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The Challenge of Global Poliomyelitis Eradication

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Introduction

Today, few Americans may remember the devastating implications and fear caused by poliomyelitis outbreaks given that there has not been an outbreak of paralytic polio in the United States since 1979. Prior to the development of effective vaccines, poliomyelitis was a seasonal epidemic disease in the United States. The number of cases peaked in 1952 when more than 20,000 cases of paralytic polio were reported.¹ Although some people recovered from paralytic polio, many suffered permanent paralysis and even death. Hospital wards filled with iron lungs and permanently disabled children served as painful visible reminders to society of the toll this debilitating disease took on young lives. With an estimated 350,000 polio cases worldwide and endemic disease in 125 countries the World Health Assembly launched the Global Polio Eradication Initiative (GPEI) in 1988, targeting the disease for eradication.

Polio as a candidate for eradication

Global eradication is currently defined as, “the worldwide absence of a specific disease agent in nature as a result of deliberate control efforts that may be discontinued where the agent is judged no longer to present a significant risk from extrinsic sources”.² Determining if a disease is a good candidate for eradication depends upon whether or not it meets four key criteria. These criteria include:

1. Humans are required to maintain the pathogen
2. Sensitive and specific diagnostic tools are available
3. There is an effective intervention to terminate human-to-human transmission
4. Proof of principle (i.e., elimination of transmission in a large geographic area)

Poliovirus requires a specific cell receptor (PVR or CD155) for infection that is expressed only on human and simian cells.³ Therefore, humans are the only host for sustained poliovirus transmission as primate population sizes are too small to maintain sustained transmission. Breaking the chains of human-to-human transmission can eradicate the virus. Although asymptomatic cases present a challenge to surveillance, Acute Flaccid Paralysis (AFP) reporting and virologic testing of stool are reliable ways to detect polio cases in populations. Although not without certain limitations, Oral Poliovirus Vaccine (OPV) and Inactivated Poliovirus Vaccine (IPV) are effective tools in preventing infection in individuals and reducing circulation of poliovirus within communities. With its low cost, ease of administration and ability to induce mucosal immunity, OPV has been a particularly useful tool in interruption of transmission in populations. Lastly, early elimination of polio in the western hemisphere served as proof of principle that eradication was possible throughout the world.

Clinical aspects of polio

Polioviruses, consisting of three antigenic types (serotypes 1,2 and 3), are positive sense single stranded RNA Enteroviruses belonging to the Picornaviridae family.³ Most poliovirus infections occur after oral ingestion of the virus followed by replication in the oral and intestinal mucosa, and most infections are asymptomatic.³ In <1% of infections, the virus attacks the motor neurons of the anterior horn cells in the spinal cord leading to destruction of those cells resulting in permanent acute flaccid paralysis of muscles. The most common cause of death from polio is respiratory insufficiency, when the infection affects respiratory muscles, occurring in about 5-10% of cases.^{3,4} Of note, is the absence of sensory abnormalities although deep tendon reflexes may be absent as a result of the impact of infection on muscle function. Nerve

conduction and electromyography studies have determined destruction of the anterior horn cells of the spinal cord to be the anatomic location of paralysis.⁵ The potential clinical course of poliovirus infections is summarized in Table 1.³

Table 1. Clinical description of poliomyelitis (Data from Sutter RW, Kew OM, Cochi SL, Aylward RB. 28 - Poliovirus vaccine—live. In: Plotkin SA, Orenstein WA, Offit PA, eds. *Vaccines (Sixth Edition)*. Vol London: W.B. Saunders; 2013:598-645.)

Consequence	Symptoms	% of infections
Inapparent infection without symptoms	None	72%
Minor illness	Transient illness; 1-3 days fever, malaise, drowsiness, headache, nausea, vomiting, constipation, or sore throat, in various combinations	24%
Nonparalytic poliomyelitis (aseptic meningitis)	Minor illness characterized as fever, sore throat, vomiting, malaise; 1-2 days later stiffness of neck or back; vomiting, severe headache, pain in limbs, back neck (lasts 2-10 days, recovery is usually rapid and complete)	4%
Paralytic poliomyelitis	Minor illness for several days, symptom free period of 1-3 days, followed by rapid onset of flaccid paralysis with fever and progression to maximum extent of paralysis within a few days.	<1%

Paralytic polio is estimated to occur in 1 in 100 to 1 in 2000 infections (average: 1 in 200). Type 1 is the most neurovirulent virus while type 2 is least neurovirulent. AFP is not specific for polio and there are many other causes of AFP.⁶ Features of the four most common diagnoses to consider in the differential diagnosis of AFP can be seen in Table 2.

