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Review Article

REVIEW ON CURRENT POLIO VACCINES: VACCINATION SCHEDULES AND ADMINISTRATION ROUTES

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ABSTRACT

R*ecent advances in the field of biotechnology have led to products containing enzymes, antibodies, and other biological agents for suitable use as pharmaceuticals for treatment of many diseases and vaccines for prevention purposes of broad range of infectious diseases. Poliomyelitis is one of serious disease caused by a virus, affecting the nervous system and resulting in paralysis in infant survivors. Oral Polio vaccine is used worldwide to eradicate the polio. Numerous challenges facing polio eradication continue to arise and differ from region to region, but one of such challenge of the Oral Polio vaccine is vaccine derived polio cases known as vaccine derived polioviruses and vaccines associated polio cases known as vaccine-associated paralytic poliomyelitis. Inactivated Polio vaccine is one of the better options to eliminate and/or prevent these cases. On the basis of past literature, we are summarized here current development in polio vaccines after applying different technology and administrative routes. Furthermore, it is necessary to improve education, so people understand the basic concept of alternative vaccines and their different administration routes, thereby assisting in creating a basic understanding of polio vaccine and its vaccinations. Communication strategies should, therefore, be aimed at increasing awareness of poliomyelitis as a real health threat and educating the populace about the safety of the vaccine. Polio eradication partners should collaborate with other agencies and ministries to improve total primary healthcare packages to address identified unmet health and social needs.*

KEYWORDS*: Polio vaccines, OPV, IPV, Sequential schedule, Administration Routes.*

INTRODUCTION

Polio (also known as poliomyelitis) is a highly contagious disease caused by a virus that attacks the nervous system. Children younger than 5 years old are more likely to contract the virus than any other group. According to the World Health Organization (WHO), 1 in 200 polio infections will result in permanent paralysis. Poliovirus (PV) is a member of the Picornaviridae family in the order of Picornavirales and a causative agent of poliomyelitis. PV is formed in non-enveloped capsid and has a single-stranded positive-sense RNA genome [1, 2]. The disease, caused by any one of three serotypes of poliovirus (PV1, PV2, and PV3,) has no specific treatment, but can be prevented through vaccination. Viruses, vaccines & disease Global eradication of polio are within grasp. Only some countries are currently considered endemic for polio because they have never eliminated indigenous polio viruses. However, thanks to the global polio eradication initiative in 1988, America, Europe, western pacific Southeast Asia regions are now certified polio-free. overall reduction in global incidence of cases has been more than 99% since the eradication efforts begun in 1988 when an estimated 350,000 persons were paralyzed by wild polio viruses (WPVs), there are still a few hundred cases of WPV-related paralysis each year (416 cases in 2013 and 359 in 2014) [1]. These cases are occurring both in the endemic countries as well as in countries re-infected via importations. PV1 is the most common form encountered in nature and is highly localized to regions in Pakistan and Afghanistan. PV2 was declared eradicated in September 2015 after last being detected in October 1999 in Uttar Pradesh, India, and PV3 has not been seen since its detection in parts of Nigeria and Pakistan in 2012. All PVs can be transmitted person to person via direct contact, contaminated food, or other fomites. Poliovirus infection is asymptomatic or mild in about 95% of infected individuals, and approximately 0.5% of those may present paralytic disease. However, due to its highly contagious nature, poliovirus infection can affect large populations.

In 2011, Singh and Kumar summarized complete information related to history, taxonomy, properties, clinical manifestation, and pathogenesis of polio viruses as well as conventional and hypothetical future vaccines in the post

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vaccination era [3]. Currently, two vaccines are using for vaccination purpose; live attenuated oral poliovirus vaccine (OPV) and inactivated poliovirus vaccine (IPV) are used throughout the world to protect against polio. In 121 countries [2], OPV is used instead of IPV for several reasons: OPV costs substantially less than IPV [4]; primary immunization with OPV induces superior intestinal immunity compared with IPV and thus has the potential to better prevent transmission of wild viruses; OPV confers contact immunity through passive immunization of unvaccinated persons from viruses shed by vaccines; and OPV is administered in oral drops, which are easier to administer than IPV injections and easier to store and transport. Despite these advantages, most developed countries have transitioned to IPV, primarily because OPV has the major disadvantage of causing paralytic disease in rare cases [5]. It can cause vaccine-associated paralytic poliomyelitis (VAPP) in vaccine recipients and close contacts at an estimated rate of about 4.7 per million births (range: 2.4–9.7) globally [6]. Typically, the risk of VAPP is highest with the first dose of OPV in industrialized countries – about 6.6-times higher for first-time recipients than those receiving subsequent doses whereas in developing countries the risk of VAPP can be lower for first dose recipients [7]. Data from India show that VAPP is largely associated with second or subsequent doses of OPV, indicating that the age of onset for VAPP is higher in lower-income settings [8]. Moreover, the live vaccine virus also can mutate in ways that confer the transmissibility and neurovirulence properties of wild viruses, leading to polio outbreaks caused by these altered viruses known as circulating vaccine derived polioviruses (cVDPVs). There has been an average of 76 reported cases of cVDPVs annually between 2005 and 2013 [1].

