Final frontiers of the polio eradication endgame

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\textbf{Purpose of review} 
Focusing on the key developments since January 2019, this review aims to inform policymakers and clinical practitioners on the latest on evolving global polio epidemiology and scientific advancements to guide strategies for eradication.

\textbf{Recent findings} 
An upsurge in wild poliovirus type 1 cases in Pakistan and Afghanistan and an expansion of type 2 circulating vaccine-derived poliovirus transmission in multiple countries threaten the remarkable progress made over past several decades by the global eradication program. These challenges have also spurred innovation on multiple fronts, including earlier detection, enhanced environmental surveillance and safer and more affordable vaccine options.

\textbf{Summary} 
A concerted effort to adapt program strategies to address context-specific challenges and continued focus on innovations to enhance detection and response capabilities will be the key to achieve and sustain eradication of all types of polioviruses.

\textbf{Keywords} 
endgame, eradication, novel type 2 oral poliovirus vaccine, polio, surveillance

\textbf{INTRODUCTION} 
Four decades since its certification of eradication, smallpox remains the only human disease to be eradicated. Two decades from its original target date, polio eradication continues to remain enticingly close to the finish line. The overall disease incidence of polio has been reduced by 99.9\% from the time the global polio eradication initiative (GPEI) was launched in 1988. Two of the three wild types of polio have been certified eradicated, with only wild polio virus type 1 (WPV1) circulating in two countries – Pakistan and Afghanistan \cite{1}. However, WPV1 transmission in these two countries intensified in recent years, with number of paralyzed children from WPV1 five times higher in 2019 compared with 2018, a concerning setback from the consistent decline in disease incidence over the past decade (Fig. 1). In addition, circulating vaccine-derived poliovirus (cVDPV) transmission is rapidly spreading with outbreaks reported from nearly 20 countries from four different WHO Regions (African, Eastern Mediterranean, South-east Asian, and Western Pacific) (Fig. 2) \cite{2,3}. Moreover, the coronavirus disease-2019 (COVID-19) pandemic has resulted in temporary suspension of supplementary immunization activities (SIAs) in polio-infected countries since early 2020 leading to a heightened risk of further spread of poliovirus in the coming months \cite{4}.

On the basis of the evolving global epidemiologic situation, the current focus for achieving and sustaining eradication is centered on a few strategic priorities, which include: improving quality of outbreak response; accelerating development of vaccines that have less risk of reversion to neurovirulence; enhancing surveillance scope and efficiency; and strengthening routine immunization activities \cite{5}. In this review, we summarize the most recent advances on these fronts for a clear understanding of the current challenges and potential solutions to direct the final phase of polio eradication.

\textbf{DISEASE EPIDEMIOLOGY: WILD POLIO VIRUS TYPE 1 ENDEMICITY AND THE VACCINE-DERIVED POLIOVIRUS 2 CONUNDRUM} 
Transmission of the only remaining WPV, type 1, is currently restricted to Pakistan and Afghanistan –
with no WPV1 case detected outside these countries since 2016 (Fig. 2). In the past 18 months, transmission within these two countries has intensified with substantial geographic expansion and circulation of multiple genetic lineages [6]. Of the two countries, Pakistan reported a striking, nearly 10-fold rise in paralysis cases from 2018 to 2019, and has documented 49 cases as of 01 June 2020, which is about six times what the country reported in 2017, the year with lowest incidence of WPV ever (Fig. 1). Poor access because of civil unrest and insurgency in parts of these two countries and vaccine avoidance behavior in subpopulations have played a key role in the uncontrolled spread of WPV1 in this geography [7,8].

Since its licensure in 1961 in the United States, widespread use of oral polio vaccine (OPV) in routine immunization and SIAs has been instrumental in interrupting person-to-person transmission of poliovirus in settings where transmission is driven by the fecal–oral route [9]. However, because of its inherent genetic instability, Sabin OPV strains can lose their attenuating mutations through reversion [9]. These strains, termed vaccine-derived poliovirus (VDPV), can re-acquire transmissibility and neurovirulence in areas with low vaccination coverage and where epidemiologic conditions favor poliovirus transmission (e.g. low socioeconomic status, poor hygiene/sanitation, and crowding) and result in outbreaks of cVDPV. Also, in individuals with

**KEY POINTS**

- Wild poliovirus type 1 endemicity in Pakistan and Afghanistan and circulating vaccine-derived poliovirus transmission in multiple geographies pose significant challenges for the final phase of polio eradication.
- Rapid detection methods with integration of sequencing results that are affordable and usable in peripheral settings hold promise to enhance surveillance reach and sensitivity.
- Major advances in vaccine development with likely introduction of novel type 2 oral polio vaccine in 2020 and expansion of affordable IPV supply options can facilitate completing eradication of all polioviruses.
- Maintaining high population immunity, implementing qualitative improvement in outbreak response, adapting to the evolving COVID-19 pandemic situation and mitigating post-eradication risks of re-introduction of polioviruses can help sustain the gains for long-term.

