PERSPECTIVE

Recurring Outbreaks of Circulating Vaccine-derived Polioviruses: Implications for Global Poliovirus Immunization Strategy

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The incidence of polio has decreased by more than 99.9% and currently, only two countries are endemic for wild poliovirus. However, increasing outbreaks of circulating vaccine-derived poliovirus globally in the last few years, with the latest ones in high-income, exclusive inactivated polio virus vaccine (IPV)-using countries have brought out a new dimension to the end game of polio eradication. The inability of the current IPV to induce efficient mucosal immunity in the intestine is likely to be one of the key reasons behind the silent transmission of the polio virus in these countries. New challenges demand concerted global efforts with renewed vigor to cross the last mile. We need to aggressively cover up areas of under-vaccination and continue large-scale genomic surveillance. Further, the availability of a novel oral polio vaccine (nOPV2), and the likely availability of Sabin IPV and a more refined IPV with mucosal adjuvant in the near future is likely to go a long way in achieving this remarkable feat.

Keywords: *Novel oral polio vaccine, Polio end game, Polio eradication.*

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Since the beginning of polio eradication efforts in 1988, the incidence of polio has decreased by 99.9%. Currently, only two countries are endemic for wild poliovirus: Pakistan and Afghanistan [1]. However, the persistence of wild poliovirus (WPV) in these two countries is not the only challenge faced by the Global Polio Eradication Initiative (GPEI), the recurring outbreaks of circulating vaccine-derived poliovirus (cVDPV) in many countries have further complicated the task. Several such cVDPV outbreaks have been reported, mostly in low- or middle-income countries and always in populations with poor vaccine coverage [2]. Although all three types of polioviruses can cause cVDPV, over 90% of these cVDPV outbreaks are caused by the type-2 virus (cVDPV2) [3]. Since the last type 2 wild poliovirus (WPW2) case was seen in 1999 [4], and over 90% of VDPV outbreaks and over 40% of cases of vaccine-associated paralytic poliomyelitis (VAPP) were documented to be caused by OPV2, OPV2 was withdrawn globally – in a coordinated manner, among all OPV-using countries in April, 2016 [3]. Thus, trivalent OPV (tOPV) was replaced by bivalent OPV (bOPV) globally, the 'global switch.'

Was the Global Switch A Failure?

While in 2017-2020, type 1 WPV (WPV1) transmission was limited to endemic countries only (Afghanistan and Pakistan), in 2021-2022 non-endemic countries, Malawi and Mozambique also reported a few confirmed cases of WPV [1]. Unexpectedly, rather than decreasing, the number of cVDPV2 outbreaks also increased significantly after the trivalent OPV (tOPV)-to-bivalent OPV (bOPV) switch. There were only two countries (with 96 cases) with VDPV outbreaks in 2017, 5 countries (71 cases) in 2018, and 15 countries (251 cases) in 2019. Overall, there have been more than 2600 cVDPV2 paralytic cases out of 100 VDPV2 outbreaks from at least 70 independent emergences affecting at least 38 countries in the last six years [2].

The global switch from tOPV to bOPV with the removal of type 2 was one of the key elements of GPEI's 'polio endgame.' However, cessation of Sabin type-2 poliovirus from tOPV for routine immunization along with shortages of IPV led to low population immunity against type-2 poliovirus, giving a foothold to the virus in many communities. Unsurprisingly, few experts are now calling the 'global switch' a failure, owing to poor risk management and sub-optimal coordination of OPV cessation [5].