Table 2. Distinguishing features of 4 common diagnoses of AFP (Adapted from Sutter RW, Kew OM, Cochi SL, Aylward RB. 28 - Poliovirus vaccine—live, Table 28-3: Distinguishing Features of Four Common Diagnoses of Acute Flaccid Paralysis. In: Plotkin SA, Orenstein WA, Offit PA, eds. *Vaccines (Sixth Edition)*. Vol London: W.B. Saunders; 2013:604-605.)

	Poliomyelitis	Guillain-Barré syndrome	Traumatic neuritis (after injection)	Transverse myelitis
Paralysis	Development of paralysis 24- to 48-h onset to full paralysis; descending; reduced or absent muscle tone in affected limbs; decreased or absent deep tendon reflexes; cranial nerve involvement and respiratory insufficiency only when bulbar involvement present	Development of paralysis from hours to 10 d; ascending; global hypotonia; globally absent deep tendon reflexes; cramps; tingling; hypoesthesia of palms and soles; cranial nerve involvement often present, affecting nerves VII, IX, X, XI, XII	Development of paralysis from hours to 4 d; reduced or absent muscle tone in affected limb; decreased or absent deep tendon reflexes; hypothermia in affected limb	Development of paralysis from hours to 4 d; hypotonia in affected limbs; deep tendon reflexes absent in lower limbs early; hyperreflexia late; anesthesia of lower limbs with sensory level
Clinical Features	High fever at onset; always present at onset of flaccid paralysis; gone when progression of paralysis stops; severe myalgia; backache;	Respiratory insufficiency in severe cases, enhanced by bacterial pneumonia; frequent blood pressure alterations; sweating; blushing; body temperature fluctuations; transient bladder dysfunction	Fever common before, during, and after flaccid paralysis; pain in gluteus	Occasional respiratory insufficiency; autonomic signs and symptoms present; bladder dysfunction
Diagnostic Tests	Inflammatory cerebrospinal fluid; abnormal nerve conduction velocity, third wk: anterior horn cell disease (normal during first 2 wk); abnormal electromyography at 3 wk	Albumin-cytologic dissociation of cerebrospinal fluid; abnormal nerve conduction velocity, third wk: slowed conduction; decreased motor amplitudes	Abnormal nerve conduction velocity, third wk: axonal damage	Mild elevation in cells of cerebrospinal fluid
Sequelae at 3 months and up to 1 year	Severe, asymmetric atrophy; skeletal deformities developing later	Symmetric atrophy of distal muscles	Moderate atrophy; only in affected limbs	Flaccid diplegia; atrophy after years

Epidemiology of polio

Wild poliovirus (WPV) is transmitted through person-to-person contact through the fecal-oral or oral-oral routes.³ Fecal-oral spread is most common in developing countries while oral-oral transmission is probably the major mode of transmission in industrialized countries, with high standards of hygiene.⁴ The incubation period is 3 to 6 days between infection and first symptoms (minor illness) and from 7-21 days from infection to onset of paralytic disease.³ Individuals are most infectious immediately before and 1-2 weeks after the onset of paralytic disease.³ Poliovirus is excreted for approximately 2 weeks in saliva and longer (3-6 weeks) in stool.³ In immunodeficient persons, prolonged shedding (more than 6 months) or chronic excretion (more than 5 years) rarely can occur, although only 45 prolonged excretors have been identified to date, largely confined to high and middle-upper income countries.³ Poliovirus transmission typically peaks in the warm, summer months in temperate climates which is why eradication efforts attempt to boost population immunity through vaccination campaigns during the cooler 'low season' in order to interrupt transmission.