**FIGURE 1.** (a) Use of different oral poliovirus vaccines in outbreak response over time. (b) Incidence of poliomyelitis cases from wild poliovirus and circulating vaccine-derived poliovirus, January 2000 – June 2020. *Cases for 2020 are those in the period 01 January to 01 June only. Data as of 03 June 2020. bOPV, bivalent oral polio vaccines; mOPV, monovalent OPV; nOPV, novel OPV; tOPV, trivalent OPV.*
primary immunodeficiency disorders (PID), inability to mount an immune response against the vaccine virus can lead to prolonged replication and chronic excretion of immunodeficiency-related VDPV (iVDPV). In addition, OPV administration can rarely result in 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 [10].

The type 2 component of trivalent OPV was responsible for approximately one-third VAPP cases and 90% of all cVDPV cases [10,11]. As the wild type 2 poliovirus was certified eradicated in 2015, a global ‘Switch’ in May 2016 resulted in cessation of all routine use of trivalent OPV (types 1, 2, and 3), and its replacement by bivalent (types 1 and 3) OPV [11]. Since then, monovalent OPV type 2 (mOPV2) released from a global stockpile on a case-by-case basis has been used to control cVDPV2 outbreaks (Fig. 1). Multiple cVDPV2 outbreaks in the post-switch period have presented a major challenge and have been designated as Public Health Emergency of International Concern (PHEIC) [3*,12]. Compared with January 2017 to June 2018, the number of reported cVDPV2 outbreaks more than tripled, from 9 to 29 between January 2018 and June 2019. As of 01 June 2020, 133 cVDPV2 cases have been reported from 17 countries across three WHO Regions. The past 12–18 months have seen the largest number of countries infected, and highest number of cases reported ever since reporting and classification of VDPVs began nearly two decades ago (Fig. 1). The cVDPV2 outbreaks since removal of tOPV have been particularly difficult to control because of rapidly waning intestinal immunity of the global population against type 2 poliovirus. Additionally, outbreak response in many affected countries has been challenging because of poor access, security concerns, and capacity constraints. Finally, because of its inherent risk of reversion as described above, an increasing number of new emergences of cVDPV2s are attributable to the use of mOPV2 in outbreak response [3*]. The expanding cVDPV2 outbreaks and the limitation of the current vaccine in certain population settings have evolved to be one of the biggest challenges in the current phase of polio Endgame [3*].

**DISEASE SURVEILLANCE: ENHANCING DISEASE DETECTION**

Paralytic poliomyelitis is a rare outcome of poliovirus infection with paralytic case to infection ratio varying by WPV serotypes – 1 in 190, 1900, and 1100 for types 1, 2, and 3, respectively [13]. Thus, a sensitive syndromic surveillance system based on reporting of acute flaccid paralysis (AFP) cases from all causes in children younger than 15 years of age forms the cornerstone of disease surveillance for polio [14]. AFP surveillance is supplemented by environmental surveillance – collection and testing of sewage samples from high-risk areas to rule out or
confirm presence of virus transmission [14]. Laboratory algorithm for poliovirus surveillance includes virus isolation from stool and sewage samples, followed by intratypic differentiation (ITD) by PCR and finally sequencing of the VP1 region to identify Sabin-like, VDPV and WPV types [14]. Overall, this process can take 2–3 weeks on average from sample receipt to availability of sequencing results and one of the components of improving outbreak response efficiency is to shorten this turnaround time.

Over the past 12–18 months, innovative approaches have been reported to strengthen existing surveillance systems and to make them more adaptive to the current epidemiology of polio. A recent report proposed spatial binning and surveillance flags analysis as two methods that could help by either identifying areas where standard AFP surveillance indicator targets are not met consistently or by analyzing unusual patterns of reporting in areas where indicator targets are met [15]. The importance of environmental surveillance has grown with the need to monitor Sabin-like viruses in the postswitch period and its unique role in detecting transmission early, and potentially before paralytic cases get reported [16,17]. Moving on from elective use of environmental surveillance from fixed sites, reactive forms of environmental surveillance deployment around outbreak response or difficult-to-access areas have been explored. For example, a one-time collection effort of sewage samples in areas with limited accessibility in Nigeria was implemented in 2017. Termed as ‘ES sweep’, this method reported a low positive isolation rate with approximately 25% samples reporting either Sabin-like viruses or other species C enteroviruses, indicating the importance of sample site selection based on epidemiologic risks among other factors [18]. Newer tools for collection and processing of sewage samples, such as the Bag-mediated filtration system (BMFS) are being evaluated with variable results depending on concentration methods, volume of sewage collected, and final volume assayed [19*,20]. Additionally, water-quality probes to evaluate physical characteristics of environmental surveillance sites have been tested with success, and could contribute to enhanced surveillance sensitivity and site performance assessment [21*].