Oral Polio Vaccine 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 [9]. Development of potent, safe and effective vaccines against polio is still under process by using advanced technologies, different administrated routes and through various vaccinated schedules anywhere in world. Therefore this review comprises the update information related to polio vaccines, vaccination schedule and their administrated routes in current scenario. The review will helpful to nourish technical knowledge of researchers, academician, scientist and other professionals, who are engaged in this research field.

Current polio vaccines:

(a) Oral polio vaccine (OPV):

This vaccine was developed in 1958 by Dr. Albert Sabin. Sabin attenuated the wild type poliovirus by passaging the virus in monkey kidney epithelial cells [10, 11]. Administration of OPV mimics the immune response to natural exposure to WPV generating both humoral and mucosal immunity [7]. IgM antibody becomes detectable as early as 2–3 days after infection, usually disappearing after 2–3 months, while IgG becomes the predominate antibody and may last for life [7]. Because it is easily administered for induce the long-lasting immunity. OPV has been the vaccine of choice throughout the developing world, and forms the backbone of the global polio eradication effort. There are three formulations of OPVs are: tOPV containing Sabin strains of all three poliovirus serotypes; bOPV containing Sabin strains for types 1 and 3; and monovalent OPV (mOPV), which has two subtypes for serotypes 1 (mOPV1) and 3 (mOPV3). In addition, monovalent OPV for serotype 2 (mOPV2) is available for research purposes as well as for response procedures should there be an outbreak of poliovirus type 2. In a randomized, doubleblind, controlled trial in India, the cumulative seroconversion rates to serotype 1 following two doses at birth and at 30 days, were 90% for mOPV1 and 86% for bOPV compared with 63% for tOPV [12]. For serotype 2, the seroconversion rates were 90% for mOPV2 compared with 91% for tOPV, and for poliovirus type 3, seroconversion rates were 84% for mOPV3 and 74% for bOPV compared with 52% for tOPV [12]. Currently, bOPV is in routine immunization globally.

(b) Inactivated polio vaccine (IPV):

In current scenario, there are two different IPV developed, which can be differentiate on the basis used viral vaccine strains. First IPV was developed against polio by Dr. Jonas Salk in 1952 and formaldehyde was used for inactivation of wild polio viruses and the vaccine is also called Salk vaccine. The IPV contains strains of all three serotypes of poliovirus (Type 1, 2 & 3), originally grown in monkey kidney cell culture and inactivated by exposure to formaldehyde [13, 14]. The following table shows strains of IPV that was discovered and used. The vaccine is a clear, colorless sterile suspension for subcutaneous injection. Clinical trials of IPV began in 1954 and results were dramatic; the cases of polio in the vaccinated test groups fell amazingly, and permission produces protective antibodies in the blood (serum immunity) [13]. After 2 doses of enhanced potency IPV (eIPV), high levels of serum neutralizing antibodies to all 3 types of polioviruses appears in 94-100% of individuals. IPV was shown to effectively immunize and protect against poliomyelitis [15].

Second IPV containing the attenuated Sabin vaccine strains of poliovirus (sIPV) would reduce the potential severity of the consequences of intentional or unintentional release of virus from an IPV manufacturing facility [16]. Thus sIPV is seen as more appropriate for manufacture in countries such as China, India, and Indonesia, where OPV is already manufactured. The vaccine is a clear, colorless sterile suspension for subcutaneous injection. Clinical trials of IPV began in 1954 and results were dramatic; the cases of polio in the vaccinated test groups fell amazingly, and permission produces protective antibodies in the blood (serum immunity) [13]. After 2 doses of enhanced potency IPV, high levels of serum neutralizing antibodies to all 3 types of polioviruses appears in 94-100% of individuals. This serum immunity prevents the spread of the virus to the CNS and provides protection against polio paralysis. The enhanced potency IPV induces mucosal immunity by inhibiting pharyngeal acquisition of poliovirus. The intestinal acquisition, yet the extent of mucosal immunity induced by IPV are far less than OPV. Therefore, while OPV can prevent the spread of wild poliovirus that indicate that IPV is a less reliable vaccine. The current formulation of IPV induces close to 100% seroconversion rates with high antibody titers to the three poliovirus serotypes after a series of three doses, when administered in schedules in which the last dose is administered at 6 months of age or older [17]. Lower rates of seroconversion are seen in the presence of high levels of maternally derived antibody. Administration of IPV at older ages, giving a chance for maternally derived antibody to wane, is associated with higher levels of seroconversion [13]. Currently accepted correlates of protection for IPV containing vaccines require neutralizing antibody levels at or above a 1:4 to 1:8 dilution threshold [19]. IPV shows a similar effect to OPV in inducing

