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Review

Polio endgame: Lessons for the global rotavirus vaccination program ☆

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ABSTRACT

Poliovirus and rotavirus share notable similarities. Although rotavirus is not amenable to eradication because of animal reservoirs, live, attenuated oral vaccines have been the bedrock of both prevention and control programs, providing intestinal and humoral immunity. Both programs have also encountered safety concerns and suboptimal immune responses to oral vaccines in low-income settings that have been challenges, prompting the search for alternative solutions. In this paper, we review the progress made by polio prevention and eradication efforts over the past six decades. Specifically, we discuss the roles of the oral polio vaccine (OPV) and the inactivated polio vaccine (IPV) in achieving polio eradication, and explore potential application of these lessons to rotavirus. Recent scientific evidence has confirmed that a combined schedule of IPV and OPV adds synergistic value that may give the polio eradication effort the tools to end all poliovirus circulation worldwide. For rotavirus, oral vaccine is the only currently licensed and recommended vaccine for use in all children worldwide, providing heterologous protection against a broad range of strains. However, parenteral rotavirus vaccines are in the pre-clinical and clinical trial stage and insight from polio provides strong justification for accelerating the development of these vaccines. While challenges for parenteral rotavirus vaccines will need to be addressed, such as achieving protection against a broad range of strains, the principle of combined use of oral and parenteral rotavirus vaccines may provide the necessary humoral and intestinal immunity necessary to close the efficacy gaps between developing and developed countries, therefore controlling rotavirus worldwide. This strategy may also potentially reduce risk of intussusception.

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☆ The finding and conclusions in this report are those of the authors and do not necessarily represent the official positons of Centers for Disease Control and Prevention.

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1. Introduction

Polioviruses and rotaviruses share notable similarities. Both viruses cause an enteric infection that can be prevented through vaccination [1–3]. Live, attenuated oral vaccines have been the bedrock of both prevention and control programs, providing intestinal and humoral immunity. Both programs have also encountered safety concerns and suboptimal immune responses and efficacy of oral vaccines in low-income settings that have been challenges, prompting the search for alternative solutions [4–11]. For poliomyelitis, an inactivated poliovirus vaccine with an excellent safety profile that is administered parenterally has been used successfully globally particularly to avoid safety concerns of oral poliovirus vaccines [12]. Parenteral rotavirus vaccines have also successfully undergone animal testing and human trials are conducted or being planned [13–15]. The development and implementation of poliovirus vaccines preceded the development of rotavirus vaccines by ~30–40 years and thus may offer valuable lessons for the rotavirus vaccine program.

2. Polioviruses

Polioviruses cause acute enteric infection that uncommonly can manifest as acute flaccid paralysis and possibly lead to death [1]. The leap that poliomyelitis took from being a historically endemic disease to its epidemic form in the late 19th century prompted a series of novel scientific discoveries that changed the landscape of polio prevention and control [16–23]. This substantially advanced the pursuit of preventing infectious diseases through vaccination. The scientific discoveries and epidemiological research culminated in the development of two vaccines: the inactivated poliovirus vaccine (IPV) by Jonas Salk and his team and the oral poliovirus vaccine (OPV) by Albert Sabin and his team (Table 1) [22,23]. Both of these vaccines have played central roles in the control, elimination, and anticipated eradication of polio. The choice of which vaccine to use has been intensely debated over the years [4,24–33]. While IPV and OPV are fundamentally different in their production, composition, cost, storage, administration, efficacy, safety, and global market, both vaccines have contributed to polio eradication (Table 2). Even though our understanding and use of these two vaccines has evolved over the past 50 years, a global consensus on the joint role of these vaccines in the polio eradication and endgame plan has only recently taken shape [12].

The large annual epidemics of poliomyelitis took a turn in 1955 with the completion of a hallmark clinical trial of IPV that involved over a million children in the United States [34]. IPV is a trivalent vaccine that targets all three poliovirus serotypes (1, 2, and 3). The trial demonstrated that IPV was safe and effective against clinical poliomyelitis, thus providing the necessary impetus for including IPV in national immunization programs both in the US and abroad. The introduction of IPV resulted in a marked and sustained reduction in paralytic poliomyelitis in the United States and other industrialized countries, with polio cases declining by some 85% within three years of IPV introduction [21]. These declines were substan-

Table 1
Comparison of characteristics relevant to the polio and the rotavirus vaccination programs.

