A Brief History of Vaccines Against Polio

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Poliomyelitis, a dreaded disease of the last century that had already crippled millions of people across the globe, is now on the verge of eradication thanks mainly to two polio vaccines, inactivated polio vaccine (IPV) and oral polio vaccine (OPV). Ever since their development in late 1950s and early 1960s, the journey of their early development process, clinical trials, licensure and ultimately widespread clinical use in different countries provide a fascinating tale of events. Oral polio vaccine has been the mainstay of global polio eradication initiative (GPEI) in most of the countries. With the advent of ‘polio endgame’, the focus has now shifted back to IPV. However, there are certain issues associated with global cessation of OPV use and universal implementation of IPV in routine immunization schedules across the globe that need to be dealt with some urgency, before proclaiming the global victory over polio.

Key words: Global polio eradication initiative, polio, vaccines, polio endgame, vaccine development.

The global polio eradication initiative (GPEI) is now in its last leg. Barring two countries, Pakistan and Afghanistan, endemic transmission of wild polio virus has been halted all over the globe. The wild polio virus (WPV) type 2 has been eradicated completely, WPV type 3 is also not detected from anywhere for more than three years, and the entire African continent has been ‘polio-free’ for more than a year [1]. This is indeed a remarkable feat. The ‘end game’ strategies are now under implementation world-over and gradual process of oral poliovirus vaccine (OPV) withdrawal has already initiated with the introduction of inactivated poliovirus vaccine (IPV) in the immunization schedules of almost all the countries hitherto using OPV in their schedules [2]. OPV has successfully eliminated WPV from major part of the world. However, circulating vaccine derived polioviruses (VDPVs) and vaccine-associated paralytic polio (VAPP) have exposed its shortcomings and paved the way for introduction of IPV in to the global vaccination schedules. The polio eradication and endgame strategies reflect the complimentary roles of the two polio vaccines in tackling the threats posed by wild and vaccine polioviruses. Whenever the history of polio eradication would be written, the selection of OPV as a preferred tool over IPV by World Health Organization (WHO) for global polio eradication shall be a source of intense, passionate debate.

POLIO VACCINE DEVELOPMENT- HISTORICAL PERSPECTIVES

A. Inactivated Poliovirus Vaccine (IPV)

Poliomyelitis was a public health scare in the 1950s, even in countries with the best health systems and hygiene practices in place [3]. The earliest attempts to develop polio vaccines turned out to be futile. In early 30s, John Kolmer from Philadelphia, and Maurice Brodie from New York University tried to make polio vaccines which unfortunately were found to be quite unsafe and resulted in few deaths and many cases of VAPP [4, 5]. During the aftermath of these deaths, a hostile media and state health administration severely criticized the researchers. The progress of polio vaccine development was halted and no new trials were undertaken for next decade [3]. However, the impasse was over in 1949 when Enders, Weller, and Robbins of Harvard Medical School, Boston, USA, published their findings on successfully growing Lansing strain of polio virus in cultures of various human embryonic tissues [6], and many laboratories restarted their work on developing polio vaccines.

Though Koprowski first tested a live attenuated, rodent-adapted strain of poliomyelitis virus vaccine in humans in 1950 at Wistar Institute in Philadelphia [7], it was Jonas Salk who succeeded in developing the first-ever licensed vaccine against polio—a trivalent inactivated poliovirus vaccine, called Salk vaccine or IPV in 1955 [8]. The Salk IPV was tested by Thomas Francis in a very large clinical trial conducted in United State (US) in 1954. This was the first and the largest controlled clinical trial involving more than 1.8 million subjects. Around 420,000 children were administered Salk IPV, 200,000 a placebo, and 1.2 million kids received nothing [3]. This vaccine was found 60 to 70% effective against poliovirus Type I, and 90% against other two strains, i.e. Types II and III [9]. The results of this trial were announced on radio (not
published in a journal) on April 12, 1955 and within 2 hours, Salk IPV was licensed in US for mass use [9]. The National Foundation for Infantile Paralysis (now the March of Dimes) which was established by US President Franklin Roosevelt in 1938, helped in industrial production of the Salk IPV. Some European countries imported the Salk IPV from the US whereas some other like the Netherlands, Denmark, and Sweden started production of Salk IPV in their own public health production units [9].