pharyngeal immunity, but has limited effect in inducing primary intestinal immunity when administered alone and thus, IPV is equivalent to OPV in reducing oral shedding following an OPV challenge but is inferior to OPV in reducing intestinal shedding when used for primary immunization in subjects who have not previously been exposed to OPV [20]. In fact, the proportion of persons who shed virus in stool following an OPV challenge in IPV vaccines is similar to the proportion who shed following a dose of OPV to unvaccinated persons. However, despite shortcomings in induction of intestinal immunity following a primary series, IPV has been shown to reduce both the duration of shedding and the amount of virus shedding in the stool (with a range between studies of 63 and 91% reduction in the total amount of virus shed). This implies that IPV may reduce transmission even in places where fecal–oral spread is thought to be the predominant mode of transmission [21, 22]. IPV alone terminated polio transmission in several Nordic countries of Europe (e.g., Sweden and The Netherlands). It is unclear whether the reason for this success is because oral–oral transmission is the predominant mode of transmission in these countries or if there was additional impact from reduction in quantity and duration of fecal shedding induced by IPV. Whether IPV alone in a developing country population in whom fecal–oral transmission is thought to predominate, can terminate transmission of wild or vaccine viruses is not clear. Since its development, IPV has been one of the safest vaccines in humans, whether used alone or in combination vaccines [23, 24]. IPV is offered as a standalone Vaccine as well as in combination vaccines for primary immunization (ten products) and for boosters (>five products) [20]. Since early in the development of IPV, it has been co-administered with diphtheria, tetanus and pertussis vaccine (DTwP and DTaP), *Haemophilus influenza* type b vaccine (Hib) and hepatitis B vaccine. No serious adverse events have been causally associated with IPV. When used alone, IPV is well tolerated.

A recent review of the US Vaccine Adverse Events Reporting System (VAERS) from 1999 to 2012 also reported that there were no concerning safety issues of adverse events for IPV [25]. A 2014 systematic review of the literature on the safety of routine vaccines recommended for children in the USA found insufficient evidence to report any association between IPV and sensitivity to food allergens (as one post-licensure study reported) and that serious adverse events are extremely rare for all routine vaccines [26]. Moreover, IPV administered before OPV reduces VAPP cases compared with OPV alone. In 2014, the Global Advisory Committee on Vaccine Safety declared IPV and IPV-containing vaccines as having an excellent Safety profile, based on available data [25].

Sequential schedule of polio vaccines:

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. 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 1 provides benefits and limitation of these two polio vaccines on the basis of comparable attributes.

Table No. 1: Benefits and limitations of current polio vaccines

S. No.	Attributes	OPV	IPV
1	Form of vaccine	Liquid suspension	Freeze dried powder
2	Route of administration	Oral	IM injection
3	Thermo stability	Heat sensitive	Heat and freeze sensitive
4	Administration schedule	Heat sensitive	At least 03 doses
5	Humoral immunogenicity	Good	Good
6	Intestinal immunogenicity	Good	Poor
7	Method of administration	Routine Immunization	Routine Immunization
8	Safety	VAPP, VDPVs	No safety issues
9	Cold storage space	Small	Small (<5–7% of total volume)
10	Cost	US$0.15/dose	US$1/dose
11	Waste Management	No risk	Sharp disposal

(a) IPV alone:

Although IPV alone has shown limited effect in inducing primary intestinal mucosal immunity, it has shown promise in the area of priming for a systemic immune response. A single IPV dose generally seroconverts a proportion of vaccines but induces immune memory (primes) in the majority of the remaining seronegative children. Data on the added protection against paralysis conferred by priming are not conclusive. In a study from Cuba, among those who did not seroconvert after one dose of IPV, 98% had a priming response (they developed significant antibody responses within 7 days of subsequent exposure) after one dose of IPV [15]. On the other hand, in a case-control study of a WPV1 outbreak in Senegal, effectiveness against paralytic polio was estimated to be 36% after one dose and 89% after two doses, values more compatible with per dose IPV seroconversion rates than with priming rates [26].

(b) OPV alone:

Although OPV alone is also a alternative way for vaccination and protective immunity through inducing intestinal mucosal immunity. Two major adverse effects of OPV are due to reversion of vaccine viruses to neurovirulece and transmissibility [27]. The first, VAPP, primarily occurs due to loss of attenuating mutations and reversion to neurovirulence during replication of the vaccine virus in the gut [28]. 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 [29]. 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). 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 [29]. 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).

(c) OPV before IPV:

Immunogenicity of IPV when given in an OPV exposed population has been studied extensively. A single dose of IPV administered to infants in Côte D'Ivoire previously vaccinated with a three-dose primary schedule of tOPV was significantly more effective than an additional dose of tOPV in achieving seroconversion at both 6 and 9 months in subjects who were seronegative after the primary series [30]. More recently, a multiarm trial in Moradabad, India compared a supplemental dose of IPV at 6–9 months to children who had completed a primary series of tOPV plus multiple doses of mOPV, to boosting with a standard and higher potency type 1 mOPV [31]. As in the Côte D'Ivoire study, higher rates of seroconversion in baseline seronegative subjects and increased titers in baseline seropositive Subjects were noted in the subjects receiving IPV compared with children who received an additional dose of OPV.