Characteristics	Polio	Rotavirus
Epidemiology (before vaccine use)	– Infects at younger age in LIC – Year round disease in LIC – Higher case-fatality in LIC	– Infects at younger age in LIC – Year round disease in LIC – Higher case-fatality in LIC
Immunity	– Correlate of protection known – Intestinal and humoral immunity both involved for protection	– No individual-level correlate of protection – Intestinal and humoral immunity both involved for protection
Global program aim	Eradication	Control
Vaccines licensed	OPV and IPV	Oral vaccines
Vaccine in development	Sabin IPV, safer OPV, adjuvanted IPV	Parenteral, other oral formulations
Years vaccines in use	Since 1955	Since 2006
Immunogenicity/Effectiveness/ Efficacy of oral vaccines	Lower in LIC Immunogenicity (seroconversion) [2][*]: Developing countries: 73% (type 1), 90% (type 2), 70% (type 3) Industrialized countries: 95%	Lower in LIC Efficacy and effectiveness [11]: Developing countries: 57–75% Industrialized countries: >90%
Safety of oral vaccines	Rare cases of polio (VAPP, VDPV)	Rare cases of intussusception and revertant strains
Parenteral vaccines	– Higher per dose seroconversion – Equivalent nasopharyngeal immunity as OPV – Inferior intestinal immunity compared to OPV – Superior humoral immunity compared to OPV – Superior intestinal and humoral immunity after OPV priming compared to OPV alone – No serious safety concerns	– Preclinical studies and early clinical trials promising – Robust intestinal and humoral immunity in animal models – Potentially superior immunity and protection as standalone or combination vaccines compared to oral vaccines – Potentially enhancing immunity and protection as booster dose after oral priming in LIC – No intussusception and revertant concerns

LIC denotes low-income countries; HIC denotes high-income countries; OPV denotes oral polio vaccine; IPV denotes inactivated polio vaccine; VAPP denotes vaccine-associated paralytic polio; VDPV denotes vaccine-derived poliovirus.

[*] Limited efficacy/effectiveness data on polio vaccines by developing country settings; seroconversion is a good correlate of protection against paralytic consequences of poliomyelitis [2].

Table 2
Advantages and disadvantages of oral and parenteral polio and rotavirus vaccines.

	Oral vaccines	Parenteral vaccines
Immune response	• In industrialized settings, effectiveness/efficacy is high with a full series, with sustained protection • In tropical developing countries, lower immune response is generally observed	• Immune response similar between industrialized and tropical developing settings for IPV • Clinical trials for IRV have not yet been conducted
Advantages	• Inexpensive • Easy to administer • Good oral and intestinal immunity • Both oral vaccine provide community protection. OPV diminishes exposure of susceptible infants and also transmits to contacts allowing secondary vaccination. ORV strains shed in stool, do not easily spread to other infants. Widespread ORV coverage diminishes exposure of susceptible infants and may delay but not prevent infection	• No risk of VAPP or intussusception (in theory) • Highly effective • May be a potential candidate for combination vaccines in the future easing logistics of administration. Children would benefit if both vaccines were administered in combination formulations together or with other vaccines administered at the same ages thus sparing the infant an extra injection
Disadvantages	▪ OPV causes paralysis in very rare cases (VAPP & cVDPVs) ▪ ORV causes intussusception in very rare cases ▪ High income populations are very risk averse. After control of poliomyelitis with use of OPV, IPV was introduced in the US due to a risk of paralysis from OPV and negligible risk from wild poliovirus. Oral RV vaccine remains tainted with a risk of Intussusception of 1:20,000 to 1 in 100,000 with the currently licensed vaccines ▪ Genetic changes, recombination, or reassortment occur with both OPV and ORV. This leads to more virulent strains for OPV but probably not for ORV.	• More costly than OPV or ORV • Cannot be administered by volunteers as it requires an injection • Does not confer transmission to contacts and thus provide secondary vaccination

OPV denotes oral polio vaccine; IPV denotes inactivated polio vaccine; IRV denotes inactivated rotavirus vaccine; ORV denotes oral rotavlrus vaccine; VAPP denotes vaccine-associated paralytic polio; cVDPV denotes circulating vaccine-derived poliovirus.

tially greater than those expected based on IPV coverage alone, indicating that the vaccine was providing herd protection. Finland, the Netherlands, Sweden, and Iceland all documented elimination of polioviruses through the exclusive use of IPV. In 1978, a more potent IPV (enhanced potency IPV) was developed which is the formulation licensed for use today [34].

OPV contains live attenuated strains of poliovirus that are also referred to as the "Sabin strains" [2]. Live attenuated polioviruses in OPV replicate in the oral cavity, intestinal mucosa, and lymphoid cells as well as in lymph nodes that drain these organs [2]. Vaccine viruses are excreted in the stool of vaccinated persons for up to six weeks after a dose. The maximum viral shedding occurs 1–2 weeks after vaccination, most often after the first dose, and viral excretion decreases after subsequent doses due to development of mucosal immunity. OPV strains may spread from the recipient to contacts, who upon exposure may be infected with vaccine virus [5]. In the early 1960s, with the demonstration of its safety and efficacy in a large clinical trial in the Soviet Union, the era of OPV began. Mass immunization programs throughout the world have led to dramatic reductions in the incidence of poliomyelitis. For several decades, the use of OPV eclipsed IPV in nearly all countries. Indeed, when the Global Polio Eradication Initiative (GPEI) was launched in 1988, the program used OPV exclusively as the vaccine of choice for polio eradication due to the lower cost, ease of administration, sustained supply, good intestinal immunity, and the possibility of indirect benefits [33]. The use of OPV globally has resulted in tremendous dividends. Over the past five decades, the incidence of polio has fallen from an estimated 350,000 cases annually in 1980s to only 22 confirmed cases worldwide in 2017, a >99.99% reduction [35].