The impact of Salk IPV: When IPV was introduced systematically in the US, ~99% reduction in polio incidence was achieved when 3rd dose vaccine coverage was only <70% in under-5 children [10]. Finland conducted nation-wide campaigns and eliminated poliovirus transmission by 1962 [11]. Wild polio virus was eliminated when 3rd dose coverage reached 54% in the total population. Clearly, incidence decreased even in the unvaccinated, due to retardation of wild poliovirus transmission (‘herd effect’).

B. Oral Polio Vaccine

Despite the success of Salk vaccine, the efforts to develop other polio vaccines, particularly the live oral vaccine were continued. Three US scientists namely Cox, Koprowski and Sabin, persisted with their quest of a live polio vaccine, the first two conducted research at Lederle Institute, and Sabin at the University of Cincinnati [3]. Koprowski later shifted with his candidate vaccine to Wistar Institute in Philadelphia. All these trials took place outside the US since it was difficult to find adequate vaccine-naive subjects due to widespread use of Salk IPV. Hence, Koprowski conducted most of his trials in Northern Ireland and Congo, Cox in Latin America, and Sabin in the Soviet Union [9]. Albert Sabin collaborated with his Russian colleagues to conduct massive trials and had administered his oral vaccine to around 15 million subjects by July 1960 [3].

Salk maintained that only a single dose would suffice for primary immunization and immunological memory generated by it would obviate the need of future boosters. Nevertheless, there was a perception amongst scientific community that probably the Salk’s vaccine could not provide long-lasting protection against paralysis and a live vaccine would be the ideal candidate needed for longer protection. On the basis of enormous trials by Albert Sabin and the positive review by Horstmann of the Russian trials, his oral candidate vaccine was considered better than other oral products developed by his contemporaries [12-14]. The Sabin vaccine was found to offer durable immunity, fast onset of action, ease of administration by oral rather than through injection, and prospect of provision of ‘contact immunization’ to unvaccinated individuals through passage of live attenuated viruses in the feces. In August 1960, the US Surgeon General recommended licensing of the Sabin vaccine [3].

OPV was licensed initially in the USA as monovalent (m-OPV) and in 1963 as mixture of types 1, 2 and 3 (trivalent, tOPV). Until 1963, both Salk IPV and Sabin OPV were used in the USA, but by the 1964 tOPV grown in monkey kidney cell culture replaced IPV in USA. So, the OPV gradually ousted its rival and by 1968, Salk IPV was no longer being administered in the USA, and manufacturers had stopped producing it [9]. Although Sabin vaccine had clear-cut advantages over Salk IPV, few European countries like the Netherlands and Scandinavia continued exclusive use of the latter in their immunization programs [9]. The risk of VAPP with Sabin OPV was for the first time suspected in 1962 in USA. In 1964, a study done there confirmed a definite albeit a very small risk of VAPP associated with the use of Sabin vaccine [9]. However, the benefits associated with the use of OPV outscored the small risks associated with its use. Consequently most US health officials voted in favor of OPV as a preferred vaccine to take on polio in US. By the end of 60s and early 70s, Sabin OPV was the main vaccine against poliomyelitis in majority of the countries worldwide [3, 9].

Later, in 1974 when World Health Organization (WHO) launched the Expanded Program on Immunization (EPI), OPV was recommended for use in all low and middle income (LMl) countries. In 1988 when the GPEI was launched, the OPV was chosen as an exclusive tool for use in all these countries [15, 16].