Molecular methods such as genomic sequencing have further contributed to the understanding of poliovirus transmission and epidemiology. As the WPV genotype naturally evolves at a rate of around 1% nucleotide substitutions per site per year, lineages can be tracked to further map geographic transmission and identify gaps in surveillance.^{3,8} 'Orphan viruses', denoted by more than 1.5% difference in nucleotide sequence in the VP1 region compared to other known viruses, can identify areas where viruses have been transmitting over time without being detected.³

Progress toward global eradication of polio

In the last several years, WPV case counts have been at record lows and Africa appears to be polio-free for the first time in history--as of June 1, 2015, the last case detected in Africa was in Somalia in August, 2014.⁹ While hundreds of thousands of WPV cases were found globally 30 years ago, only 359 WPV cases were seen in 9 countries in 2014, and 23 cases as of May 14, 2015.⁹ In 1988, 125 countries were considered endemic (never having interrupted poliovirus transmission) while only 3 are classified as such today (Figure 1). All of the recent WPV cases reported are type 1. The last case of type 3 WPV was seen in November 2012 while the last naturally occurring case of type 2 WPV was found in 1999.⁹ Four out of six WHO regions encompassing >80% of the world's population have been certified polio free, meaning at least 3 years have passed in the presence of high-quality surveillance with no WPV cases occurring.

Figure 1. Progress in polio eradication from 1988-2014 (Data from The Global Polio Eradication Initiative. Data and Monitoring. 2015).

Data from: The Global Polio Eradication Initiative. Available from: <http://www.polioeradication.org/Dataandmonitoring.aspx>

Although 2012 saw near cessation of international spread of WPV, 2013 brought an increase in cases with evidence that adult travelers were contributing. During the low season of 2014, WPV exportation occurred in several countries leading the International Health Regulations Emergency Committee to declare the situation a “Public Health Emergency of International Concern” in May, 2014.¹⁰ This led to additional travel recommendations and increased vigilance among the global community.¹¹

Eradication strategies

The main strategies for eradication up until this point have been ongoing strengthening of routine immunization coverage, continued Supplementary Immunization Activities (SIAs), extensive surveillance to find the virus, and mopping up efforts in areas with continued transmission. SIAs are mass vaccination campaigns conducted within a few days, multiple times a year, vaccinating all children <5 regardless of vaccination history. Strategies such as finger and house marking can allow independent monitors to survey the area after the campaign to identify missed children and assess the quality of the campaign. Satellite and GIS technology have also been utilized to track vaccinators and further improve campaign quality.

AFP surveillance is the gold standard for detecting cases of polio. The Global Polio Laboratory Network (GPLN) consists of 146 WHO-accredited laboratories following standardized protocols for the following analyses: poliovirus detection by PCR and/or viral isolation, serotype, determination if the virus is wild or vaccine type (i.e., wild or Sabin-like or vaccine-derived poliovirus (VDPV)), and genomic sequencing.¹² Sequencing results are closely analyzed by comparing nucleotide sequences in the VP1 coding region of isolates to track

pathways of poliovirus transmission and guide vaccine choices and strategies through the last stages of the eradication program.¹² In addition to AFP surveillance, environmental surveillance is being increasingly used to monitor for the presence of poliovirus in pooled sewage or other environmental samples and to provide insight into international spread of the virus, particularly in areas in which termination of transmission has been difficult.

Available vaccines

Oral Poliovirus Vaccine (OPV)

OPV consists of live attenuated polioviruses, originally developed by Albert Sabin. Multiple presentations of OPV are available including: trivalent OPV (tOPV) containing types 1, 2 and 3, bivalent OPV (bOPV) containing types 1 and 3, monovalent OPV (mOPV) for types 1 and 3. Type 2 mOPV has also been developed recently and will be important for use in stockpiles available for potential outbreak control in the post eradication era.

While seroconversion rates to tOPV approach 100% in developed countries against all 3 serotypes, developing countries generally have much lower rates of detectable antibodies following vaccination with three doses of tOPV particularly to types 1 and 3. An analysis of seroconversion studies found an average rate of only 73% to type 1 and 70% to type 3.¹³ Data suggest that the type 2 component in OPV as well as ubiquitous enteric viruses present in developing countries interfere with responses to types 1 and 3.¹³ The inferior immunogenicity in developing countries can be overcome by additional doses (sometimes more than 10) of OPV, which lead to population immunity levels exceeding herd immunity thresholds for stopping transmission. Additionally, OPV is sensitive to heat and must be transported in an intact cold chain which proves difficult in rural and hard-to-reach areas, locations where the last reservoirs

of WPV remain.