Four formulations of OPV are currently available—bivalent OPV (bOPV, containing types 1 and 3), monovalent OPVs 1, 2 and 3 (mOPV) [2]. Prior to April 2016, trivalent OPV (vaccine containing types 1, 2, and 3) was the most commonly used OPV worldwide. However, because wild type 2 poliovirus was certified to be eradicated in September 2015, and because of the rare but continued neurologic consequences of the type 2 component of OPV, it is no longer used in routine immunization, and production and use of tOPV ceased as of 2016 [36]. Currently, bOPV is the most commonly used polio vaccine for routine and supplementary immunization in low and middle-income countries and mOPV2 is used for campaigns in response to outbreaks of type 2 vaccine-derived poliovirus.

3. Challenges with OPV

Despite the great successes achieved through the use of OPV, the program has suffered setbacks and missed polio eradication timelines, largely due to programmatic challenges resulting from civil unrest in war- and conflict-affected areas and poor performing immunization programs. However, two unique features of OPV have also contributed to setbacks and posed challenges to eradication of all poliomyelitis: adverse events and lower per-dose efficacy in low income country (LIC) settings.

3.1. Adverse events

Two types of rare outcomes of paralysis occur following use of OPV. OPV contains live attenuated polioviruses that can rarely lead to paralysis in the recipient or a close contact after spontaneous reversion to neurovirulence of one of the attenuated Sabin viruses in the vaccine [5]. The attenuating mutations vary by strain type, but these mutations are unstable and occasionally revert to virulence as OPV infects the intestine, sometimes in only 3–5 days. Due to reversion, the WHO estimates that the risk of vaccine-associated paralytic polio (VAPP) is ~4.7 cases per million births, leading to a global burden estimate of ~500 cases [8]. In addition, vaccinated individuals can shed slightly modified polio vaccine viruses into the community. Where there are pockets of lower population immunity to polio because of under-vaccination, continued circulation of these modified polio vaccine viruses in the community can lead to accumulation of mutations, particularly in cases of lower population immunity to polio. With sufficient mutations, these vaccine viruses may revert to neurovirulence with the same transmissibility and virulence as wild polioviruses--referred to as circulating vaccine derived polioviruses (cVDPVs). These viruses have not originated from contact with a recent vaccine recipient as is seen in contact cases of VAPP [5]. cVDPVs were first detected in 2000 in Hispaniola and have since altered the strategy for eradicating polio globally. The new strategy has been altered from relying on OPV alone for eradication followed by complete cessation of OPV after eradication, to considering a role for IPV after OPV cessation. IPV does not generate cVDPVs or cases of VAPP [20]. Prior to the global discontinuation of the use of the type 2 component of OPV in April 2016, almost all cVDPV outbreaks (>90%) were caused by type 2 OPV-derived virus [37,38]. Other very rare forms include VDPVs in persons with a primary immunodeficiency syndrome who chronically shed virus following direct or indirect initial vaccination (immunodeficiency-associated VDPVs or iVDPVs) [5].

3.2. Lower immunogenicity and effectiveness

Studies in developed countries demonstrated that three doses of tOPV resulted in seroconversion of >95% of infants to all types of poliovirus, providing long-lasting immunity [1]. However, in the 1970s Dr. T Jacob John reported that many infants in Vellore, India who were immunized with OPV developed a significantly lower immune response to all 3 serotypes of polio compared to children living in higher income settings [4,31,39]. Subsequent studies in developing countries demonstrated an average of 73%, 90%, and 70% of children seroconverted to poliovirus types 1, 2, and 3, respectively following three doses of tOPV [7]. A problem unique to OPV has been that the type 2 component of OPV has been demonstrated to reduce immunogenicity to types 1 and 3 probably due to competition in the gut. Vaccine "take" has varied by setting and formulation with effectiveness and immune responses being significantly lower in the poorest settings with high population density, poor sanitation and hygiene [40,41]. Mucosal immunity induced by some OPV formulations has also been lower in northeastern regions of India where vaccine efficacy has been impaired compared to other regions of India [40]. Reasons for the reduced potency of OPV have not been fully identified but may include co–infections with enteric viruses, higher maternal antibody titers, micronutrient deficiency, and gut enteropathy due to differences in the intestinal microbiome [7,30–32,42]. Also, intestinal immune responses to OPV wane significantly within one year of vaccination [43].