C. Improved Salk IPV-the eIPV

Netherlands continued to manufacture Salk IPV indigenously and also use it in their immunization program. Their scientists persisted with their efforts to improve it in their research laboratory, Rijksinstituut voor Volksgezondheid (RIV), in Bilthoven. The IPV produced in the Bilthoven facility was sufficient to meet the entire country’s need. Later, Hans Cohen, a microbiologist at RIV successfully produced a combination of Salk’s IPV and DTP vaccine [17]. However, this process necessitated enhancement in the potency of IPV which needed large amount of monkey’s kidney cells. The institute’s requirement was around 5000 Rhesus monkeys per year that had to be imported from Asian countries. This was one of the major constraints to produce a refined IPV since around 20% of imported monkeys would die soon after arrival. Two Dutch microbiologists, Paul van Hemert and Anton van Wezel later succeeded in improving the molecular genetic techniques to grow...
polioviruses that reduced the annual consumption of live rhesus monkeys at the institute to just seven by 1978. van Wezel grew large quantities (>thousand folds) of monkey kidney cells along with polioviruses on the surface of small plastic beads filled in to the stainless steel vessels. The unit at RIV that used to grow large quantities of microorganisms was called ‘Bilthoven Unit’. The process was adapted by Van Wezel, and known as the ‘Bilthoven process’. It thus became possible to produce a higher potency Salk’s IPV with a more refined manufacturing process with proper standardization. Later in 1978, this improved, high-potency IPV was field tested in Mali and Burkino Faso by a research establishment formed by Salk, Cohen, and Charles Mérieux. The new IPV, ‘enhanced-potency IPV’ (eIPV) was found highly efficacious with just two doses [18]. The Bilthoven process was further improved by propagating the virus in a cultured monkey kidney cell line at Institut Mérieux. So the incentives for the Netherlands to develop a more potent and refined IPV were their determination to become self-sufficient in their domestic requirement of the vaccine, to administer IPV in a combo DTP-IPV form, and of course, to avoid their dependency on imported wild monkeys [9]. Today only the improved eIPV is manufactured and supplied to whole world including USA.

VACCINE CHARACTERISTICS

A. Inactivated Poliovirus Vaccine (IPV)

The current generation IPV is made by formalin inactivation of laboratory-maintained and vero-cell grown wild poliovirus (WPV) strains known as Mahoney (type 1), MEF-1 (type 2) and Saukett (type 3). Although IPV is considered safe, there is a risk of exposure to the wild type strain during the manufacturing process. During monovalent bulk preparation, vero cells are expanded using two pre-culture steps and cell culture followed by virus culture. The poliovirus is purified using normal flow filtration for clarification, tangential flow filtration for concentration and followed by two chromatography steps involving size exclusion and ion exchange chromatography. Purified virus is inactivated using formaldehyde [19]. Subsequently, the virus harvest is concentrated by ultrafiltration and cellular proteins and DNA removed by column chromatography, prior to inactivation [20, 21]. Then the three types are mixed to obtain 40, 8 and 32 D antigen units of types 1, 2 and 3, respectively [18]. Potency is determined by its antigen content, which is designated D [19]. Due to the need to cultivate large amounts of the live polio virus which involved complex manufacturing and purification processes, exposure of workers to the live virus must be safely guarded. There is no adjuvant added to IPV. Since the preservative thiomersal affects IPV potency, in combination products with DTP it is either avoided or replaced with 2-phenoxy-ethanol [19]. On account of fear of seed-virus leak, IPV production in low and middle income (LMI) countries is not allowed for bio-safety reasons. The WHO has set BSL-4, a very high bio-safety measure, as a requirement for manufacturing IPV at current manufacturing sites.

Jonas Salk, as described above, did argue in favor of a single dose of IPV for primary immunization. However, the later trials in Senegal proved that a single dose of even the new generation enhanced-potency IPV provided only 36% protection to vaccinated individuals [22]. Although vaccination schedules vary between countries, the principle of ‘prime-boost’ is common to all. One dose is sufficient to ‘prime’, but two are better. ‘Priming’ means generation of immune memory cells by the first dose of a vaccine that results in a sub-optimal immune response but ensures a rapid and stronger immune response to the subsequent dose of the same vaccine. Since residual maternal passive antibody reduces immune response, the first dose is ideally delayed beyond 2 months of age. A second dose given two or more months later completes priming and also acts as partial booster [23]. Long-lasting immunity will be achieved with a third dose (booster) given ideally several months later [24-26]. A fourth dose is given a few years later in some countries (e.g. USA, UK, Sweden) but it may not be needed to maintain life-long immunity [26]. IPV causes little or no local or systemic reactions; in combination vaccines reactions to other antigens must be expected. Although anaphylaxis is theoretically possible, none has so far been reported. Although IPV has an excellent track record on efficacy, it has poor induction of intestinal immunity, require strict cold-chain maintenance, need booster injections and has expensive and potentially dangerous manufacturing processes with the wild type virulent virus [19].