Thus far, OPV has been the mainstay of polio eradication. The live vaccine is inexpensive (less than 15¢ per dose through UNICEF), simple to administer (does not require a trained health worker or produce sharps waste) and induces intestinal mucosal immunity in reducing transmission in settings where fecal-oral transmission predominates. A systematic review of mucosal immunity of polio vaccines found that individuals vaccinated with OPV were protected against shedding of poliovirus in stool samples collected after challenge (an indicator of induction of intestinal mucosal immunity) compared with unvaccinated individuals (odds ratio = 0.13, 95%CI [0.08-0.24]).¹⁴ In contrast, the proportion of IPV recipients who shed following an OPV challenge is not different than naïve persons receiving OPV for the first time (see below for further discussion of IPV).

Risks of OPV

Vaccine Associated Paralytic Polio (VAPP)

During the replication process, the Sabin strains of OPV can mutate and very rarely revert to neurovirulent variants causing paralysis clinically indistinguishable from that caused by WPV.¹⁵ VAPP, causes paralysis in OPV recipients and close contacts. In a recent review of epidemiology and burden, the global risk of VAPP was determined to be 4.7 cases per million births or approximately 500 cases of VAPP estimated globally, per year, with 90% estimated to occur in low- and lower-middle-income countries.¹⁶ 26-31% of VAPP cases were associated with the type 2 component of trivalent OPV (tOPV).¹⁶

Circulating Vaccine Derived Poliovirus (cVDPV)

Vaccine virus can rarely mutate and regain both the neurovirulence and transmissibility

properties of wild polioviruses, causing outbreaks of polio. When prolonged replication of the vaccine virus takes place (isolates having >1% divergence (0.6% for type 2) from the original OPV strain), the virus is considered a VDPV.³ VDPVs fall into one of three categories: 1) immunodeficient VDPVs (iVDPVs) isolated from individuals with B-cell immunodeficiency who maintain chronic infection after vaccination with OPV; 2) circulating VDPVs (cVDPV) requiring evidence of person-to-person transmission in the community (e.g., cluster of ≥ 2 AFP cases); and 3) ambiguous VDPVs (aVDPVs) which do not fall into either previous category.³

The largest risk factor for generation of cVDPVs is low overall population immunity allowing vaccine viruses to mutate and spread within a susceptible population.^{17,18} cVDPV outbreaks have recently occurred in areas with complex challenges such as those with insecurity, poor infrastructure and low immunization coverage and can easily spread beyond borders causing outbreaks and sporadic cases elsewhere. Outbreaks in Pakistan, Afghanistan, Nigeria and Somalia have occurred in conjunction with WPV outbreaks in areas where groups of children remain unvaccinated due to conflict and poor access. Repeated SIAs using OPV containing the parent Sabin strain of the strain causing the outbreak have been shown to stop cVDPV outbreaks.¹⁹

Inactivated Poliovirus Vaccine (IPV)

The current IPV formulation contains 40-8-32 D-Antigen (D-Ag) units for poliovirus type 1, 2 and 3 respectively and is available in stand-alone vaccine or as multi-valent presentations.²⁰ Made from selected WPV strains grown in Vero cell culture or human diploid cells, IPV establishes a strong immune response in recipients. Nearly 100% seroconversion rates and high antibody titers to all 3 serotypes are seen following 3 doses, and >90% seroconversion rates

after 2 doses when administered after 8 weeks of age.²¹ Immunogenicity depends upon the number of doses as well as the age of administration due to interference of maternal antibodies in infants. In a study in Puerto Rico comparing U.S. schedules (2, 4, and 6 months) with EPI schedules (6, 10 and 14 weeks), seroconversion rates were lower for types 1 and 2 in the EPI schedule study arm, where maternal antibody levels were higher.²²

In another study in Cuba, 63% of infants seroconverted to type 2 after a single dose of IPV when administered at 4 months of age.²³ Among those who did not seroconvert after 1 dose of IPV, 98% had a priming response to a subsequent dose of IPV--that is, they developed significant antibody responses within 7 days of subsequent exposure to IPV.²³ While seroconversion is associated with protection from paralysis, questions remain as to whether persons who are primed are protected from disease (i.e., can antibody be made quickly enough following exposure to provide protection). Experience in Hungary, which had a major problem with VAPP, showed that VAPP was eliminated when the country chose a sequential IPV/OPV schedule with one dose of IPV followed by OPV, suggesting priming is protective.²⁴ Conversely, an outbreak of WPV1 in Senegal was associated with 36% effectiveness after one dose and 89% effectiveness after two doses, a finding more compatible with the need to seroconvert to assure protection.²⁵