4. Challenges with IPV

Similar to OPV, challenges with IPV have also led to periodic setbacks that may be relevant for future development of parenteral rotavirus vaccines. The safety profile of the IPV formulations that are currently licensed and used worldwide indicate that serious adverse events are very rare. However, historically, IPV has encountered obstacles largely related to its manufacturing process. One of the most serious safety lessons for vaccine manufacturing occurred after the first IPV was developed from formalehyde-inactivated wild polio viruses and efficacy against paralytic polio was demonstrated in a hallmark clinical trial in US children. Within a year of the trial, an event known as "the Cutter incident" was linked to 61 cases of vaccine associated paralytic poliomyelitis, 80 family contact cases, 17 community contact cases and 11 deaths [44,45]. Subsequent investigations identified inadequate inactivation of the polio viruses during the manufacturing process [46] and confirmed that the Cutter incident caused ~70,000 illnesses, 200 cases of children with permanent paralysis, and 10 deaths. Subsequently, regulations and modifications in manufacturing techniques were implemented to ensure sufficient inactivation and avoid the potential to inject live polio viruses. These processes to ensure safety resulted in IPV preparations with reduced immunogenicity and efficacy, with a resurgence in polio cases in the US [47]. The subsequent decline in confidence in IPV was followed by efforts that led to improvements in the quality of IPV to its current formulation which was historically known as "enhanced-potency" IPV [48,49].

5. Overcoming challenges to OPV in developing settings

5.1. Programmatic amendments

One of the major obstacles to the eradication of polio has been achieving high levels of tOPV coverage through the routine immunization program, or "failure to vaccinate." Even when relatively high tOPV coverage was attained through the routine immunization program, some settings with high population density and poor sanitation, such as Gaza, West Bank, and Northern India, continued to have polio outbreaks or apparent "vaccine failure" among children receiving more than 1 dose of OPV [41,50]. Additional doses beyond the three doses administered as part of the routine infant schedule are required to improve seroconversion and achieve high levels of intestinal immunity in low-income settings [41]. Achieving and maintaining high levels of population immunity in these settings has generally necessitated multiple doses of OPV through the use of supplementary immunization activities (SIAs) to interrupt transmission of wild poliovirus. However, conducting quality SIAs in some regions has been extremely challenging due to civil unrest in war- and conflict-affected areas and in areas with hard-to-reach or noncompliant populations. These challenges have resulted in a resurgence of poliomyelitis cases in countries where polioviruses were endemic and spread of virus to countries that had been declared to be polio-free [51].

5.2. Formulation changes

The lower effectiveness of tOPV in some lower income settings posed challenges for the polio program. The type 2 component of tOPV reduces immunogenicity to types 1 and 3 [7]. The apparent elimination of type 2 wild poliovirus globally in 1999 allowed for the removal of this component of OPV during SIAs, through use of first mOPV then bOPV, resulting in improved per-dose immunogenicity and effectiveness against poliovirus types 1 and 3. For example, despite overall high rates of tOPV coverage, outbreaks of type 1 polio continued to occur in two states of India with the highest force of transmission. In 2005, the India polio program replaced tOPV with mOPV1 for their SIAs, gaining marked improvements in per dose effectiveness [40]. In 2009–2010, the global polio program strategically shifted to using bOPV in campaigns instead of tOPV, resulting in higher per-dose immune responses to types 1 and 3 than achieved previously with tOPV [51]. The India program during 2009–2010 also accelerated its efforts to vaccinate the undervaccinated, highly mobile population.

6. Sequential or combined uses of IPV and OPV

Many studies have evaluated the sequential or combined uses of IPV and OPV for countering adverse events and lower potency of OPV. The underlying rationale for this schedule is to provide both humoral and intestinal immunity through the unique properties of each vaccine. The vast preponderance of the published studies have been from middle and high income settings where efficacy of either IPV or OPV alone is high and added gains in efficacy from combined use of the vaccines are small [52]. Most studies in the published literature have assessed the sequential use of one or more doses of IPV followed by booster doses of tOPV hypothesizing that the humoral immunity induced by IPV would prevent VAPP from booster doses of OPV. One specific example of the benefits of a sequential IPV-OPV schedule is from Hungary where VAPP was eliminated after the adoption of a sequential IPV-OPV schedule [2,53,54]. In other high-income settings, this approach was also successful in reducing or eliminating VAPP.

In high-income settings, gains in effectiveness with the sequential schedule are minimal because immune response is excellent with either IPV or OPV [34,52]. However, the combined schedule of IPV and OPV has also been demonstrated to augment the lower immune response of OPV in developing nations where its added value over either vaccine alone has proven to be substantial. In three particular settings with high force of transmission [50,55,56], the use of a sequential IPV-OPV schedule as well as the OPV-IPV schedule have both demonstrated superior intestinal and humoral immunogenicity than either vaccine alone.

6.1. Gaza

During the 1970s, the persistence of polio cases and outbreaks despite achieving >90% coverage with tOPV in Gaza and the West Bank led authorities to suspect tOPV failure in these settings of high population density and poor sanitation [50]. This prompted the national authorities to implement a combined ("intercalated") OPV-IPV program that included 5 doses of OPV and 2 doses of IPV. In Gaza, OPV was administered at 1, 2.5, 4, 5.5, and 12 months of age, with IPV at 2.5 and 4 months. In the West Bank, all OPV doses except the fifth dose were administered a month later than in Gaza. Ecologic data collected from 1968 and 1988 demonstrated a dramatic decline in the incidence of polio after the combined schedule compared to the decade prior when only tOPV was used. Comparison of serologic data confirmed increases in seroconversion to all three types of poliovirus from 56% to 74% during years of tOPV use to 98%-100% after switching to the combined OPV-IPV schedule. This increase could not be explained by coverage alone and confirmed the gains in protection due to the combined schedule in settings with a high force of transmission and lower tOPV effectiveness. However, the combined schedule also increases cost and complicates logistics, which has hindered broader use of this strategy in resource-poor settings.