Application of molecular epidemiology principles to sequencing results of polioviruses plays an important role to track geographic origins and patterns of spread of the virus. A recent review highlighted the need of incorporating modern molecular technologies to accelerate poliovirus detection [22]. Direct detection of viral RNA using PCR methods has the promise of faster identification of virus transmission. However, lower sensitivity and challenges with sequencing viruses from mixed samples have complicated wider use of direct detection methodologies. A nested PCR and nanopore sequencing protocol have recently demonstrated high sensitivity for detection of WPVs, VDPV2, and Sabin-like viruses from approximately 150 samples in Pakistan, with generation of sequencing results in less than 3 days from the time of initiation of sample [23].

DISEASE CONTROL: RESEARCH AND DEVELOPMENT

Recent reviews and randomized control studies have documented the limitations of inactivated poliovirus vaccine (IPV) in inducing primary intestinal immunogenicity [24*,25]. This is relevant in the current context as a dose of IPV given at 14 weeks per Expanded Programme on Immunization (EPI) schedules is now the only source of protection against type 2 poliovirus in most countries using OPV. The significantly lower ability of IPV to induce intestinal immunity in naïve children limits its role in outbreak response in settings of poor hygiene and sanitation. However, some observational studies have reported possible gains in interrupting WPV transmission when IPV is used with OPV compared with OPV alone [26,27]. Adjuvanted IPV with enterotoxin-based mucosal vaccine antigens, such as the double-mutant heat-labile enterotoxin (dmLT), has shown some promise of induction of intestinal immunogenicity in preclinical experiments and with other antigens, demonstrated by rise in fecal IgA secretion and upregulation of expression of the intestinal homing receptor α4β7 [28]. Given the first-in-human study with dmLT-IPV given intramuscularly is yet to begin, availability for program use for near-term is unlikely.

Several new research initiatives have reported advancements on options to use IPV in a way that could address its cost and supply constraints. Fractional dose (one-fifth of standard dose) administration of IPV via intradermal route has been studied extensively in the past. Given the challenges of vaccine administration via this route compared with the intramuscular route, a randomized controlled clinical trial conducted in infants in Cuba went a step further. It demonstrated noninferior seroconversion rates for all three serotypes for fractional intramuscular IPV compared with fractional intradermal IPV after two doses, given at 4 and 8 months of age [29**,30]. If the favorable immunogenicity pattern holds for younger age groups and different schedules, it could expand options of affordable IPV delivery. As another option for cost and supply constraint mitigation, an alum-adjuvanted IPV
formulation with one-tenth antigen content compared with the current IPV was reported to be well tolerated and immunogenic through phase III studies conducted in two different geographies with different immunization schedules, resulting in its WHO prequalification in 2020 [31,32]. Use of alternative delivery methods for IPV, such as microarray patches (MAP) are under evaluation and a recent report summarized the potential of such methods to boost equitable access to vaccines in low-income and middle-income countries. Also, advances in developing IPV and laboratory assays from noninfectious or less infectious sources, such as the attenuated Sabin strains or S19 strains hold promise to minimize risks from accidental release of infectious strains from polio-essential facilities into the community in the posteradication era [33–37].

Given the limitations of IPV in inducing intestinal immunity, major focus of polio vaccine development over the recent past has been to develop OPV strains that would be more genetically stable than the current Sabin strains and thereby would have less risk of losing the attenuations that leads to reversion to neurovirulence. On the basis of knowledge and experience gathered on the structural and functional aspects of Sabin OPVs, novel type 2 OPV (nOPV2) strains were designed with specific modifications in the virus genome. Such modifications included changes in ribonucleic acid (RNA) sequence in the 5′ untranslated region (5′ UTR), the capsid protein-coding region (P1), the nonstructural protein 2C, and the polymerase 3D [38**,39**]. Most of these changes were incorporated to stabilize the genetic sequence against reversion in either the 5′ UTR or capsid regions. Following successful preclinical experiments, the first-in-human study with nOPV2 candidates was implemented under contained conditions in Belgium in 2017 [40*,41,42]. Results from this study demonstrated favorable safety and immunogenicity with enhanced genetic and phenotypic stability of the novel strains [40*]. Given the urgent need of a type 2 OPV that does not have the same risk of causing VDPV and VAPP as with current Sabin mOPV2, phase II studies, and manufacturing processes were accelerated [43]. In February 2020, the WHO Executive Board emphasized the critical importance of rapid nOPV2 assessment and roll-out, including review through the WHO Emergency Use Listing (EUL) procedure – a process to expedite the availability of unlicensed medical products for PHEICs [44].