Vaccine-Derived Polio in IPV-Using High-Income Countries: A Cause for Concern

The recent detection of poliovirus in sewage samples and new outbreaks of cVDPV in some of the non-OPV-using developed countries like Israel, England, and the USA has turned global attention again toward polio eradication and polio immunization strategies [6]. While paralytic cases were reported from Israel (single case, unvaccinated) and the US (single case, unvaccinated), England reported cVDPV2 (the first evidence of polio transmission since

1984) in the sewage only. Though, over 30 countries have reported cases or isolates of VDPVs in 2022 [3], those in Israel, the UK, and the USA have received greater attention since these are high-income countries with excellent Water, Sanitation, and Hygiene (WASH) infrastructure and good overall IPV coverage. These countries had eliminated WPV long back and are not using OPV for over 18 years. Moreover, genotyping of the isolates from these three countries was found to be genetically linked (>99.0% identity), indicating a common source in an unknown fourth country, still using OPV. This incident indicates multi-country, community transmission [7] and is thus of grave concern.

Why outbreaks of cVDPVs in IPV-using countries?

The above incidents have amply demonstrated that the terminal 0.1% of the eradication initiative, the 'end game,' is going to be as challenging as the first 99%. But the most concerning aspect is why IPV-using countries are facing outbreaks of cVDPVs despite excellent immunization coverage. Though large inter-state and intra-state variations in the vaccination coverage in some regions and growing vaccine hesitancy among certain communities may have a significant impact, the key reason might be the failure of the current IPV to induce effective mucosal immunity in the intestine that provides resistance to poliovirus replication and shedding upon oral exposure to the live virus – vaccine or wild. While the inactivated vaccine offers excellent individual protection against paralytic disease to the vaccinees by virtue of high titers of serum-neutralizing antibodies, it fails to prevent viral transmission, especially the poliovirus replication at the intestinal border, which may explain the silent transmission of poliovirus in some developed countries [8].

Intestinal Mucosal Immunity: The Key Determinant of Polio Transmission

The concept of mucosal immunity is distinct from the serum response, and the notion that transudation of serum antibodies to the intestinal border elicits mucosal resistance to viral shedding in IPV-immunized individuals does not hold in the light of new understanding about intestinal mucosal responses. Early studies also suggested that the transudation of serum antibodies makes a minimal contribution to total antibody concentrations in the mucosa [9]. Recent studies have proved that IgA, particularly the isotype IgA1, mediates the mucosal neutralization of poliovirus at the intestinal border [10].

The mucosal immunity at the gut level is induced by secretory IgA, mucosal IgG, and to some extent through tissue-resident memory T (TRM) cell populations. In the absence of enteric IgA against poliovirus in older children and adults, TRM cells may provide some resistance to poliovirus replication in the intestine through cytokine-mediated recruitment of both innate and adaptive immune cells [11]. However, the IgA at the intestinal border is the most abundant antibody providing the first-line defense against invading pathogens. Mucosal IgA level correlates with viral neutralization in the gut, not the mucosal IgG level [12]. A recent paper examining SARS-CoV-2 nasal IgA responses after natural infection and vaccination concludes that parenteral vaccination after COVID-19, boosted nasal and plasma IgG but had a limited impact on nasal IgA [13].

Traditionally, IPV is known to elicit excellent mucosal immunity at the pharynx that helps in curbing 'oral-oral' virus transmission, the main mode of poliovirus circulation in countries having temperate climates. However, due to poor mucosal immunity at the intestinal level, the imported live virus could circulate unhindered in the intestines of IPV-immunized individuals. In a recent study, children aged 1-5 years who had already received up to four doses of IPV were challenged with a mOPV2 dose. Only about one-third of children developed type-2 specific neutralization titers (>32) in their stools and continued to shed the vaccine virus in the stools even after the second challenge dose [14]. Studies have even shown that vaccine naïve children excrete less amount of vaccine virus for a shorter duration following the second challenge dose of the same strain of OPV than IPV-immunized children [8,15]. Many studies on mucosal immunity conducted recently in a few Latin American countries and Europe conclude that initial receipt of IPV during the primary immunization schedule may lead to compromised development of intestinal immunity that results in greater shedding after a live polio vaccine challenge in older children than those who received OPV during their primary immunization series [8]. These studies further demonstrate that the type-specific enteric antibodies to poliovirus in infants are stimulated by the replication of the live virus in the intestine. In vaccine-naïve children, receipt of an IPV-only primary series is insufficient to induce significant levels of enteric IgA and virus-neutralizing activity in the absence of OPV. This limitation of IPV regarding intestinal immunity was known since the early 60s, and has got huge implications for the polio eradication initiative [15].