Studies have shown neutralizing antibodies against poliovirus to persist for at least 5 years in all vaccine recipients after a primary immunization series of 3-4 doses.^{26,27} Antibody may decline over time in some people, although no association has been seen with antibody below detectable levels and increased susceptibility to paralytic disease.²⁸ As all high income countries administer 3 or more doses, the precise duration of immunity for one or two doses of

IPV remains less understood.²⁸

Concerns raised with IPV

IPV, whether given alone or with other vaccines, is considered to be very safe and has not been causally associated with any serious adverse events.²⁸ The high immunogenicity provided by IPV leads to high levels of individual protection against paralysis in the recipient. However, IPV is less effective in inducing intestinal mucosal immunity than OPV among previously unvaccinated individuals, although quantity and duration of shedding may be reduced.¹⁴ For this reason, IPV does not provide the same amount of community protection against transmission that OPV does. In addition, IPV is more expensive than OPV, with negotiated costs for developing countries of \$1 or more per dose when compared with 15¢ for a dose of OPV. IPV, a vaccine administered intramuscularly, requires trained health workers and produces sharps waste. As IPV is produced from WPV strains, there is a risk of accidental release during production, as has happened in The Netherlands in 1992 and Belgium in 2014.^{29,30} Because a release in a developing country with crowding, poor hygiene and sanitation is more risky than in an industrialized country, IPV manufacture from wild poliovirus strains is limited to a few developed countries, limiting global production capacity.

Israel (and the entire WHO European Region) was certified polio free in 2002. Israel initiated an IPV only schedule in 2005 and also has an extensive environmental surveillance system to detect viruses. In early February, 2013 WPV1 was isolated indicating an introduction into the Southern districts although no paralytic polio cases were detected.³¹ Officials responded with intensified environmental surveillance, a bOPV SIA and an addition of 1 dose of bOPV back into the routine immunization schedule.³¹ WPV circulation took place for over 1 year

with termination of transmission in March of 2014. The experience alerted the public health community to the continued need for OPV in areas where fecal-oral spread of wild viruses is predominant, the value of environmental surveillance in addition to AFP surveillance in countries at particular risk, and the need for mOPV stockpiles in the post-eradication era in case wild viruses are reintroduced.³²

In contrast, Yogyakarta, Indonesia switched from OPV to IPV-only in 2007. In this experience, no cVDPVs emerged. Thus, IPV may be more effective in preventing the emergence of a cVDPVs because of the lower force of infection of polio vaccine viruses compared to wild viruses versus curtailing transmission of WPVs or existing cVDPVs.³³ Additionally, IPV alone has eliminated polio in Nordic countries and other industrialized countries that have switched to IPV only, where oral-to-oral transmission is thought to be predominant mode of transmission. With the exception of Israel, all of these countries have maintained a WPV-free status.³⁴

Using OPV and IPV together

Administration of IPV before OPV has been shown to prevent the incidence of VAPP in some areas, a schedule that theoretically employs the humoral and mucosal strengths of both vaccines.²⁸ Effective reduction in VAPP after introduction of IPV/OPV sequential schedules has been seen in Denmark³⁵ (3 doses of IPV followed by 3 doses of OPV), Hungary²⁴ (1 dose of IPV followed by 3 doses of OPV) and the United States³⁶ (2 doses of IPV followed by 2 doses of OPV).

Studies examining IPV use in children previously vaccinated with tOPV have suggested that IPV is effective at closing immunity gaps, especially for type 2 poliovirus.^{37,38} In fact, a single dose of IPV in infants and children previously vaccinated with multiple doses of OPV reduced

the prevalence of shedding by 39-76% and boosted mucosal immunity for types 1 and 3 after OPV challenge, compared to no vaccination.^{39,40} A birth dose of OPV allows for induction of mucosal immunity before infants are exposed to enteric pathogens as well as increases seroconversion rates.²⁸

Simultaneous use of OPV and IPV in developing countries has shown induction of high antibody responses to all 3 poliovirus types.²⁸ In a three country study, concomitant administration of OPV and IPV at 6, 10 and 14 weeks after a birth dose of OPV yielded the highest seroconversion rates in Oman and The Gambia when compared to OPV only given at the same schedule. The third country, Thailand, illustrated similar seroconversion rates in both groups.⁴¹

Endgame strategy and timeline

Despite the significant gains made in reduction of polio cases due to OPV, the rare adverse events including VAPP and VDPVs require the phased withdrawal of all OPV use in the final stage of the eradication process.⁴² The 2013-2018 Eradication and Endgame Strategic Plan⁴² describes complete interruption of transmission and elimination of all polio disease which includes WPV, VDPVs and VAPP, utilizing the available tools of OPV and IPV followed by withdrawal of OPV use.