Two recent studies done in India have shown that one dose of IPV given to prior recipients of OPV boosts intestinal immunity for types 1and 3 [32, 33]. In children with history of multiple doses of OPV, the proportion of children excreting the challenge poliovirus was significantly lower for those given a booster dose of IPV followed by a bOPV challenge than those who did not receive any booster prior to the bOPV challenge [33]. The duration of this boost in intestinal immunity is, however, unknown. A dose of OPV given at birth increases seroconversion rates [34] and provides an opportunity to induce mucosal protection in infants before they are exposed to enteric pathogens. WHO recommends a birth dose of OPV for polio-endemic countries and countries at high risk for importation and subsequent spread [35].

(d) IPV before OPV:

Vaccination regimens employing sequential combinations of IPV and OPV have been utilized in a number of countries, including in the USA. In developed countries where elimination of polio was achieved, VAPP was seen as a major public health problem and resources were available to address the increased costs of using IPV in a sequential IPV to OPV schedule. The intent of this schedule was to acquire the advantages of both IPV and OPV while minimizing adverse reactions: initial immunization with IPV to promote humoral immunity, which gives children protection from VAPP, and subsequent OPV vaccination to induce higher levels of intestinal immunity and maintain population-level protection. In Hungary, a country with a significant problem with VAPP cases [36] a sequential schedule comprising one dose of IPV followed by OPV led to a complete disappearance of VAPP [30, 31]. Another study in Hungary found that one or three doses of IPV followed by three doses of OPV resulted in individual protection against paralytic poliomyelitis as well as reduced cases of VAPP in the population [37, 38]. Additional experiences in India and the USA have shown that receiving IPV before OPV appears to protect against VAPP [12, 34, 36]. In addition, the sequential schedule of IPV followed by OPV in developed country settings achieved high seroconversion rates, with optimal effect obtained using two doses of IPV followed by two doses of OPV, a regimen that also produced intestinal immunity comparable to three doses of OPV [39]. The efficacy of this strategy has also been studied in the developing world: a trial of IPV followed by OPV in Guatemalan infant's demonstrated robust humoral immunity even after only two doses of IPV [40]. Also, use of mOPV in an outbreak control setting in a population who received a dose of IPV is likely to lead to higher immunity levels than a single dose of mOPV in a completely susceptible population, as the IPV-vaccinated population would already be partially protected with the existence of neutralizing antibodies from previous administration of IPV [39, 41].

Polio end game and its barriers:

Led by WHO, the United Nations Children's Fund (UNICEF), Rotary International and the CDC among other organizations, the Global Polio Eradication Initiative (GPEI) has developed the Polio Eradication and Endgame Strategic Plan was aimed to wipe out the last cases of polio from all causes by 2018 [35]. Because type 2 virus accounts for more than 95% of cVDPV outbreaks detected in recent years and approximately 30% of VAPP cases, a critical intermediate step to replace the trivalent OPV (tOPV), which with an aim of reviewing current scenario of polio vaccine this article is written, protects against types 1, 2 and 3, with a bivalent OPV (bOPV), which protects against types 1 and 3. The plan also calls for the addition of at least one dose of IPV (all currently licensed IPV is trivalent and protects against all types of polio) in routine immunization (RI) programs by 2015 in the OPV-only countries. IPV will provide immunity to a substantial proportion of the population [42] during this proposed OPV switch as well as during complete OPV withdrawal post-eradication in case of the possible emergence of type 2 cVDPVs, as well as in case of potential breaks in laboratory containment of wild or vaccine viruses. Such a plan is expected to change the landscape of global polio vaccine use in an incredibly short span of time The 2013–2018 strategic plan is expected to cost US$5.5 billion over the course of the program with continued investment by countries, but promises to yield up to US$25 billion in additional net benefits over the next 20 years. Substantial funding will be required throughout the end game to support core program costs, planned and supplemental immunization activities, surveillance, emergency response and containment. Total eradication of polio will lead to major reductions in public health spending on medical care, vaccine financing and programmatic costs once cases are reduced to zero and control activities can be scaled back [35].