6.2. Cote d'Ivoire

A study from Cote d'Ivoire compared the immunogenicity of a supplemental dose of IPV with tOPV among infants who failed to mount an immune response after 3 doses of tOPV [56]. Among these tOPV-vaccinated seronegative infants, one dose of IPV induced a superior seroconversion rate to all three poliovirus serotypes (67%–100%) compared to an additional dose of tOPV (5%-53%) [56]. Thus, IPV closed the immunity gap in a developing country setting among children who failed to respond to tOPV.

6.3. India

Similarly, in India, infants previously vaccinated with tOPV and mOPV1 who remained seronegative to types 2 and type 3 poliovirus had seroconversion rates of 90–100% and significantly higher titers after IPV [55]. Because most children had received on average 3 doses of tOPV and 7 doses of mOPV1, nearly all (99%) had already seroconverted and already had very high titers to type 1 prior to receiving IPV.

6.4. Sequential OPV-IPV use and intestinal immunity

Transmission of polio can either be oral-oral (thought to be the predominant mode of transmission in developed settings) or fecal-oral (thought to be the predominant mode of transmission in developing, high population density, and low sanitation settings). OPV provides superior intestinal immunity (i.e. reducing fecal shedding) compared to IPV, but both are equally effective at inducing oropharyngeal immunity (i.e. reducing oral shedding) [57]. Ecologic data support these findings that exclusive use of IPV in developed country settings has demonstrated effective herd protection, likely related to the effect of IPV on reducing oral shedding. IPV also reduces the duration of shedding (and, to a limited extent, the amount of virus) in the stool, as well as excretion of virus in those previously immunized with OPV [19,58,59]. [60–62].

It is important to note that the aforementioned studies have assessed sole use of IPV versus OPV at a young age, likely prior to wild virus exposure. Research has also demonstrated that prior mucosal exposure to OPV can substantially enhance the effect of IPV boosting on intestinal immunity (i.e., prime-boost effect). A study from Cuba demonstrated that viral titers in stool after IPV vaccination versus unvaccinated controls were 0.5–1 $\log_{10}$ lower at day 7 after OPV challenge and the excretion period was shortened by half (median of 10–12 days after two IPV doses versus > 20 days in unvaccinated controls) [63,64]. In India, a single IPV dose (compared to no IPV) in infants 6–11 months, 5 years, and 10 years of age who received multiple prior OPV doses reduced excretion prevalence of polioviruses by 39%-74% after a challenge with bOPV [19]; moreover, the reduction in fecal shedding was greater with supplemental dose of IPV compared to bOPV. These findings are consistent with previous research demonstrating that IPV can induce significant intestinal immunity among children with prior mucosal exposure to OPV or wild poliovirus [65].

7. The polio endgame: OPV withdrawal and IPV introduction

To avoid risks of re-emergence of polioviruses, the World Health Assembly has also recommended that all countries introduce at least one dose of IPV into their routine immunization programs [12,66]. Until the WHA decides on a date for OPV withdrawal globally, the recommendation is for IPV to be administered in addition to bOPV, which is the current formulation in all countries using OPV worldwide [12,38,67]. The combined use of IPV and bOPV provides additional humoral and intestinal immunity that mitigates the risks of wild poliovirus and risks of VAPP and cVDPV from type 2 poliovirus. This combined use improves protection against polioviruses, and reduces the need for use of all OPVs, to attain the goal of eradicating both wild and vaccine-derived polioviruses. Recently, SAGE recommended that after global OPV withdrawal countries should include at least 2 doses of IPV in their routine immunization schedule, the first at or after 14 weeks and the second dose $\geq$4 months after the first dose [68].

8. Rotavirus vaccine program

Rotaviruses cause an acute enteric infection that clinically presents as gastroenteritis with nearly all children worldwide acquiring a rotavirus infection by age 5 [3]. Although dehydration is treatable with intravenous or oral rehydration, rotavirus infection can be fatal in resource-poor settings with limited health care infrastructure and access causing an estimated 150,000–200,000 deaths per year in developing countries [69]. Rotavirus was discovered in 1973 and the first candidate vaccines were developed and tested in the 1980s and 1990s [70–72]. Second-generation rotavirus vaccines have undergone large-scale clinical trials in developed and developing countries, and are now recommended by the WHO for all children worldwide [72]. To date, more than 82 countries have adopted rotavirus vaccines in their routine immunization programs resulting in large declines in diarrhea hospitalizations [73–80], diarrheal deaths [81–83], as well as providing providing community protection [74,84].