In recent years, the serotype profile of cVDPVs have shifted with type 2 related cVDPVs representing a larger proportion of all cVDPV cases (97% of the 628 cases of cVDPV from 2006-2013).¹⁹ This trend can be seen in Figure 2 and is thought to be due to increased use of bOPV in campaigns in recent years, leading to reduced population immunity to type 2, a risk factor for

cVDPV emergence.^{43,44} Additionally, type 2 WPV appears to have been eradicated with the last naturally occurring case detected in 1999. Because type 2 also causes a proportion of VAPP cases, type 2 vaccine virus is causing harm and potentially doing little good. Thus, the strategic plan calls for global, synchronized replacement of tOPV with bOPV after prior introduction of at least 1 dose of IPV into routine immunization schedules in all 125 OPV-only using countries.⁴² Introduction of IPV will ensure that a proportion of the population is protected against type 2 polio, boost immunity to types 1 and 3 and mitigate other risks associated with the switch.

Figure 2. Reported paralytic cases of cVDPV by type worldwide, 2000-2014* (Adapted from: Patel M, Zipursky S, Orenstein W, Garon J, Zaffran M. Polio endgame: the global introduction of inactivated polio vaccine. Expert Rev Vaccines. 2015 Jan 19;1–14.)

cVDPV denotes circulating vaccine derived polioviruses

*As of 12 May 2015; data from:

<http://www.polioeradication.org/Dataandmonitoring/Poliothisweek/Circulatingvaccinederivedpoliovirus.aspx>

After IPV introduction, the globally synchronized switch is currently scheduled to occur in April, 2016. WHO will assess global readiness and monitor the absence of all persistent cVDPV2's globally as a precondition for implementing the switch. These events represent a public health effort unprecedented in time and scope and will require coordination and partnership across many global, national and local organizations as well as public-private partnership.

Challenges and Opportunities

India, one of the last countries to eradicate smallpox, was believed by some to be a near impossible location for the eradication of polio due to high population density, poor sanitation, weak immunization systems, remote villages and massive migrant populations. But due to strong ownership and resource investments from the local to national level, accountability and international partnerships, India (and the entire South-East Asian region) was certified polio free by WHO in March 2014.^{45,46} Important lessons learned from India's exceptional polio eradication effort include development of detailed plans to maintain high coverage in SIAs, close monitoring and supervision, robust communication strategies and research and innovation to overcome operational barriers to ensure every child is vaccinated.⁴⁷

Pakistan, on the other hand, currently remains the engine of WPV transmission. In 2014, 85% of WPV cases seen worldwide were detected in Pakistan and many cases in neighboring Afghanistan were imported across the border from Pakistan.⁹ For years after mid-2012 when local authorities banned polio vaccination, nearly 350,000 children in some districts of the Federally Administered Tribal Areas (FATA) had not received polio vaccine during SIAs.⁴⁸ That

number has since decreased to less than 50,000.⁴⁹ In other areas of Pakistan, polio workers (often women), have been attacked and killed. Although great strides have been made in the last year, until all children in conflict-affected areas can be reached with vaccine, Pakistan remains a major challenge for interruption of WPV. Substantial progress has been made in Nigeria and the African region is on the verge of being declared polio-free representing a substantial milestone in the eradication effort.

Post eradication Risks and mitigation

As WPV cases continue to decrease and the world inches closer to polio eradication, considerations of late-stage risks are essential. Reintroduction of WPV and release from manufacturers or laboratories are of ultimate concern. The endgame plan calls for appropriate handling and containment of all infectious poliovirus stocks from biomedical facilities to insure that wild poliovirus cannot be transmitted to an increasingly susceptible community.⁴² Shedding of VDPV among adults and children with primary B-cell immunodeficiency constitutes a long term risk as those individuals have been shown to shed virus for up to several years following administration of OPV, a consideration as long as OPV vaccination continues.⁵⁰

The cost for maintenance of current levels of vaccination, program implementation, surveillance and laboratory capacity and outbreak response are estimated to be US \$5.5 billion dollars for current global strategic plan.⁴² The cost of abandoning global eradication efforts completely is substantial in terms of program costs, treatment costs and human lives lost. Estimated incremental net benefits of the GPEI between 1988 and 2035 amount to approximately \$40–50 billion saved through eradication efforts.⁵¹ Letting the pressure off now

is expected to result in skyrocketing numbers of cases. GPEI is the single largest internationally coordinated public health effort in history and there is strong economic justification for finishing the job completely.⁵¹