While it has been shown that IPV integrated into RI programs will indeed reduce the prevalence of paralytic polio within a population, uncertainties remain on IPV's role in impacting transmission as part of a global polio eradication strategy as evident with the situation in Israel in 2013–2014 with more than a year of WPV1 isolation in sewage samples as discussed before [43]. On the other hand, Yogyakarta in Indonesia also switched to an all IPV schedule and has not detected any VDPVs since the chang. Yogyakarta had very high coverage and improved economic and public health infrastructure which may limit generalizability of this case to the low-income settings. Also, the force of infection of a vaccine virus may be different than that of a WPV, and IPV may be more effective against the former than the latter. It will be important to continue to monitor for circulation of type 2 viruses in particular as IPV becomes the only inducer of immunity to type 2 with switch of tOPV to bOPV. For countries with a routine Expanded Program on Immunization (EPI) schedule of 6, 10 and 14 weeks and deciding to give only one dose of IPV, that dose should be given at 14 weeks of age, at the same time DTP3 is normally administered. Addition of IPV does not impact the use of OPV at this time, which should be continued. Thus, for a child the dose

of IPV would usually be administered with the third dose of OPV for countries without a birth dose of OPV or fourth dose of OPV in countries with a birth dose. OPV-only countries have the flexibility to consider alternative schedules (such as 6, 10 and 14 weeks, 2, 3 and 4 months or 2, 4 and 6 months) and more than one IPV dose but are encouraged to develop a plan for IPV introduction by the end of 2014, based on tiered priority of countries related to risk of cVDPV emergence and spread [33]. Introduction of IPV in RI preceding the global withdrawal of Sabin type 2 is expected to have several important implications:

New Polio Vaccine Research:

Kind of vaccine desired for the end game and post eradication period would ideally have high humoral and intestinal immunity, long duration of protection, low cost, simple administration, widespread safe production, limited waste and heat and freeze stability, among other characteristics

(a) Monovalent IPV-2:

Currently available IPV is formalin inactivated trivalent vaccine comprising the three poliovirus serotypes, type 1, 2, 3 and is manufactured based on enhancements of methods developed in the 1950s by Jonas Salk. Following the development of the D-antigen (D-Ag) potency assays in the 1970s, the D-Ag content of 40, 8 and 32 D-Ag units for poliovirus type 1, 2 and 3, respectively for current IPV was established based on the historic immunogenicity studies by Salk [44-46]. Based on the data from the dose ranging studies and as a compromise between protective immune response in children and the quantity of vaccine that could be optimally manufactured with cost considerations, WHO defined in 1981 the 40-8-32 D-Ag units composition as the specification for the antigenic content for all trivalent IPV formulations [47]. Under the best of circumstances if only a single dose of IPV is used at 4 months of age, a study in Cuba found only 63% of recipients seroconvert to type 2. A higher antigen content monovalent IPV type 2 (m-IPV2) could be an option for the polio end game immunization strategies as a source of more effective primary immunogenicity against type 2, particularly during the period when bOPV would be used in RI. For this purpose, Bilthoven Biologicals company has formulated the m-IPV2 with an antigen content (type 2) of 32 D-Ag units, four-times the current dose of type 2 in the trivalent IPV. A Phase I study on safety in adults with m-IPV2 is now completed, and a Phase II study on safety and immunogenicity in infants is underway with this product (Table 3). Results from these studies are expected to be available by 2015, and should provide important information on any potential role of m-IPV2 in the polio eradication end game [48, 49].

(b) Adjuvant-IPV:

To support incorporation of IPV into global immunization programs, a range of approaches are being supported with goals of reducing the cost and increasing the supply of IPV. This includes developing formulations of IPV combined with an adjuvant to improve the immune response and decrease the amount of polio antigens needed. Adjuvant have been shown to influence factors such as onset, magnitude, duration and/or quality of the immune response [50, 51]. Such enhanced immune responses could translate into reduction in antigen dose or in the number of immunizations required, which could translate into the reduction of the costs of vaccination. Some adjuvants have also been shown to induce different types of immune responses, such as the enhancement of intestinal immune responses [52], which would improve the chances of interrupting transmission of both WPVs and VDPVs. In light of the increasing demand for IPV to be used to boost humoral immunity in individuals to protect against paralytic disease during the planned switch from tOPV to bOPV and all OPV cessation by 2019, IPV adjuvantation strategies have prioritized. A high priority has been given to efforts to evaluate and, if warranted, to clinically advance IPV formulations adjuvanted with aluminum salts, given that aluminum adjuvants have been shown to promote dose-sparing, have a broad safety database and are already widely used in childhood vaccines, including IPV containing combination vaccines. Furthermore, regulators have already approved aluminum as an adjuvant for other vaccines such as DTP, having considered aluminum salt adjuvants as both safe and effective. Planning for clinical studies to evaluate such a formulation with Salk IPV is currently ongoing with funding support from the Bill and Melinda Gates Foundation. As another example, an aluminum hydroxide-adjuvanted Sabin IPV has also recently been clinically evaluated [53]. The development of IPV adjuvanted with novel adjuvants that may enhance intestinal mucosal immunogenicity is also being explored as an important risk-mitigating strategy because some of the adjuvants, such as double-mutant heatlabile enterotoxin ('dmLT'), have been shown in studies conducted with other vaccine formulations to enhance mucosal immune responses in the intestine [54, 55]. The hope is that the adjuvanted IPV would have the potential not only to prevent paralytic disease (which can already be accomplished with the current unadjuvanted IPV formulations) but also to significantly enhance intestinal mucosal immunity and thereby reduce the risk for shedding and environmental transmission of polioviruses. Due to the anticipated more complex and thus, longer regulatory pathway required for a formulation involving a novel adjuvant such as dMLT, the regulatory approval timeline of such an IPV product would be anticipated to be several years after OPV cessation.

