

MOVING FROM ORAL POLIOVIRUS VACCINE TO INACTIVATED POLIOVIRUS VACCINE: THE RATIONALE AND CHALLENGES

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Abstract

Oral polio vaccine (OPV) has served as the cornerstone of polio eradication efforts over the past 30 years, trivalent inactivated polio vaccine (IPV) has re-ascended to prominence in the past year, now acting as the sole source of protective immunity against type 2 poliovirus in routine immunization programmes. The Polio Eradication and Endgame Strategic plan 2013–2018, developed by the Global Polio Eradication Initiative (GPEI) outlines the phased removal of OPVs, starting with type 2 poliovirus-containing vaccines and introduction of inactivated polio vaccine in routine immunization to mitigate against risk of vaccine-associated paralytic polio and circulating vaccine-derived poliovirus.

Key words: Poliomyelitis, Vaccine-associated paralytic polio, Circulating vaccine-derived poliovirus

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Introduction

Poliomyelitis (polio) is a communicable disease caused by poliomyelitis virus, a RNA enterovirus belonging to Picornaviridae family. There are three serotypes of poliovirus, which differ antigenically and protection against one serotype does not provide protection against the others.¹ Humans are the only reservoir of polio disease. The predominant transmission mode of this disease in developing countries is the fecal/oral route, since the virus replicates in the intestines and is basically excreted in feces. If sanitation conditions and personal hygiene are inadequate, others can be infected through dirty hands or contaminated food and water. Thus, intestinal immunity is important in order to prevent transmission. The incubation period is usually 7 to 10 days, though it can be 4 to 40 days.² Polio disease can strike at any age, but it mainly affects children under five years' old who have not been vaccinated.³ Infection can be inapparent (without

symptoms) in approximately 72% of cases; in about 24% it causes mild disease with transitory fever, discomfort, somnolence, headache, nausea, vomiting, constipation, and sore throat, in various combinations; it manifests as aseptic meningitis in about 4% of cases; and on rare occasions (<1%) it presents as paralytic poliomyelitis.⁴ Paralytic poliomyelitis manifest as acute flaccid paralysis (AFP), of sudden onset, with maximum progression within a few days (<4 days). It is usually asymmetrical, with the reduction or absence of tendon reflexes, without alterations of the sensory system.² Most people with paralytic poliomyelitis never recover completely, having residual paralysis of varying severity for the rest of their lives. Weakness or paralysis still present 12 months after onset is usually permanent.⁵

Globally, from estimated 350,000 polio cases in more than 125 endemic countries in 1988, it dropped to a total of 33 cases in 3 countries, in 2018.^{6,7} Since 1988,

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sustained use of polio vaccines worldwide has led to a precipitous drop in the global incidence of poliomyelitis by over 99%.⁵ In 2012 and 2013, 223 and 403 respectively poliomyelitis cases were reported. Globally, the last case of poliomyelitis caused by naturally circulating WPV type 2 (WPV2) occurred in India in 1999. No case due to WPV type 3 (WPV3) has been detected since 10 November 2012.⁸ Though worldwide use of poliovirus vaccines has brought a drastic reduction in cases of polio, failure to implement strategic policies has led to ongoing transmission of poliovirus in Afghanistan, Nigeria and Pakistan, which are still considered endemic from 2014 for transmission of WPV type 1 (WPV1). Failure to stop poliovirus transmission in these last remaining areas has the potential of causing as many as 200,000 new cases globally every year, within next 10 years.⁶ There is risk of importation and subsequent chance of spread in the countries with low immunization coverage and bordering the endemic countries.¹

IPV and OPV: characteristics and global implementation to date

Two polio vaccines are commonly used throughout the world to protect against poliomyelitis. The first was developed by Jonas Salk in 1952; the second was an oral vaccine developed by Albert Sabin in 1961.⁹