The parallels in epidemiology between polioviruses and rotaviruses can shed light on the prevention approach of vaccination early in life before natural infection occurs (Table 2). Transmission dynamics of both viruses are similar [1,3,21,71]. They are both spread person-to-person by the fecal-oral route, particularly in regions with poor sanitation and hygiene. In settings with high standards of hygiene, oral-oral transmission is also likely to be common. Historically, polio was an endemic disease, but with improvements in hygiene, sanitation, and vaccination, polio became established as an epidemic disease in developed countries, such as Northern Europe and United States, especially in populations that refused immunization [2,21]. However, until recent progress with global eradication efforts, polioviruses infected children year-round in developing countries with a high force of infection and year-round transmission due to poor sanitation and hygiene. Rotavirus seasonality also differs by setting, maintaining a highly seasonal endemic pattern in developed countries and a year-round pattern in developing countries. Studies have demonstrated that high birth rates and transmission rates influence seasonality of rotavirus more than environmental conditions [85,86]. In addition, both viruses infect children early in life, with infection occurring at a younger age in developing countries compared to developed ones.

In contrast to poliovirus, eradication of rotavirus is unlikely because rotavirus has animal reservoirs. In addition, the two gene segments that encode the surface rotavirus proteins (VP4 and VP7) can segregate independently in vivo and in vitro, and theoretically lead to more than 100 different surface protein combinations [87]. However, five rotavirus strains are responsible for 80–90% of the global burden of severe rotavirus disease and vaccines currently introduced in the country programs have provided protection against the circulating strains [121]. Lastly, while cases of paralytic polio are few worldwide because of eradication efforts globally, rotavirus disease continues to cause an estimated 215,000 deaths worldwide, accounting for some 37% of all diarrhea-related deaths and hospitalizations in children <5 years worldwide [88].

Mechanisms of immunity to rotavirus infection have not been fully elucidated but both intestinal (secretory IgA and IgG) and humoral responses (total serum IgA, IgG and neutralizing antibodies) are likely to play a role in modulating infection [89,90]. Rotavirus infection, unlike polio, presents as a gastrointestinal illness. Augmenting intestinal immunity as a primary line of defense has been the focus of the oral rotavirus vaccine (ORV) strategy [3,72]. Therefore, all rotavirus vaccines licensed to date have been live oral vaccines. These ORVs have had a similar efficacy profile as OPV and other oral vaccines with high efficacy (>80%) in high- and middle-income settings and lower efficacy (40–67%) in low-income settings despite having high vaccination coverage [3,71,72,91–95]. Reasons for the lower efficacy remain unclear and interventions to improve efficacy in developing settings (e.g. withholding breastfeeding, adding buffers, micronutrient supplementation) have failed to yield definitive or actionable results [10,96]. However, despite modest efficacy, the burden and thus the absolute fraction of severe disease that is preventable through vaccination is much greater in low-income compared to middle and high-income settings [97].

9. Safety of rotavirus vaccines

Another key hurdle for the rotavirus program has been safety concerns related to the live oral vaccines [98]. Although the health benefits of rotavirus vaccines have far outweighed the safety concerns with the oral preparations of rotavirus vaccines [99,100], these adverse events are of concern and could potentially derail a successful vaccination program.

9.1. Intussusception

In 1999, a previously licensed rotavirus vaccine, RotaShield, was abruptly withdrawn from the US market after post-licensure evaluations identified a strong association between the vaccine and intussusception, a potentially fatal cause of bowel obstruction among infants [101]. The two currently licensed rotavirus vaccines, Rotarix and RotaTeq, subsequently underwent large clinical trials with over 60,000 infants each, which did not result in a risk of intussusception similar to RotaShield [102,103]. However, following scale-up of large-scale immunization programs, both vaccines have been demonstrated to be associated with a very low risk of intussusception (1 per 20,000–100,000 infants) in middle- and high-income settings but no apparent risk of intussusception in low-income settings of sub-Saharan Africa [100,104–109]. The pathogenesis of intussusception after rotavirus vaccines remains unclear, but the consistency in findings suggests a similar effect from both of these live ORVs in some settings.

9.2. Vaccine virus reassortants

Studies have identified rare detections of vaccine-derived rotavirus strains in children with acute gastroenteritis [98,110,111], mostly in children with underlying medical conditions such as immunodeficiency disorders. It is also unclear whether these vaccine-derived strains are more virulent than the parental ones and transmission in the community has not yet been observed. Consequently, while detection of these vaccine-derived strains is not yet of public health significance, the experience with OPV indicates that ongoing monitoring and evaluation of diseases related to vaccine-derived strains will be important as rotavirus vaccine programs mature.

9.3. Vaccine contamination

In 2010, both RotaTeq and Rotarix were discovered to be contaminated by porcine circoviruses and the Rotarix vaccination program was temporarily suspended [112]. The suspension was lifted when the US FDA further examined the data and determined that the contamination did not pose a threat to human health. The contamination also led to a temporary suspension of vaccine programs in Panama and Spain. Subsequent investigations identified that the contamination was due to use of porcine-derived trypsin during the cell-culture growth process of vaccine production [113]. Therefore, the contamination was present in the cell line prior to the clinical trials of the vaccines. Although health benefits of both vaccines were determined to far outweigh any theoretical risks of the contamination, these detections were quite disruptive to vaccination programs in several countries.