B. Oral Polio Vaccine (OPV)

OPV is a live attenuated vaccine given by oral route. OPV immunizes after infection (“take”) in the intestine. The schedule of OPV recommended in ‘high income’ countries was three doses given at intervals of four or more weeks, beginning at or after 2 months of age. The WHO EPI recommends a dose soon after birth and three more at 6, 10 and 14 weeks of age particularly for developing and LMI countries [27]. The ‘take’ frequency and antibody response rate are lower in many LMI countries than in high income countries; the adverse factors are environmental, not ethnic/genetic or nutrition-related [28,29]. By mid-1980s, approximately half the
children with polio in India had already received 3-doses of OPV. On the other hand, vaccine failure was never a problem in high income countries [30]. Five-dose primary vaccination substantially increases the antibody response rate [30]. Additional doses are necessary to close immunity gaps particularly to types 1 and 3. In some parts of Northern India, even 10 doses of OPV failed to provide adequate immunity needed to stop transmission of WPV [31]. According to one study, the per dose efficacy of tOPV was calculated as low as 9% [31]. High incidence of malnutrition, diarrhea, and interference by other non-polio enteroviruses were blamed as the main reasons for poor efficacy in these regions [31].

Until 2005, only tOPV was used but thereafter m-OPV types 1 and 3 were licensed in several countries that had not interrupted transmission of WPV 1 or 3 [32, 33]. Type 2 is dominant in tOPV and interferes with ‘take’ and immune response to types 1 and 3. The type-specific immunogenicity of m-OPVs is 2-3 times higher than that of tOPV [32]. A bivalent OPV without type 2 (bOPV) was licensed in 2009 for use in countries that continued to have endemic WPV 1 and 3. The immunogenicity was found to be non-inferior to mOPVs [33].

**Safety issues with oral polio vaccine:** Vaccine polioviruses contained in OPV are attenuated so that they do not retain their ‘original’ neurovirulence and transmissibility. Nevertheless, two major adverse effects of OPV are due to reversion of vaccine viruses to neurovirulence and transmissibility [34]. The first, VAPP, primarily occurs due to loss of attenuating mutations and reversion to neurovirulence during replication of the vaccine virus in the gut [35]. 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’) [35]. The frequency of VAPP varies widely — the estimated rates are 1 per 750,000 first dose recipients in the USA, 1 per 145,000 birth cohorts in India, and 1 per 100,000 birth cohorts in Norway [27,36,37]. According to a recent review, the global risk of VAPP is estimated to be around 4.7 cases per million births (range, 2.4-9.7) [38].

The second major adverse event associated with OPV is VDPV which was recognized relatively late in the process of GPEI operations in the Dominican Republic and Haiti during 2000-2001 [39]. They arise due to mutation and recombination with other enteroviruses in the human gut and are usually 1-15% divergent from the parent vaccine virus. The VDPV cases appear in communities with very low rates of coverage with OPV. Some VDPVs become efficient transmitters — they circulate in children and cause polio – if 2 cases of polio are caused by one lineage it called ‘circulating VDPV’ (cVDPV) [39]. The mutations accumulate at a relatively constant rate — around 1% a year. The outbreaks caused by VDPVs had biological properties indistinguishable from those of wild poliovirus [39].

**Table 1** provides key differences in the characteristics of VAPP and VDPVs. Rarely, vaccine polioviruses establish chronic intestinal infection in persons with B cell related immunodeficiencies. The vaccine viruses undergo genetic reversions over time and such viruses are called ‘immune deficiency-associated VDPV’ (iVDPV) [40]. Immunodeficiency is also associated with several-fold higher risk of VAPP and polio developing months or years after chronic infection.

**CONTROVERSIES SURROUNDING THE POLIO VACCINES**

**The Cutter Incident**

After his success with invention of an effective polio vaccine, Jonas Salk got a lot of media attention and public adulation, but at the same time he was also targeted by his detractors for the way his vaccine was tried, tested, and licensed [3]. Unfortunately, soon after the launch of Salk-IPV, an incident known as ‘Cutter Incident’ came to the light in which more than 250 vaccinees and their contacts