The Salk vaccine, or inactivated poliovirus vaccine (IPV), is based on 3 virulent reference strains - Mahoney (type 1), MEF-I (type 2) and Saukett (type 3) grown on human diploid cells (MRC-5) and inactivated with formalin.¹⁰ The original IPV contained 20, 2 and 4 D antigen units of PV types 1, 2 and 3.⁹ The Salk vaccine provides immunoglobulin G-mediated immunity in the bloodstream, which prevents infection from progressing to viremia and protects the neurons.¹⁰ The duration of immunity induced by IPV is not known with certainty, although a complete series is thought to provide protection for many years.¹¹ The IPV now available is termed enhanced IPV (eIPV) because of a new method of production developed (more potent IPV containing 40, 8 and 32 D antigen units of types 1, 2 and 3) in 1978 that results in higher potency per dose and significantly greater immunogenicity than the original IPV.⁹ Trials with this eIPV showed greater than 90% seropositivity against all 3 serotypes after one dose and 99-100% seropositivity after two doses.^{11,12}

Oral polio vaccine (OPV) is a live attenuated vaccine produced by passage of poliovirus through nonhuman cells at a subphysiological temperature, which causes spontaneous mutations in the viral genome.⁹ OPV is superior to IPV in ease of administration, and there is no need for sterile syringes, as with IPV and making the vaccine more suitable for mass vaccination

campaigns. OPV also provides longer immunity than does the Salk vaccine, it provides both humoral immunity and cell-mediated immunity.^{13,14} One dose of OPV produces immunity to all three poliovirus serotypes in roughly 50% of recipients.¹⁵ Three doses of live-attenuated OPV produce protective antibodies to all three poliovirus types in more than 95% of recipients. OPV produces excellent immunity in the intestine, the primary site of wild poliovirus entry, which helps prevent infection with wild virus in areas where the virus is endemic.¹⁶ The live virus used in the vaccine can rarely shed in the stool and can rarely spread to others within a community. However, OPV has strict requirements for transport and storage, and this is a big problem in some hot or remote areas.¹³ As with other live-virus vaccines, immunity initiated by OPV is probably lifelong.¹¹

The only rare serious adverse events associated with OPV are the occurrence of vaccine-associated paralytic poliomyelitis (VAPP) and the emergence of vaccine-derived polioviruses (VDPVs).⁸

VAPP is caused by a strain of poliovirus that has genetically changed in the intestine from the original attenuated vaccine strain contained in OPV. It is associated with a single dose of OPV administered in a child or can occur in a close unvaccinated or non-immune contact of the vaccine recipient who is excreting the mutated virus. The weakened virus may paralyze the child or his or her contact, but does not spread to cause other cases of paralysis.¹⁷ This is a very rare event that in about two to four in every million doses of oral polio vaccine (OPV) given. VAPP can be proven by a laboratory test that detects vaccine virus in a clinical case of polio.¹⁸

A VDPV is a very rare strain of poliovirus, genetically changed from the original strain contained in OPV through prolonged replication in an individual or in a community, re-acquire the neurovirulence and transmissibility characteristics of WPV.^{8,17} On very rare occasions, under certain conditions, a strain of poliovirus in OPV may change and revert to a form that may be able to cause paralysis (VDPV) in humans and develop the capacity for sustained circulation. The latter is known as a circulating VDPV (cVDPV). that cause cases or outbreaks of paralytic poliomyelitis.^{8,19}

VDPVs are genetically divergent forms of the original Sabin vaccine virus conventionally defined by >1% genetic divergence for PV1 and PV3 and >0.6% for PV2. These viruses are further subdivided into 3 categories: (1) circulating VDPVs (cVDPVs), when evidence of person-to-person transmission in the community exists; (2) immunodeficiency-associated VDPVs (iVDPVs), which are isolated in rare cases from people

with primary B-cell and combined immunodeficiencies (with defects in antibody production) who have prolonged VDPV infections (in individual cases excretion has been reported to persist for 10 years or more)²⁰; and (3) ambiguous VDPVs (aVDPVs), which are either clinical isolates from persons with no known immunodeficiency, or sewage isolates of unknown source.²¹

A cVDPV is associated with sustained person-to-person transmission and is circulating in the environment. "Persistent cVDPVs" refer to cVDPVs known to have circulated for more than six months. Low vaccination coverage is a major risk factor for cVDPV emergence. A fully immunized population will be protected against both vaccine-derived and wild polioviruses. It takes many months for a cVDPV to emerge. cVDPV outbreaks have the ability to become endemic, can be spread in any under-vaccinated communities, and can be imported to other countries.¹⁷