Another factor that may have facilitated the transmission of poliovirus in vaccinated individuals is the finding that mucosal immunity in the intestine either fails to develop or wanes progressively, after primary series of vaccination in older children, adolescents, and adults, thus creating an 'immunological gap' in this population [8]. Though, this defect in intestinal immunity is starker with IPV, studies have shown that even OPV reci-

pients experience partial waning after a year of primary series [16]. The transient nature of mucosal IgA response is further confirmed in the above-cited SARS-CoV-2 study, wherein nasal IgA levels waned after nine months of natural infection and could not be induced by subsequent intramuscular vaccination [13]. Studies conducted in adult popu-lations who had received IPV during the primary infant series demonstrated the absence of polio neutralizing antibodies and enteric IgA in stools following mOPV1/nOPV2 challenges despite excellent serum-neutralizing antibodies response [8]. This phenomenon may explain the involvement of the adult population in the transmission of the polio virus noted in the recent outbreaks of cVDPV in IPV-using countries.

HOW TO TACKLE THE GROWING MENACE OF VDPV: THE WAY OUT

Reaching the unreached

Maintaining high coverage of available vaccines has been the crux of GPEI which has led to the eradication of two of the three WPVs. However, recent outbreaks like that in New York have clearly demonstrated that pockets of under-vaccination exist even in highly immunized countries and can pose a serious threat to the program. It is imperative to tackle these on a war footing, with a special focus on the last person in the queue: the zero-dose children, those who have not received a single dose of any basic vaccine.

Continuing large scale genomic surveillance

Right from the early phase of GPEI, genotyping of specimens isolated from cases and from the community played a crucial role in the whole program. However, paralysis is a relatively rare outcome of poliovirus infection and can be a lagging marker for significant circulation. Detection and the pro-active management of outbreaks in Israel and the UK have demonstrated that identification of silent transmission by viral culture and/or molecular surveillance of wastewater is going to be crucial, going forward.

Development of novel vaccines

Novel oral polio vaccine against type 2 (nOPV2): Both OPV and IPV are effective and time-tested vaccines. However, increasing instances of VDPV have amply demonstrated their drawbacks: rare risk of reversion of virulence of vaccine strains with OPV, and lack of intestinal immunity with IPV: both contribute to the threat of VDPV. The GPEI experts realized the need of developing a safer alternative that keeps the merits of OPV intact. The development of a new OPV, a 'novel' OPV against the type-2 virus (nOPV2), must be viewed as an effort in this regard [17]. The new nOPV2 contains up to five more mutations in its genome than the existing vaccine, which are needed to regain neurovirulence [18]. The nOPV2 has been rolled out in Africa without any safety signal, even after the administration of over 500 million doses.

Till recently, mOPV2 was being used for tackling cVDPV outbreaks, which ironically re-introduces OPV2 in the community that can further lead to the emergence of new VDPV strains. The use of nOPV2 in place of mOPV2 for this purpose would be a lot safer. The CDC, USA is also contemplating its use in areas with persistent poliovirus circulation to tackle the ongoing cVDPV outbreak [19]. Deployment of nOPV2 and the availability of nOPV types 1 and 3 in future should help diminish the threat of future VDPV outbreaks.

Mucosal IPV: While the development of nOPV is an attempt to solve one of the major limitations of the Sabin-OPV, innovations are similarly needed to develop better IPV also. Development of Sabin-IPV can lead to ease of manufacturing of IPV as it would require less stringent biosafety measures to handle Sabin strains instead of WPVs [20]. However, this move does not address one critical issue: the failure of IPV to induce efficient intestinal immunity. A large meta-analysis concludes that while tOPV/bOPV effectively limits the viral replication in the intestine, the addition of one or more doses of either fIPV or full-dose IPV will not increase intestinal immunity to the type-2 virus, hence, will not prevent transmission or circulation of type 2 poliovirus [21].