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Vaccine-Associated Paralytic Poliomyelitis (VAPP)</th>
<th>Vaccine-derived poliovirus (VDPV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year of discovery</td>
<td>1956</td>
<td>2000</td>
</tr>
<tr>
<td>Place of discovery</td>
<td>Republic of Belarus, Russia</td>
<td>Haiti and Dominican Republic</td>
</tr>
<tr>
<td>Mode of transmission</td>
<td>Single-vaccine recipients and immediate contacts</td>
<td>Well-immunized communities and areas of low population immunity</td>
</tr>
<tr>
<td>Types</td>
<td>Recipient and contact VAPP</td>
<td>Circulating (cVDPV) and ‘immune deficiency-associated VDPV’ (iVDPV)</td>
</tr>
<tr>
<td>Recombination with other enteroviruses</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Probability of occurrence</td>
<td>1 out of several hundred thousand vaccinees</td>
<td>1 out of 2.4 million vaccinees</td>
</tr>
</tbody>
</table>
developed paralytic polio [3]. Later investigations found that most of the adverse reactions were caused by the vaccine developed by one manufacturer, Cutter Laboratories. The entire polio vaccination program was temporarily suspended for the detailed investigations; and after resumption, more strenuous safety tests were introduced in the program.

**The Simian Virus 40 Episode**

In 1960, it was found that the rhesus monkey kidney cells used to prepare both inactivated and live polio vaccines, were infected with a new virus called Simian virus 40 (SV40) [3]. Later investigations revealed that the SV40 had escaped inactivation of polio vaccines with formaldehyde during their development process. After recognition of this incident, proper precautions were taken to ensure complete removal of the virus from vaccine lots. However, this incident had caused a great deal of anxiety and alarm since SV40 was found to cause tumors in rodents and many animal species, and was associated with certain malignancies in humans also. It was feared that hundreds of millions of individuals across the globe may have been exposed to SV40 by receiving contaminated polio vaccines [3]. However, studies undertaken later to analyze any deleterious effects associated with the vaccines contaminated with the SV40 virus in the recipients, did not find any added risk particularly from cancers associated with administration of these vaccines [41, 42].

Another controversy erupted in 1990s in which accusations were made against the late 1950s trials conducted by Koprowski in Congo with his experimental oral polio vaccine. It was stated that a Simian virus contaminated few batched of this vaccine which had facilitated transmission of ‘simian immunodeficiency virus’ (SIV) from chimpanzees to humans and was ultimately responsible for appearance of HIV/AIDS in humans. This hypothesis was also refuted by the studies conducted later [43].

**OPV versus IPV: Which is the Ideal Vaccine?**

Considering the history of inactivated and live polio vaccine development, and later their public use globally, any discussion on the superiority of one over the other is replete with passionate arguments. None of these two vaccines can be termed as an ideal polio vaccine. Both these vaccines have certain merits and demerits yet they proved to be having a great complimentary role as far as polio eradication effort is concerned. **Table II** provides attributes of an ‘ideal’ vaccine and evaluates the two polio vaccines on those parameters. While IPV provides

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**Table II ‘Ideal Vaccine’ Characteristics Compared with Currently Available Polio Vaccines**

<table>
<thead>
<tr>
<th>Attribute</th>
<th>‘Ideal vaccine’</th>
<th>Oral polio vaccine (OPV)</th>
<th>Inactivated polio vaccine (IPV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of administration</td>
<td>Non-injectable</td>
<td>Oral</td>
<td>IM injection</td>
</tr>
<tr>
<td>Thermo-stability</td>
<td>Heat and freeze stable</td>
<td>Heat sensitive</td>
<td>Heat and freeze sensitive</td>
</tr>
<tr>
<td>Humoral immunity</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Mucosal immunity</td>
<td>Good</td>
<td>Good</td>
<td>Poor</td>
</tr>
<tr>
<td>Onset of action</td>
<td>Fast</td>
<td>Fast</td>
<td>Slower than OPV</td>
</tr>
<tr>
<td>Geographic variation in immunity</td>
<td>No</td>
<td>Marked variation</td>
<td>No</td>
</tr>
<tr>
<td>Safety</td>
<td>No safety issues</td>
<td>VAPP, VDPV</td>
<td>No safety issues</td>
</tr>
<tr>
<td>Safe production</td>
<td>Widespread and low risk</td>
<td>Widespread and low risk</td>
<td>Only in select countries, risk of reintroduction of WPV from manufacturing sites</td>
</tr>
<tr>
<td>Cost</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Administration schedule</td>
<td>One dose</td>
<td>Multiple doses</td>
<td>At least 3 doses</td>
</tr>
<tr>
<td>Duration of immunity</td>
<td>Life long</td>
<td>Probably lifelong</td>
<td>Probably lifelong</td>
</tr>
<tr>
<td>Administration in NIP</td>
<td>Routine immunization and SIAs</td>
<td>Routine immunization and SIAs</td>
<td>Routine immunization and small-scale SIAs</td>
</tr>
<tr>
<td>Cold storage space</td>
<td>Small</td>
<td>Small</td>
<td>Small (&lt;5–7% of total volume)</td>
</tr>
<tr>
<td>Waste management</td>
<td>No risk</td>
<td>No risk</td>
<td>Sharp disposal</td>
</tr>
</tbody>
</table>