(c) New OPV formulations:

Vaccination against polio is likely to continue for at least 5 years after cessation of all OPV to ensure that both WPV and VDPV are extinct, and do not re-establish circulation. Current plans are to use mOPV2 in SIAs to control outbreaks should a WPV2 or cVDPV2 be found to be circulating in the post-eradication era. A new OPV-2 that is genetically more stable than Sabin type 2 could avert the unwanted potential for generating new type 2 cVDPVs with mass use of mOPV2, by significantly reducing the risk of neurovirulence and transmissiblilty. Several approaches are being undertaken to develop new and safer type 2 OPVs that are significantly less likely to cause VAPP or cVDPVs. Some of the concepts being explored alone or in combination include [56-64]:

1. Stabilizing the Sabin-2 attenuation phenotype by modifying the nucleotides in the 5′UTR;
2. Ensuring the maintenance of the modified 5′UTR or increasing attenuation by relocation of a genetic element (*cre*), which is required for replication, to the 5′UTR of the viral genome;
3. Reducing the rate of mutation in the viral genome through the selection of mutations that increase the fidelity of RNA-dependent RNA polymerase;
4. Attenuating the virus by modifying the nucleotide sequence of the viral capsid by a method called codon deoptimization such that the amino acid sequence of the viral polyprotein is unchanged.

Successful development of a genetically stable type 2 OPV could pave the way for developing genetically stable

vaccines against serotypes 1 and 3. If a new OPV-2 could be successfully developed, it would be an important tool for the control and elimination of cVDPVs in the concluding phases of the polio eradication initiative.

(d) Sabin IPV:

As the global eradication program moves closer to the achievement of zero virus transmission, and cessation of all OPV use, production facilities for IPV would possibly be the only source of WPVs. Therefore, an additional measure to minimize the risk of reintroduction of WPV from IPV manufacturing facilities would be to develop IPVs that are formulated from an attenuated live poliovirus [65]. IPV is usually made from WPV strains such as Mahoney (Salk type 1), MEF-1 (Salk type 2) and Saukett (Salk type 3) which are grown in Vero cell culture or in human diploid cells [66].Successful development of IPV based on the attenuated Sabin virus strains has led to the licensure of the Sabin IPV in Japan and subsequent introduction of DTP-Sabin IPV formulations in routine immunization program in the country [65]. Although still a risk, Sabin polioviruses are much less likely to cause problems if released accidentally from a production laboratory given that they are less virulent and less transmissible than WPVs. However, the costs, efficacy and feasibility of large-scale production are currently being evaluated, and further research to explore operational and immunological impact of Sabin IPV and standardization of assessment of antigenic content would be important to inform near- and post-eradication vaccination policies [65, 66].

(e) Synthetic polio vaccine:

Poliovirus (PV)-like particles from all three PV serotypes, containing either the wt coat protein or coat proteins with stabilizing mutations, were successfully expressed in plants. These were generated by co-expression of the structural polyprotein P1 and the proteinase 3CD. Sufficient quantities of purified particles could be obtained for structural and immunological analysis. Mice carrying the gene for the human PV receptor were protected from wild-type PV when immunized with the plant-made stabilized PV vlps. Structural analysis of the stabilized mutant of PV3 at 3.6 A resolution revealed a structure almost indistinguishable from wild-type PV3, with the stabilizing mutations having no effect on the antigenic surface of the particle. To make the product more attractive to the vaccine industry, tobacco BY-2 cells have been successfully tested for the transient expression of the above-mentioned PV mutant vlps using the cell-pack method.

(f) Transient-Expresion:

1. Use of virus free particle (eukaryotic):

PV vaccines have systematically reduced polio virus spread and paved the way for eradication. Immunization will continue posteradication to ensure against reintroduction of the disease, but there are biosafety concerns for both OPV and IPV. They could be addressed by the production and use of virus-free virus-like particle (VLP) vaccines that mimic the “empty” capsids (ECs) normally produced in viral infection. Although ECs are antigenically indistinguishable from mature virus particles, they are less stable and readily convert into an alternative conformation unsuitable for vaccine purposes. Stabilized ECs, expressed recombinantly as VLPs, could be ideal candidate vaccines for a polio-free world. However, although genome-free PV ECs have been expressed as VLPs in a variety of systems, their inherent antigenic instability has proved a barrier to further development. In a study, thermally stable ECs of type 1 PV (PV-1) selected. The ECs are antigenically stable at temperatures above the conversion temperature of wild-type (wt) virions. We have identified mutations on the capsid surface and in internal networks that are responsible for EC stability. With reference to the capsid structure, we speculate on the roles of these residues in capsid stability and postulate that such stabilized VLPs could be used as novel vaccines [67].