Several hypotheses are offered to explain the lack of intestinal IgA responses observed in older children and adults with a history of childhood IPV: active suppression of intestinal IgA by IPV given during infancy, inadequate T cell-mediated stimuli for IgA induction, immune tolerance in the intestine, and the suppressive effects of T-regulatory cells (Tregs). Recent studies have indicated that Tregs play an essential role in shaping mucosal IgA responses to infections and vaccination [8].

Certain adjuvants could help enhance mucosal immunity, potentially mimicking the protection against intestinal virus shedding seen with OPV. One such adjuvant is LT(R192G/L211A) or dmLT, a heatlabile enterotoxin of *Escherichia coli*-based mucosal vaccine antigen that has been shown to modulate human Tregs and Th17 cells to induce strong antigen-specific Th17 responses that enhance mucosal IgA production. The dmLT enhances intestinal immunity when included in IPV immunization by ID or IM delivery in animal studies [22]. GPEI is conducting clinical trials of dmLT co-administered with IPV in adults that will provide valuable information on the impact of targeted modulation of cellular responses for induction of long-lived polio-specific mucosal IgA and virus-

neutralizing responses in the intestine.

Development of new polio vaccines: The GPEI is also exploring the possibility of developing some new, non-infectiously (non-live virus) produced polio vaccines based on mRNA and virus-like particles (VLPs) technology. Development of these vaccines may offer considerably more opportunities for managing polio endgame risks, particularly during the post-eradication era [5].

ARE THERE OTHER OPTIONS?

Going back to Sabin tOPV: Some modelling studies suggest that the current trajectory for eradication of type 2 Sabin virus is not on its way even with the use of nOPV2 [5]. Though the new nOPV2 has been aggressively employed to tackle emerging cVDPV2 outbreaks, particularly in OPV-using countries, there is still no real-world data from these countries. There are speculations on the performance of this new nOPV2 – it may perform better than or equal to mOPV2 depending on its effectiveness in real populations. Since the GPEI has selected a low dose nOPV formulation for use in the field [17,23], the overall effectiveness of the new nOPV2 may be less than the existing mOPV2. Further, there may be different relative take rates for the three types of OPV when combined with the current bOPV. Modelling by Thomson, et al. [5] suggests that abruptly ending all OPV use in 2023 and relying exclusively on IPV to prevent paralysis would lead to re-established endemic transmission of poliovirus with a significantly large number of polio cases, particularly type 1 and 2. They find betterexpected health and economic outcomes associated with ending IPV use and restarting tOPV, given the current global performance on OPV cessation in OPV-using countries [5].

Abandoning global polio eradication and settling for control: Few experts have recently urged the WHO/GPEI to consider refocusing on eradicating poliomyelitis as a disease, rather than eradicating the virus itself [24]. Unarguably, the GPEI has delivered immense good to mankind with a 99·9% reduction in the global incidence of polio, saving more than 1·5 million lives and an estimated 16 million people from paralysis. Two of the three serotypes of WPV types 2 and 3 have been certified as eradicated worldwide. Thus, the demand of abandoning eradication at this juncture may not only prove to be highly demoralizing to the entire scientific community and health workers but may also jeopardize the future effort to eradicate any life-threatening disease.

CONCLUSIONS

Though the GPEI has succeeded in bringing WPV transmission to an extremely low level, the silent circulation of live polioviruses in countries with high IPV immunization coverage demonstrates the limited ability of the IPV to stop poliovirus transmission. Through the development of nOPV2, the GPEI has made a great stride to address one of the key limitations of the live polio vaccine, it is time to address the dwindling mucosal immunity at the intestinal border, the major limitation of the current generation of the IPV. The GPEI needs to urgently address the threat posed by cVDPVs by improving geno-mic surveillance, investing in a more efficient IPV and closing the immunity gaps since the 'window of oppor-tunity' will not remain open indefinitely.

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