10. Parenteral rotavirus vaccines

To overcome the pitfalls of live oral vaccines, the lower vaccine efficacy in low-income countries, and the low-level risk of intussusception, there have been ongoing efforts to develop rotavirus vaccines for parenteral administration. The aim of these parenteral vaccines would be to improve the efficacy and reduce the risk of intussusception and gastroenteritis in vaccinated children. Since parenteral administration is not subject to risk factors associated with oral vaccination, the hypothesis is that they could be equally effective for all children regardless of socioeconomic status. In addition, the potential of combining a parenteral rotavirus vaccine with other routinely administered pediatric vaccines could eliminate additional administration costs, and cold-chain and storage challenges, thus making programmatic implementation easier compared to oral vaccines [13,14].

One of the parenteral candidate vaccines is an intact rotavirus, CDC-9 strain, that is heat inactivated. This inactivated rotavirus vaccine (IRV) is a single-gene reassortant with the VP3 gene from a DS-1-like strain and the remaining 10 genes from a Wa-like strain [114]. The G1P[8] strain is the most common rotavirus genotype worldwide. CDC-9 grows abundantly (up to 10^8 ffu/mL) and shows profound stability, as evidenced by structural integrity of triple-layered particles in Vero cell culture and during the downstream purification process. In addition, this virus provides high yield of antigen in a scale-up manufacturing process after the virus has been completely inactivated by heat. The relatively easy traditional manufacturing process and the stability of the virus are unique features that could have added value for creating a low cost and effective IRV.

Animal studies have demonstrated that the CDC-9 IRV, when formulated with alum gel and administered intramuscularly, induces neutralizing antibodies to homotypic and heterotypic human rotavirus strains in animal studies [115]. Despite the IM administration, IRV can induce intestinal immunity in mice and is effective in mediating protection from oral challenge with a virulent human rotavirus in gnotobiotic pigs [116–118]. With the establishment of a pilot manufacturing process and proof of concept in pre-clinical studies, studies are in progress to advance the IRV to clinical trials in humans. Future studies will need to assess a potential regimen of priming children with an ORV followed by boosting with the parenteral IRV, similar to successful combined OPV and IPV schedules. Studies are also in progress to combine IRV with other pediatric vaccines (e.g., IPV) and develop an IRV-containing combination vaccine [119].

In addition to IRV, several other parenteral rotavirus vaccines are in development [14]. A parenteral P2-VP8-P[8] subunit rotavirus vaccine is the most advanced as it has been tested and found to be well tolerated and immunogenic to homologous strains in infants [15]. A phase 1/2 trial of a trivalent P2-VP8 (P[4], P[6], and P[8]) subunit vaccine is underway among infants in South Africa. It remains to be determined whether this subunit vaccine alone is more effective than oral vaccines or an oral prime-parenteral boost schedule with this subunit vaccine can enhance the performance of oral vaccines in children. In addition, similar to ORVs, parenteral vaccines will also need to be designed to provide protection against a broad range of strains, either though ensuring heterologous immunity or through inclusion of vaccine antigens that cover the predominant strains circulating globally.

11. Lessons the polio program has for rotavirus prevention

The polio program has over 60 years of accumulated experience that is of substantial relevance to the global rotavirus vaccine program. The polio program from the outset had the advantage of two fundamentally different vaccines, OPV and IPV, each with their specific pros and cons (Table 2). Research and practical experience over the years have confirmed that both vaccines offer intestinal and humoral immunity of various degrees, and that the two vaccines in a sequential schedule have a synergistic effect that is superior to the exclusive use of either vaccine. OPV has been the primary tool for polio eradication worldwide; however, higher-income countries have switched over to IPV during the past two decades in order to avoid the safety concerns of OPV (VAPP), particularly as wild polioviruses were eliminated in these regions and global circulation of wild poliovirus has decreased. OPV has been beneficial for SIAs in developing countries due to its low cost and delivery efficiency; however, this efficiency has been somewhat offset by its lower per dose effectiveness. Overcoming the lower effectiveness in some settings has required multiple doses (>10 in some countries) through resource-intensive SIAs, outside of a country's routine immunization program. In some countries with poorly functioning routine immunization programs, many children receive vaccines only through SIAs. Such intensive immunization efforts are not likely to be used for rotavirus vaccines which are currently given only through routine immunization programs.

The rotavirus program has made substantial advances resulting in large reductions in hospitalizations and deaths related to diarrhea. While a low-level risk of intussusception also continues to plague these vaccines, the health benefits of vaccination far outweigh the potential dangers. That said, the polio program has imparted several lessons that warrant attention. First, a strategy of combining both OPV and IPV has been demonstrated to offer substantial theoretical advantages to administering either vaccine alone due to improvements in intestinal and humoral immunity. The administration of IPV after initial priming of the gut with OPV substantially narrows the immunity gap in high transmission settings. Could a similar strategy, priming with a live oral vaccine follwed by boosting with a parenteral vaccine, for rotavirus vaccine programs also reduce the efficacy gap between low and high-income settings?