**CONCLUSION**

The global polio eradication program is at a decisive juncture in 2020. There has been unprecedented success in eliminating a highly infectious, paralyzing disease from nearly every country in the world, including those with difficult-to-access, high disease burden, and densely populated settings. However, intensification of endemıcity of WPV1 in Pakistan and Afghanistan in recent years highlights the need for a reassessment of approach in select subpopulations where the ability to reach children for immunization is often complicated because of political unrest or lack of trust in vaccines. In addition, given the unique epidemiologic situation following cessation of routine use of Sabin OPV2, inability to effectively interrupt the on-going cVDPV2 outbreaks with reduction of risk of seeding new emergences puts the global program at risk of failure. Therefore, optimal use of the current vaccines in areas of need and rapid development, evaluation, and introduction of more genetically stable vaccine options, such as the nOPV2 will be of paramount importance. Improving efficiency of outbreak response is dependent on successful development of direct detection and sequencing protocols that would enable rapid detection and characterization of poliovirus from stool and sewage samples with use of bioinformatics platforms for standardization and visualization of sequencing data.

Finally, in the posteradication era, risk of re-introduction of poliovirus transmission from chronic excretors, and from laboratories, vaccine production sites, and other facilities where live poliovirus stocks are maintained needs to be effectively managed [45]. Therefore, development of surveillance tools, and polio antiviral drugs to identify and treat individuals at risk of prolonged shedding will be important [46,47]. Application of poliovirus containment strategies would reduce risk of virus introduction from polio essential facilities into the communities [48]. Adjusting current program priorities with the evolving COVID-19 pandemic and its impact on population dynamics and economic factors will be pivotal to maintain ability to respond to the on-going outbreaks. GPEI has prioritized support for the pandemic response and at the same time is stepping up preparations to restart polio immunization activities based on country-readiness and continuous risk assessment. Adaptive program strategies that are sensitive to social, political and epidemiologic factors and innovative technological solutions that are affordable and applicable in real-world settings would be critical to overcome the last remaining bottlenecks in the battle to eradicate polio.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

◆ of special interest
◆◆ of outstanding interest


This article summarizes the epidemiology of type 2 vaccine-derived poliovirus since 2016, and using a statistical model illustrates that recent outbreaks have been seeded by the mOPV2 vaccine in outbreak response campaigns.


20. Zhou NA, et al. collected environmental samples in Nairobi, Kenya using two collection/ concentration methodologies: the Bag-Mediated Filtration System (BMFS) and grab sample with two-phase separation. This study demonstrates that BMFS can be used for poliovirus environmental surveillance and established a feasible study design for future research.


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28. Clements JD, Norton EB. The mucosal vaccine adjuvant LT1(LR92G/L11A) or dMLT. mSphere 2018; 3:e00215–18.


30. This study shows that fractional IPV administered intramuscularly is noninferior compared with intradermal administration. The importance of this is that intramuscular IPV can be an option for dose-sparing strategy in countries that have been reluctant to use IPV because of the programmatic difficulties in intradermal administration.


39. Detail the development of the two candidate (C1 and C2) nOPV2. Both candidates were engineered from Sabin 2 OPV; however, different approaches were taken for each candidate to further attenuate the Sabin virus. These two nOPV2 candidates (C1 and C2) have progressed to human clinical trials with accelerated clinical development.


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Van Damme P, De Coster I, Bandyopadhyay AS, et al. The safety and immunogenicity of two novel live attenuated monovalent (serotype 2) oral poliovirus vaccines in healthy adults: a double-blind, single-centre phase 1 study, Lancet 2019; 394:148–158. The first in-human clinical trial of the two candidates (C1 and C2) of nOPV2. This phase 1 trial was conducted in complete containment in a purpose-built containment facility at the University of Antwerp Hospital, to minimize the risk of environmental release of the novel OPV2 candidates and demonstrated both candidates were well tolerated and immunogenic in IPV-immunized adult. This data supported the further development of nOPV2, which is currently under evaluation for WHO Emergency Use Listing.


