the Polio Eradication and Endgame Strategic Plan 2013-2018 was developed [11]. WHO now recommends at least one dose of IPV into RI as a strategy to mitigate the potential risk of re-emergence of type-2 polio following the withdrawal of Sabin type-2 strains from live OPV [12]. IPV could also be put to use in future polio outbreaks [13]. India has already introduced a single dose of IPV at DPT3 contact in RI schedule. Recent research studies have provided useful information on potential routes (full/fractional), doses, schedule, immunogenicity, priming effect and mucosal response associated with IPV introduction in RI [6,7,14,15]. Many gaps; however, still persist in the understanding related to IPV use:

- (i) IPV given to OPV-primed individuals is known to boost mucosal immunity [6,7]. However, not much is known on the duration of mucosal response induced by a dose of IPV in these individuals; an important fact needed to predict population mucosal immunity and the nature of response, should an outbreak occur during the polio endgame.
- (ii) Depending upon the global epidemiology of polio in the future, the program may either switch to mOPV1 (plus IPV at DPT3) from bOPV (plus IPV at DPT3) or opt for an all IPV in the RI schedule. As these are definitive futuristic vaccine options, it is important to understand the immunogenicity of IPV against poliovirus types 2 and 3 when administered with mOPV1 at DPT3 contact in RI schedule.
- (iii) The polio program needs to understand better the number of doses, schedule and immunogenicity of an IPV-only schedule in RI, after the final cessation of all live OPV.
- (iv) In the concluding phase of global polio eradication, bio-security and containment concerns would require that wild poliovirus is not used by manufacturers to produce IPV. Sabin-IPV or possibly a virus-free polio vaccine may be considered. Additional data on immunogenicity and safety of Sabin-IPV formulation will be required before its potential use in India.

Mucosal Immunity/Response

Data from several sources suggest a strong likelihood of older individuals participating in international spread of polioviruses [16]. Indian infants have high levels of humoral immunity with seroprevalence rates >90% for all

poliovirus types [17]. Humoral protection alone; however, cannot guarantee the interruption of poliovirus transmission in a community. A good intestinal mucosal immunity prevents infection of gut with poliovirus and subsequent multiplication, excretion and spread among communities. Research studies indicate that the intestinal mucosal immunity wanes significantly after vaccination with OPV [7,18]. Outbreaks of polio may continue to occur if intestinal mucosal immunity is not sustained at high levels until global polio eradication is achieved [16,19]. Given the importance of mucosal immunity in the final push towards eradication of poliovirus, many studies have addressed issues related to mucosal immunity [6,7,18]. Nonetheless, further studies are required to address the remaining gaps pertaining to the polio endgame strategy:

- (i) Due to a waning of the mucosal immunity, older age groups may participate in the transmission of poliovirus. In the eventuality of a wild poliovirus (WPV) importation in a polio-free country or the circulation of Sabin virus in the community, the older age group may facilitate the spread of WPV or the emergence of cVDPV, especially after tOPV-bOPV switch. The potential role of older age groups in future transmission of poliovirus requires a better understanding by assessing the mucosal immunity profile of young and elderly population.
- (ii) It will be very helpful to be aware of the precise number of polio campaigns required and the 'lead-time' needed for effective development of mucosal immunity in the community to interrupt transmission during an outbreak of polio in future.
- (iii) To keep the populations continually 'sanitized' against WPV and VDPVs, after an outbreak, it is important to keep the mucosal immunity to such levels that WPV importations or emerging VDPVs do not re-establish transmission. This needs a precise knowledge of duration of mucosal protection after the last dose of OPV or IPV in immunized populations. This information will help to precisely plan the intervals between OPV/IPV campaigns against any future outbreaks.
- (iv) As mucosal immunity takes center stage towards the final push for eradication, an easy and rapid correlate (surrogate marker) of mucosal immunity will be very valuable (such as serum IgA and secretory IgA levels, gingival fluid IgA and ELISPOT test). A consensus on this matter is needed through further research and analysis.