In 2005, it was reported that children in a small village in the United States had contracted vaccine-derived polio.¹⁴ In Nigeria, 170 cases have been reported.²² In 2006, 1600 cases of vaccine-induced polio occurred in India, according to the Indian Medical Association Sub-Committee on Immunization's report on the Polio Eradication Initiative.¹⁴ In 2008, many cases of polio were reported in all provinces of Pakistan. These cases were reported during repeated mass-immunization campaigns in which repeated doses of OPV were administered.²³ In 2012, 9 countries reported cases of paralytic poliomyelitis associated with cVDPVs, most of them with type 2. The largest numbers of such cases were reported in the Democratic Republic of the Congo (n=17) and Pakistan (n=16). In 2013, 7 countries reported cases of paralytic poliomyelitis caused by cVDPV, all associated with type 2, of which Pakistan reported the greatest number of 44 cases.²⁴ Cases of cVDPV also occur with type 1 and type 3.¹⁷ These vaccine-related cases became big challenge for the scientific community if the polio-eradication goal is to be achieved. In many countries where wild polio has been eliminated, programmes have switched to using inactivated (killed) polio vaccine (IPV), a more expensive vaccine that does not carry the risk of VAPP and cVDPV.²⁵

Switching from tOPV to bOPV and IPV introduction

Trivalent oral poliovirus (tOPV) vaccine was licensed for use in 1963 and preferred by most of the countries and was the preferred poliovirus vaccine in the expanded programme on immunization as well as the polio eradication programme.¹ Trivalent OPV (tOPV) contains all three poliovirus serotypes (against wild types 1, 2, and 3) was an important component of

routine immunization programmes in 155 countries and territories around the world until April 2016. The tOPV has been used to nearly eradicate polio infection worldwide.²⁶ The use of tOPV has led to the eradication of wild poliovirus type 2 (WPV2), with the last case occurring in 1999. The last detected case of WPV3 was in 2012. Furthermore, four of the six WHO regions have been certified as polio-free. Led by The Global Polio Eradication Initiative, 155 countries switched to use the bivalent (against wild type 1 and 3) between 17 April and 1 May 2016.²⁷ The bivalent OPV (bOPV) was licensed in 2009, which is effective against type 1 and 3 but does not cover type 2.²⁸ Even as the remaining strains of wild poliovirus are being eradicated, the switch from tOPV to bOPV was a major step to combat cVDPV and VAPP. Over 90% of cVDPV cases, and approximately 40% of VAPP cases are due to the type 2 component of tOPV.²⁹ The type 2 component of tOPV also interferes with the immune response to poliovirus types 1 and 3.³⁰ Given the risk the type 2 component of tOPV poses to a world free of WPV2, thus tOPV was replaced with bOPV in routine programmes and supplementary immunization activities (SIAs). However, the switch from tOPV to bOPV will not eliminate all cVDPV cases. The purpose of the switch is to eliminate persistent cVDPVs associated with the type 2 serotype and to boost protection against wild poliovirus types 1 and 3 (the switch will not prevent type 1 or type 3 cVDPVs).³¹

The switch from tOPV to bOPV was coupled with the introduction of IPV at age e"14 weeks, which will provide immunity against type 2 after removal of type 2 OPV (OPV2) as recommended by the Strategic Advisory Group of Experts on Immunization (SAGE).⁵ The introduction of IPV will help to reduce risks associated with the withdrawal of OPV type 2 and hasten eradication by boosting immunity to poliovirus types 1 and 3.²⁷ However, studies have not evaluated yet if type 2 antibody titers and immunological priming responses persist, and for how long they persist after the single dose of IPV.

The global demand for IPV has therefore substantially increased in just a few years. However, the current global inactivated poliovirus vaccine (IPV; 0.5 mL, full-dose) supply shortage dramatically limits the number of doses available for an effective outbreak response. Therefore, GPEI has proposed use of intradermal administration of a booster of fractional IPV (fIPV; 0.1 mL, one-fifth the full-dose) as a dose-sparing strategy to stretch the limited global IPV supply while further improving population immunity by increasing the number of children vaccinated.³² Multiple studies have assessed immunogenicity of intradermal fIPV compared with the full intramuscular dose and

demonstrated encouraging results. These studies conducted in Cuba,^{33,34} Oman,³⁵ Philippines,³⁶ and Bangladesh³⁷-evaluated the immunogenicity by examining seroconversion rates and antibody levels following vaccination.