2. Plant as a expression system (eukakatyotic):

Two different ways to express pharmaceuticals, including VLPs, in plants and suspension cultures: (i) stable transformation of either the nuclear or plasmid genome or (ii) transient expression. Transient expression uses the soil bacterium *A. tumefaciens* which causes crown gall disease, to deliver foreign sequences to plants. Since the 1970`s it has been known that this gram-negative bacterium can transfer a part of its special Ti (tumor-inducing) plasmid into the plant cell where it then integrates into the host genome [68]. The gene of interest is inserted into the T-DNA region of a binary plasmid which will then be expressed in the plant cell. This allows screening and production in a matter of days. However, expression is limited to the infiltrated tissue but large-scale production and processing has been developed [69]. Transient expression is not as tightly regulated as transgenic plants; mainly because the gene of interest is not introduced into the germline and hence not heritable and also transmission through pollen is impossible. Transient expression is more established and accepted with Medicago`s influenza vaccine currently undergoing phase 3 clinical trials [69]. It allows the rapid production of high protein yields ideal for emergencies such as vaccines and prophylactic antibodies, as seen in the recent outbreak of Ebola virus disease in West Africa [70].

Administration routes of polio vaccines:

Vaccine delivery is a crucial aspect in addressing the challenges in vaccine development as it encompasses both administration of the vaccine formulation to specific target sites and delivery of the antigen to and activation of relevant cells of the immune system [71]. Since alternative delivery methods and improved formulations have the potential to make vaccine delivery easier and safer, several alternatives for needle-based vaccination are currently being developed. Needle-free delivery approaches are preferred for multiple reasons;

I. It might reduce costs since it does not require trained health-care personnel.
II. Logistic problems associated with the supply and disposal of syringes and needles and safety risks related to injection would be diminished [72].
III. Vaccine logistics could be further simplified by the use of dried vaccine formulations, which can be smaller and lighter than liquid formulations when packaged correctly.
IV. The independence of a cold-chain for storage and distribution could further reduce the costs.

Besides the route of administration, other aspects need to be considered in the design of an affordable (needle-free) polio vaccine, such as the use of an adjuvant serving as a delivery system and/or immune potentiator and an acceptable shelf-life, which will require formulation excipients. In the end, the roper designed delivery device, primary packaging, and the vaccine formulation together determine the storage conditions and shelf-life [71]. We are described here well established conventional vaccines such as OPV and IPV and their possible administrative routes. On the basis of available literature, there are other possible administrative routes of these vaccines.

(a) Dermal Immunization:

Driven by the fact that the dermis and epidermis of the human skin are rich in antigen presenting cells, and the ease of access to the skin, there is renewed interest in dermal vaccine delivery. The skin's structural and cellular composition enables it to function as a physical and immunological barrier, suggesting that delivery of vaccines to the dermal layers, rather than parenteral vaccine delivery, should be more efficient and induce protective immune responses with smaller amounts of vaccine antigen. At present, the ID route of immunization is only used for the administration of two currently-licensed vaccines: Bacille Calmette-Guérin (BCG vaccination against tuberculosis) and rabies. Currently there are three different intradermal (ID) delivery methods, which are used for administration purpose of vaccines by needle and syringe, jet injectors, and microneedles. Nevertheless, a PATH and WHO report reviewed the capability of ID delivery with vaccines against eleven diseases; including polio especially for IPV [73].

1. Needles and syringes:

IPV has been administrated in the developing world; the initial experiments of Jonas Salk anticipated its use via the ID route. In 1953, Salk demonstrated the immunogenicity of IPV administrated both intramuscularly and intradermally [70]. Despite these and more promising results in the mid-1950s [74-77], the ID route was only in Denmark the most abundant route for IPV vaccination at that time [77, 78]. With the purpose of developing a more affordable IPV for the lower-income countries and increase its use in the post-eradication era, different studies investigated ID polio vaccination [79]. Trials of ID administration of the enhanced-potency IPV, which was, with its higher content of poliovirus antigen, responsible for highly improved seroconversion rates for all three serotypes [80], have been ongoing in India since the early 1990s. Satisfactory seroconversion rates were obtained with fractional (one-fifth) doses delivered ID in subjects who had been previously immunized [81], or had never been immunized against polio [82].

2. Bio-needles:

Bioneedles are small hollow mini-implants from biodegradable polymers that can be filled with antigen followed by a lyophilization process. After sub-cutaneous delivery, the implant dissolves and thereby releases the antigen. Pre-clinical data of IPV with different antigens showed the feasibility of Bioneedles as vaccine delivery system [83-86]. A first phase1 clinical study with solid Bioneedles (without antigen) revealed good tolerability [87]. Besides, if formulated properly, vaccines in Bioneedles are thermostable, which can diminish the dependence on the cold-chain.