Secondly, safety concerns of OPV have been an impediment to the eradication aims of the polio program with generation of cVDPVs in areas with low vaccination coverage. Inactivated vaccines do not have these safety concerns. While logistics of training health workers, the requirement for fixed-post immunization only and costs in manufacturing and supply may be substantially higher with parenteral vaccines, adverse events with oral vaccines have the potential risk of derailing immunization programs and may be associated with substantial unforeseen costs that also warrant consideration. As has been done through the combined use of OPV and IPV, safety of the rotavirus program could also potentially be improved with a combination oral and parenteral schedule, or possibly even a switch to a parenteral rotavirus vaccine depending on the setting and the efficacy data. Because intussusception rarely occurs before 10–12 weeks of age, restricting oral vaccines to the first EPI visit at 6 weeks or 2 months of age followed by one or two doses of a parenteral rotavirus vaccine has the possibility of reducing the safety concerns associated with ORVs.

Third, as OPVs will be phased out after the eradication of polio, ORV will be the only oral vaccine in EPI. The added advantage of a parenteral rotavirus vaccine could be that it allows for a combination vaccine added to IPV or potentially other parenteral vaccines. A combination vaccine would ease the logistics of vaccine administration and reduce the time burden of vaccination in busy clinics. Applying program experience and lessons learned from the polio endgame initiative where over 120 countries worldwide introduced IPV between 2014 and 2016 and co-administered both OPV and IPV in their routine immunization programs may facilitate such an initiative for a parenteral rotavirus program. Success factors for advancing this polio endgame initiative at a global and country level included having a global mandate and recommendations, clarity in policy, standardized guidance, financial resources, technical support, engagement of national immunization technical advisory groups, supply considerations, advocacy efforts, regulatory approvals, and country support to address operational challenges such as cold chain, wastage, training, and acceptability of vaccine [36].

Challenges remain ahead in pursuit of development and ultimate implementation and acceptability of parenteral rotavirus vaccines. Demonstrating safety, immunogenicity, and efficacy of these vaccines in humans, particularly in a broad range of settings will be necessary. Scientific and practical considerations of co-administration of parenteral rotavirus vaccines with IPV and other products need further examination. Assessing for potential interference as well as ensuring lack of enhanced reactogenicity will be key. While intussusception has been a concern for ORV, the vaccine has an otherwise safe profile with extensive postmarketing experience that will need to be replicated for acceptance of parenteral vaccines. The speed with which these evaluations are conducted and combination products are brought forth to the market may also influence the ultimate willingness of countries adopting these products because the immunization landscape is evolving and global experts have not agreed upon the duration of IPV use in routine programs after polio eradication. Importantly, with increasing antigens being included in routine immunization programs, concern exists regarding the acceptability and feasibility of administration of multiple injections at a single visit. The polio endgame experience and available research on this topic indicate that countries, decision-makers, providers, and parents would be willing to accept multiple injections with appropriate rationale and understanding of the benefits of multiple injections [120]. However, barriers do exist with regard to developing the evidence base, communications, training on vaccine co-administration practices, and operational recommendations that appropriately address concerns of multiple injections. Specific comparative research will need to address whether acceptability will be as high with parenteral versus oral rotavirus vaccines.

Ensuring the accelerated and coordinated development of parenteral rotavirus vaccines could substantially advance the global goal of preventing severe and fatal rotavirus diarrhea using safe and effective vaccines. A funded research agenda to pursue these promising candidate vaccines and alternative vaccination strategies could go far to address the shortcomings of live, oral vaccines in low-income settings. Such an agenda would need to consider human safety and immunogenicity evaluations, identifying possible correlates of protection, efficacy studies, and cost evaluations of developing and employing these vaccines. Moreover, technical and programmatic feasibility of combining parenteral rotavirus vaccines with other childhood vaccines such as IPV would also need priority attention for these vaccines to come to fruition. Consultation from experts in mature vaccine programs such as the polio eradication program may also inform the feasibility of parenteral rotavirus vaccines and possibly accelerate the development and testing of promising candidate products and strategies in a timely manner.

After six decades of controversy over the optimal vaccine for eradicating polio, the combined use of IPV and OPV may assist in achieving eradication of poliomyelitis. Although the decision to use OPV and IPV in a combined manner globally was taken for reasons unique to the polio program, the science and the policy may offer lessons for the rotavirus program as it aims to deliver vaccines of the highest quality and safety to children worldwide. Developing a research agenda to assess the combined use of oral and parenteral rotavirus vaccines could offer unique immunologic advantages in developing countries compared to either vaccine alone thus improving the effectiveness of the vaccine program. Such an improvement may indeed close the effectiveness gap between high- and low-income settings, and could potentially double the number of lives saved and hospitalizations averted through the use of rotavirus vaccines.

Conflict of interest

CDC holds the patents for rotavirus strains and inactivation methods developed by Drs. Jiang and Glass for the inactivated rotavirus vaccine described in this paper. Dr Patel has no conflicts of interest to declare.

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