The studies found that cumulative seroconversion rates (a e⁴-fold increase over the expected decline in maternally derived antibody titers) for all polio serotypes following the complete vaccination series were comparable between the fIPV and intramuscular IPV groups when there was less interference with maternal antibody (that is, when the first dose was given at or after 2 months of age). On the other hand, the results were varied when the vaccination series started earlier (such as at 6 weeks of age). The Philippines study showed equivalent immunogenicity between fIPV and intramuscular IPV when each vaccine was administered at 6, 10, and 14 weeks of age.³⁶ However, studies in Cuba (using the same schedule of immunization at 6, 10, and 14 weeks) and in Bangladesh (using a 2-dose schedule at 6 and 14 weeks) showed slightly lower cumulative seroconversion rates in the fIPV group than in the

intramuscular group.^{33,37} Because most OPV-using countries have added a single dose of IPV in their primary vaccination series, it was also useful to compare the immunogenicity of 2 fIPV doses with that of a single full intramuscular dose. In all studies, 2 fIPV doses (i.e., total of 0.2 mL) resulted in substantially higher seroconversion rates for all poliovirus serotypes than a single intramuscular dose.^{33-37,38} After reviewing these data in October 2016, WHO's Strategic Advisory Group of Experts on Immunization (SAGE) reiterated the recommendation it first made in April 2016 that countries should start preparing for a 2-dose fIPV schedule (at 6 and 14 weeks of age), in lieu of a single intramuscular dose at 14 weeks.³⁹ Prior to the SAGE recommendation, 8 states in India and the country of Sri Lanka had already made this change to their immunization schedule. India will expand the use of fractional doses to an additional 8 states in August 2016 and to all 36 states in April 2017. In addition, Bangladesh has decided to introduce fIPV in their routine schedule in 2017.⁴⁰ This option would not only address the immediate IPV shortage but also serve as an affordable and immunogenic option for routine