Research Needs

These final stages of the polio eradication endgame have revealed unique challenges to eliminating the disease from areas with the last reservoirs of virus, leading to innovation in vaccine technology and delivery. At this stage in the polio endgame focus is being placed on new innovations such as technology to help achieve lower cost IPV, strategies to make vaccine manufacture safer and operational advances to make vaccine administration simpler.⁴⁴

Specifics on areas of research on OPV and IPV can be seen in Table 3.⁵²

Table 3. Ongoing research on current and future tools for polio eradication (Adapted from Bandyopadhyay AS, Garon J, Seib K, Orenstein WA. Polio vaccination: past, present and future. *Future Microbiology*. March 2015;1-18. doi:10.2217/fmb.15.19.)

Research question/Tool	Importance	Status
Current Tools		
Combination schedules of IPV and OPV	Understand role of IPV and bOPV when used together in recommended schedules in developing countries	Immunogenicity (humoral and intestinal) of ≥1 IPV dose combined with bOPV in 6-10-14 week mixed schedules (Colombia-Dominican Republic-Guatemala-Panama, India, Bangladesh) Immunogenicity (humoral and intestinal) of IPV → bOPV in 2-4-6 month sequential regimen (Chile) Duration of protection of boosting of intestinal immunity induced by IPV in OPV primed populations (India)
Fractional doses of IPV	Reduced cost	Immunogenicity with fractional IPV doses via ID route (The Gambia, Bangladesh)
New tools		
Immunogenicity of Monovalent IPV -2 (m-IPV2)	Improved humoral and intestinal immunogenicity Reduced cost with one dose of m-IPV2	Phase I (Belgium) study on safety completed Phase II (Panama) study underway to evaluate safety and immunogenicity
Immunogenicity	Reduced cost	Clinical studies being planned to evaluate

of IPV adjuvants	Increased supply Potential for enhanced mucosal immunity	potential for aluminum salts adjuvants and for dmLT (double-mutant heat-labile enterotoxin) adjuvants for IPV
Feasibility of novel routes of administration	Operational advantages Potential for use in SIAs Concomitant use with other vaccines	Studies in humans being planned or implemented to evaluate impact of IM and ID delivery of IPV through use of disposable jet injectors, micro needle patch and other novel delivery techniques
Development of genetically stable OPV and attenuated IPV seed strains	Potential use in outbreak control (reduced risk of VDPVs and VAPP) or in routine immunization if IPV is considered inadequate in reducing transmission risk Further attenuated and less infectious seed strains for safe IPV manufacture	In pre-clinical development or planning phase
Immunogenicity with Sabin IPV	Minimize risk of reintroduction of WPV from IPV manufacturing facilities	Sabin IPV has been licensed in Japan Efficacy and feasibility of large scale production are currently being evaluated

Role of North American Physicians

Even though naturally occurring paralytic poliomyelitis has not been seen in the United States since 1979, physicians play an important role in the global polio eradication effort.

Current Advisory Committee on Immunization Practices (ACIP) recommendations for routine polio immunization include 4 doses of IPV to be given at ages 2, 4, 6-18 months and 4-6 years.⁵³

Physicians should ensure that all patients receive routine childhood polio immunization and that travelers are vaccinated with an additional dose of IPV if they will be visiting a polio-infected country.¹¹ New International Health Regulations require proof of vaccination of a dose of polio vaccine when leaving a polio infected country (long term travelers staying for > 4 weeks). The dose should be given at least 4 weeks and no more than 12 months prior to departure.¹⁰

Although, diagnosis of poliomyelitis in the U.S. is rare, physicians should suspect polio in a patient who presents with a clinically compatible case. There may not be a history of travel to a polio endemic or epidemic country as the transmitting infection could be subclinical. At least 2 stool samples should be collected, 24 hours apart, ideally within 14 days of the onset of paralysis. A single case of suspected paralytic polio demands immediate attention. Timely notification of state health department and CDC is critical. Finally, U.S. physicians should advocate for and support introduction of IPV in developing countries as well as US government support for the overall initiative. As long as WPV exists anywhere, risk of importation exists everywhere.⁵⁴

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