The salient findings of few important studies on

mucosal immunity on polio are detailed in **Table I**.

Outbreak Responses to cVDPV2 post OPV Switch

One of the greatest risks to polio program in the immediate future is the outbreak of cVDPV2 post bOPV-tOPV switch. Research and global consensus is needed on VDPV detection, mitigation strategy and best response to an outbreak. Few urgent questions are as follows:

- (i) What are the best vaccine options to respond against a cVDPV2 outbreak (mOPV2 *vs* IPV *vs* combined or sequential response)?
- (ii) What is the immunogenicity and safety profile of m-IPV2 (increased type-2 antigen content monovalent IPV) in children and adults?
- (iii) Is there a need to redefine the VDPVs to a lesser number of nucleotide changes on VP1 segment of the poliovirus genome (presently 6 nucleotide changes for VDPV2 and 10 for VDPV 1 and 3) for early detection and pro-active response?

Immunodeficient Long-term Poliovirus Excretors

A small number of immunodeficient individuals may exhibit prolonged excretion of VDPV (iVDPVs) following infection with oral poliovirus vaccines. These individuals pose the risk of reintroduction of live poliovirus even after global wild poliovirus eradication has been achieved [23].

- (i) Intensified efforts are needed to develop mechanisms to identify individuals whom are long-term poliovirus excretors in the communities and develop anti polio viral drugs to clear iVDPV infections in these patients.

TABLE I SALIENT FINDINGS OF IMPORTANT STUDIES ON POLIO MUCOSAL IMMUNITY

1. bOPV given in routine schedule with IPV at week 14 provides the best mucosal response against poliovirus types 1 & 3 but poor mucosal response against type 2 [6].
2. IPV in OPV primed individuals boosts intestinal mucosal immunity [7].
3. Intestinal mucosal immunity after infection with OPV appears to wane significantly within a year of vaccination [18].
4. IPV alone does not induce sufficient intestinal mucosal immunity [20].
5. The mucosal response correlated with seropositivity for neutralising antibody against poliovirus [21].
6. Supplementary dose of IPV given to OPV primed children substantially boosts intestinal immunity [22].

(ii) Research studies are needed to be undertaken to better understand the genomic dynamics and characterization of Sabinvirus in the emergence of VDPVs, especially in immunodeficient long-term poliovirus excretors. Could a genomic profile be standardized to indicate the progression in a person towards long-term excretor status and ‘catch them early on’?

Interference Between Polio Vaccines and Other EPI Vaccines

Interference by other vaccines co-administered with OPV/IPV is known to occur [24]. It is known that IPV diminishes antibody response to the pertussis vaccine [25]. Somewhat lower responses against poliovirus type 2 were observed after co-administration of both PHiD-CV and 7vCRM vaccine [26]. As programs introduce range of newer vaccines, interference between polio and other RI vaccines may have an unexpected interference. (*e.g.* rotavirus, pentavalent, Yellow fever, PCV, measles etc.). Studies are needed to better understand any such interference.

EFFORTS TO ADDRESS INFORMATION GAPS

As the world gets closer to global polio eradication, research studies to fill major information gaps will have to continue, for a confident, scientifically sound and effective traction of the polio endgame. Many international agencies including the WHO, UNICEF, US-CDC, BMGF, PATH, national governments, academic institutions and other organizations are already working to address many of the concerns listed in this article; many in coordination with the global Polio Research Committee (PRC) at WHO headquarter. The India Expert Advisory Group (IEAG) on polio eradication and the Immunization Technical Advisory Group (ITAG) and Advisory Committee on Health Research (ACHR) of the South East Asia Region of WHO have endorsed many studies to fill gaps relevant for the planning and implementation of the polio end game strategy. India has lined up many collaborative research projects on vaccine trials, mucosal immunity and seroprevalence studies addressing the gaps pertaining to the implementation of polio endgame. These studies are proposed to be done in partnership with the WHO, the Government of India, Indian Council of Medical Research (ICMR), and medical institutes and other stakeholders across India.

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