(b) Novel Routes of administration only for the IPV:

This is an exclusive for IPV better understandings of the feasibility of IPV use with different modes of administration and concomitantly with other childhood vaccines that have the potential to be used in sias are crucial research issues. The intradermal (ID) route of vaccine administration stimulates the immune response by delivery of vaccine antigen directly to dermal dendritic cells, the antigen-presenting cells that drive the generation of follicular T-helper cells and the subsequent activation and isotype-switching of naive B cells [88]. The ID route of administration allows a fractional dose (1/5th of the antigen used in intramuscular (im) administration) to elicit a similar immune response and therefore has the potential to reduce the cost of vaccination with IPV. Studies conducted to date with one, two and three IPV doses (and a booster dose in the Philippines study) have confirmed the immunogenicity of fractional dose ID delivery [39, 89-93]. However, although some studies have reported that seroconversion rates following ID administration of IPV for primary series or priming are lower no inferior to rates after a standard dose of intramuscular. IPV, other studies have found that seroconversion rates after ID administration of IPV have been inferior. Further, geometric mean titers and in some cases median titers induced by ID administration were consistently lower in all studies [89-92]. The benefits of disposable-syringe jet injector (DSJI) approach compared with needle and Syringe relates to ease of IPV delivery into the skin. The introduction of such an approach into Programs in place of intramuscular Or ID administered IPV would require more quantitative information.

(c) Mucosal immunization only for the OPV:

Due to their large surface area and immunological competence, mucosal tissues are attractive target sites for vaccination. An important characteristic of mucosal vaccination is the ability to provoke local immune responses, which already can protect against infection at the point of pathogen entry. Because mucosal surfaces are generally exposed to loads of environmental antigens, over-reaction of the immune system is prevented by tolerance mechanisms. Therefore, deliberate vaccination by a mucosal route can effectively induce immune suppression. To overcome tolerance and obtain a protective immune response, strong mucosal adjuvants and/or special antigen delivery systems are required for mucosal vaccine formulations unless vaccination is done with live attenuated viruses, like OPV.

The only marketed needle-free vaccination strategy against polio to date is oral vaccination by OPV given as an oral liquid. Oral vaccination has the potential to address all the prerequisites for a successful needle-free vaccine and may facilitate vaccine efficacy when formulated appropriately [71]. The gastrointestinal and respiratory tracts are common sites of entrance for many pathogens, so the immune surveillance at these sites is high. On or just beneath the epithelial linings all the machinery is present to elicit optimal protective immunity in both mucosal and systemic immune compartments and to generate cross-protective immunity at more distant mucosal sites as well as systemic immunity. The mucosal immune system has a certain level of compartmentalization. As a result, depending on the inductive site and the immunogenicity of the antigen (local) immune responses can be induced at more distant effector sites In the case of polio it is expected that immunity in the gut will give rise to protection against polio, as a result, nasal vaccination, which induces mucosal immunity in the gut (that is more distant from the inductive site), is an interesting vaccination route for polio vaccination.

1. Novel mucosal vaccine delivery nasal vaccination:

Intranasal vaccination can avoid degradation of vaccine antigen by digestive enzymes and low ph. As a result, nasal vaccination may require smaller doses of the antigen when compared to oral immunization [95]. However, for nasal vaccination also to date no vaccine is on the market on the basis of inactivated pathogens or subunits/proteins. In 2012, Cochi and Linkins marked that intranasal vaccination is also a possible way for IPV [96]. A major drawback of intranasal immunization is the possible deposition of antigen in the central nervous system through the olfactory bulbs and olfactory nerves, which can cause temporary facial paralysis (Bell´s palsy) [97]. This has been seen with a marketed virosomal influenza vaccine that was adjuvated by heat labile enterotoxin of *E. Coli* (LT) and has been withdrawn from the market due to this side effect. To date, no

efforts have been published that address nasal vaccination with polio vaccine formulations. Extensive reviews on nasal delivery of vaccines are available: [98-100].

2. Sublingual and buccal:

There are various traditional administrative routes like oral administration for OPV to induce mucosal immunity in human. Heleen kraan mentioned about another possible route for inducing mucosal immunity against polio was used viz. sublingual and buccal routes. These routes have been used for many years for the delivery of low-molecular-weight drugs to the bloodstream. During the past few years, these routes become more and more popular in research on vaccine delivery. Important advantages of sublingual and buccal delivery over the oral route are the relatively low enzymatic activity in the mouth, and avoidance of the low gastric pH, which could affect the antigen [101].

CONCLUSION

There is currently, a strong advocacy by the World Health Organization (WHO) for countries using only oral polio vaccine (OPV) to introduce inactivated polio vaccine (IPV), in different combinations with OPV. Introduction of IPV shares the contextual influences of both an existing vaccine and an entirely new vaccine, while previous vaccine hesitance studies have been on vaccine hesitancy to already available vaccines. There is a potential of vaccine hesitancy towards IPV when introduced and OPV is still retained in the immunization schedule, especially if the clinical reasons behind introduction of IPV are not adequately disseminated to the people.

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 IPV. In spite of this, researchers are also trying to explore other possible administrative routes of these vaccines, which may comparative better in way of effectiveness, safe and potent for candidates. 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 . 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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