(Adapted from Bandyopadhyay AS, Garon J, Seib K, Orenstein WA. Polio vaccination: past, present and future. Future Microbiol. 2015;10:791-808.)

im.: Intramuscular; IPV: Inactivated polio vaccine; OPV: Oral polio vaccine; SIA: Supplemental immunization activity; VAPP: Vaccine-associated paralytic poliomyelitis; VDPV: Vaccine-derived poliovirus; WPV: Wild polio virus; NIP: National immunization program.
The coordinated use of OPV and IPV has eliminated wild polio from the entire globe, barring two endemic countries [1]. The strategies to eliminate risks of polio due to vaccine viruses contained in OPV referred as ‘endgame’ in GPEI’s parlance, are now underway. The process of administration of at least a single dose of IPV in national immunization schedules of all the OPV using countries has been already initiated and global ‘switch’ from tOPV to bOPV has occurred in April 2016 [44]. Hopefully, IPV will be successful in providing adequate individual protection against both wild as well as vaccine derived polio. However, there are substantial financial and logistical challenges to its implementation worldwide. Furthermore, there are certain scientific issues that must be addressed before universal IPV use is deemed permanent and safe.

High cost and limited supply of IPV are the two major constraints associated with widespread use of IPV in resource-limited LMI countries. To address these issues, GPEI is pursuing different approaches that include cutting down the number of IPV doses for routine immunization (RI), sparing doses via intradermal fractional-dose administration, and employing adjuvants to reduce antigen quantity [45]. To sort out the operational difficulty associated with intradermal injections with needles and syringes, other alternative delivery systems like microneedle adapters and intradermal needles, needle-free jet injectors, and microneedle patches are explored. Recently, IPV type 2 vaccine delivered to rat skin via high density microprojection array (‘Nanopatch’), has elicited potent neutralizing antibody responses in rats [46].

The shortage of adequate amount of IPV in global market is the greatest challenge in front of GPEI today. A stable, uninterrupted supply of IPV for use in LMI countries will likely require substantial increases in worldwide production capacity. Scaling up the existing manufacturing base has failed to meet the demand of the vaccine in some large countries like India. The issues of supply can only be addressed by allowing and building production facilities of IPV in developing countries. However, ensuring containment of wild-type polioviruses, from which the current IPV is made, in new production facilities that lack experience and that are situated in regions with inadequate population immunity raises major concerns. Thus, development of IPV from non-pathogenic strains becomes a top priority. Many such options are available [47], but development of ‘Sabin IPV’ (both adjuvanted and unadjuvanted forms) with the use of Sabin vaccine virus as seed virus is the only option currently in advanced stages of completion [48].

As far as improvement in existing OPV formulations or development of ‘novel’ OPV is concerned, the research has reached almost to a ‘dead end’ since oral vaccine is on its way of phasing out gradually from the global usage under cover of universal IPV. However, the GPEI will stockpile and utilize monovalent OPVs during post-eradication era to deal with any new outbreaks of wild or vaccine viruses.

In conclusion, thanks to these vaccines, the world is now on the verge of eradication of yet another vaccine-preventable disease after smallpox. Perhaps the success could have been achieved much earlier, and with less intensive effort had different tactics were adopted right from the beginning to tackle limitations of these two vaccines [49]. Nevertheless, the fact remains that the transmission of all types of WPVs has almost been halted globally from all the countries barring two. Now the GPEI has to expedite WPV elimination from the remaining countries along with efficient removal of vaccine polioviruses contained in OPV under cover of universal IPV use in a globally synchronised manner so that the gains achieved so far are made permanent.

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