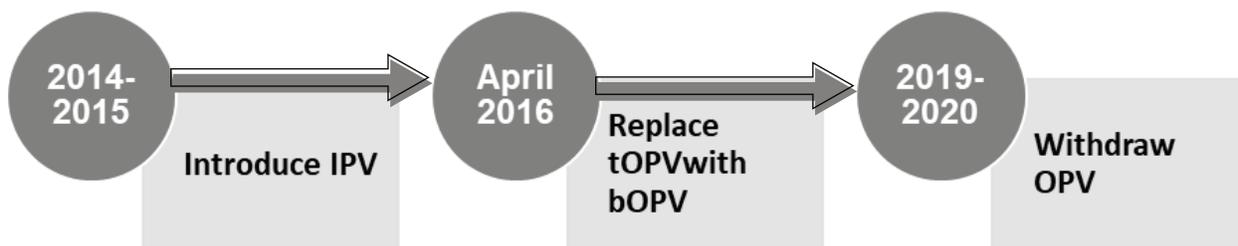


Fig.-1: Ongoing routine immunization strengthening²⁷

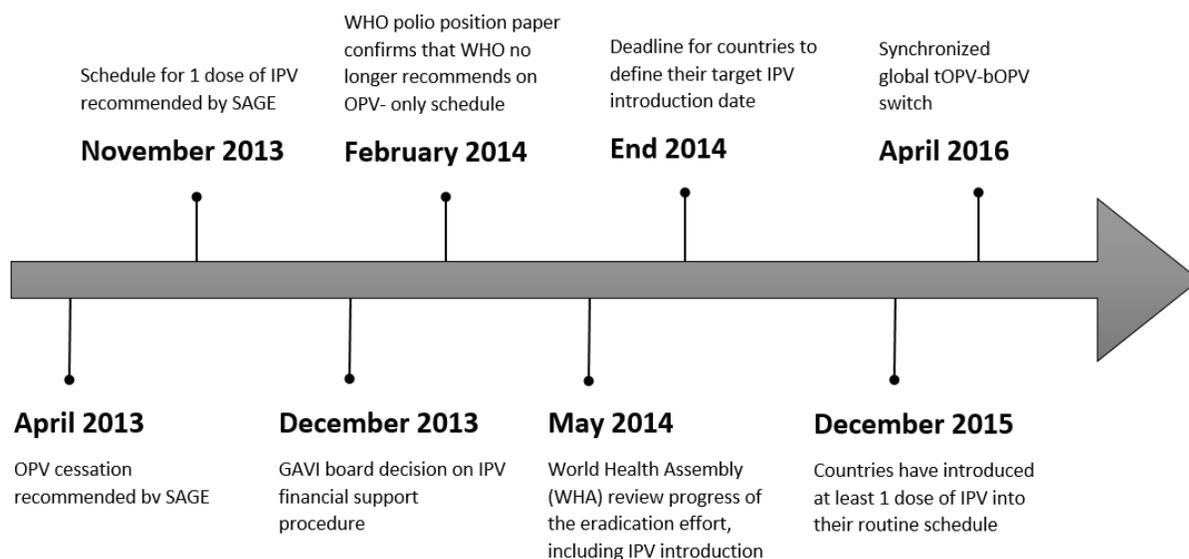


Fig.-2: Timeline for IPV Introduction and the Switch⁵

immunization after global polio eradication has been achieved.³² Additional research is also desirable to better understand the role of fIPV in inducing mucosal immunity and long-term immunity to provide further evidence to support the implementation of this strategy.

However, monovalent versions of oral polio vaccine (mOPVs) had been licensed earlier in 1950s but were abandoned in favor of the tOPV to simplify immunization schedules. mOPVs confer immunity to just one of the three serotypes of OPV.⁴¹ A few previous trials of mOPVs had suggested that mOPV type 1 was two to three times as immunogenic as tOPV⁴² because it eliminated interference from the other two polio-virus serotypes. The Global Polio Eradication Initiative issued an urgent call and mOPV type 1 and mOPV type 3 were licensed again in 2005 and used to enhance the impact of supplementary immunization activities 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 polioviruses in certain settings, and promoting the fast track development of a completely new bOPV in 2010.⁴³ Once WPV1 and WPV3 are certified as eradicated, use of bOPV will no longer be required, and it will need to be withdrawn. mOPV2 has been stockpiled in the event of a cVDPV2 outbreak. Stockpiles of monovalent type 1 OPV and type 3 OPV will be needed for responding to any outbreaks of polio that occur after bOPV withdrawal.⁴⁴

Vaccination Schedule

In countries with endemic polio or where there is a high risk of imported cases, the WHO recommends OPV vaccine at birth followed by a primary series of 3 OPV and at least one IPV doses starting at 6 weeks of age, with a minimum of 4 weeks between OPV doses. In countries with >90% immunization coverage and low risk of importation, the WHO recommends one or two IPV doses starting at 2 months of age followed by at least two OPV doses, with the doses separated by 4–8 weeks depending on the risk of exposure. In countries with the highest levels of coverage and the lowest risks of importation and transmission, the WHO recommends a primary series of 3 IPV injections, with a booster dose after an interval of six months or more if the first dose was administered before 2 months of age.⁸

Conclusion

Interruption of person-to-person transmission of the virus by vaccination is important in the global polio eradication,⁴⁵ since no long-term carrier state exists

for poliovirus in individuals with normal immune function, polio viruses have no nonprimate reservoir in nature,⁴⁶ and survival of the virus in the environment for an extended period of time appears to be remote. OPV contains live poliovirus, which can mutate and acquire neurovirulence. Therefore, OPV cessation is a necessary prerequisite to achieve poliomyelitis eradication. One of the most critical points for success of IPV introduction and the switch to bOPV was the global structure to support the regions. There were many international organizations working together to support the 126 countries across the globe that needed to introduce IPV and make a synchronized switch. The issues with global vaccine supply and vaccine delays were major obstacles that had to be dealt with at international, regional and national levels. It is expected that within 2 years of certification of global eradication of wild polioviruses, OPV use will cease and IPV will be used for routine polio immunization.

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