HHS Public Access

Author manuscript

J Infect Dis. Author manuscript; available in PMC 2023 October 03.

Published in final edited form as:

J Infect Dis. 2021 January 04; 223(1): 7–9. doi:10.1093/infdis/jiaa393.

The Long and Winding Road to Eradicate Vaccine-Related Polioviruses

Stephen L. Cochi[1], **Mark A. Pallansch**[2]

[1]Global Immunization Division, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

[2]National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

As the vaccine of choice for the Global Polio Eradication Initiative (GPEI), oral poliovirus vaccine (OPV) is inexpensive, easy to administer, and can provide good protection against poliomyelitis and poliovirus infection, through durable humoral immunity and induction of intestinal mucosal immunity. Even though trivalent OPV is a safe and effective vaccine and has a remarkable disease elimination record, all 3 strains are live attenuated RNA viruses capable of genetic mutation during replication. This means that polioviruses in OPV can undergo genetic changes in vaccine recipients to reverse attenuation. This inherent in-stability represents a key disadvantage of OPV that is manifest in some of the current polio eradication challenges.

It has long been known that sporadic cases of vaccine-associated paralytic polio (VAPP) occur in recently vaccinated individuals (recipient VAPP) and in susceptible persons indirectly exposed to vaccine virus, such as close contacts of persons recently vaccinated or community contacts (contact VAPP). The global burden of VAPP was estimated in 2011 to be approximately 250–500 cases per year [1]. In countries using OPV, of the 3 poliovirus vaccine serotypes, type 3 is the predominant serotype isolated from the stool of recipient and contact VAPP cases, followed by type 2 and then type 1 [1, 2]. The higher frequency of type 2 and type 3 VAPP may be related to the fewer nucleotide substitutions responsible for the attenuated phenotype in types 2 and 3 virus strains, making reversion easier [2]. As global eradication progressed in the decade following the World Health Assembly declaration of the global eradication goal in 1988, many countries achieved the elimination of all 3 types of indigenous wild polioviruses, including many in the developing world. However, these newly polio-free countries were now completely dependent on vaccination to maintain immunity against polio in the population. The continued use of OPV with low coverage led to a widening immunity gap and revealed another manifestation of the genetic in-stability of the polioviruses in OPV. In this case, instead of OPV-related polio being restricted to vaccine recipients and contacts, the vaccine virus continues to transmit from

Correspondence: Stephen L. Cochi, MD, MPH, Global, Immunization Division, Centers for Disease Control and Prevention, 1600 Clifton Road, NE; MS-A04, Atlanta, GA 30329 (scochi@cdc.gov).

Potential conflicts of interest.

Both authors: No reported conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

person to person and while continuing to mutate, resulting in the emergence of genetically divergent vaccine-derived polioviruses (VDPVs) capable of causing paralytic polio [3]. These circulating VDPVs (cVDPVs) have acquired the neurovirulence and transmission characteristics of wild polioviruses and were first described in an outbreak in Hispaniola in 2000–2001 [4]. In the years since, many additional cVDPV outbreaks of paralytic polio due to all 3 types have occurred [3, 5, 6].

Because global polio eradication is predicated on the achievement of the eradication of paralytic polio due to all live polioviruses, including vaccine-related viruses [7], eliminating the risk of VAPP and cVDPVs will require stopping all use of OPV in routine immunization services and supplementary immunization activities [8, 9]. The Global Commission for the Certification of the Eradication of Poliomyelitis certified the eradication of type 2 poliovirus in 2015 [10] following the last case in 1999 and type 3 poliovirus in 2019 following the last case in 2012 [11], making type 2 and type 3 polioviruses the first human pathogens to be eradicated since smallpox. These certification events reinforced that the last naturally occurring type 2 wild poliovirus case in the world was in 1999 and type 3 wild poliovirus case in 2012, and enabled implementation of a plan for a phased withdrawal of trivalent OPV beginning with the type 2 component, and introduction of inactivated poliovirus vaccine (IPV) to provide immunity against type 2 [7].

The first phase of OPV withdrawal took place in 2016 with the global switch from trivalent OPV (tOPV) to bivalent OPV (bOPV) in the 155 OPV-using countries of the world, through cessation of all manufacturing and distribution of tOPV and its rapid withdrawal from clinics and storage facilities [8, 9]. The type 2 vaccine virus was prioritized for removal because type 2 cVDPV (cVDPV2) cases comprised approximately 95% of all cVDPV cases during 2006 to May 2016 and approximately 30% of all VAPP cases. Additionally, the type 2 OPV vaccine virus is the most infectious and immunogenic of the 3 vaccine virus strains and interferes with the replication of other vaccine strains in the intestinal tract and, hence, the type 1 and 3 vaccine effectiveness using tOPV was lower [2, 8, 9]. A stockpile of monovalent type 2 (mOPV2) vaccine was established to respond to potential outbreaks of cVDPV2. In addition to the global switch from tOPV to bOPV, the World Health Organization Strategic Advisory Group of Experts recommended for the 126 countries in the world not using IPV in their routine childhood immunization schedules to introduce at least 1 dose of IPV to provide a high likelihood of protective immunity against type 2 [12].

In this issue of *The Journal of Infectious Diseases*, a study from a western province of China (Xinjiang Province) [13] documents an example of the consequence of the tOPV to bOPV switch in 2016 that occurred in some of the126 non-IPV–using countries that introduced IPV into the routine childhood immunization schedule. A large unanticipated global shortage of IPV, particularly impacting lower middle-income countries, led to a disastrous inability to uniformly implement the IPV recommendation, resulting in millions of children unvaccinated against type 2 poliovirus until 2019 when the shortage was finally alleviated [14]. The authors showed a substantial decrease in seroprevalence of type 2 antibodies from 91.6% in the preswitch group to 67.4% in the partially vaccinated postswitch group. The findings demonstrate vulnerability to cVDPV2 outbreaks in China and likely in other countries in similar circumstances of only 1 dose IPV coverage, and

strongly support the need to include a second dose of IPV in the routine childhood schedule to achieve sufficiently high protective immunity against type 2 poliovirus. The study is a further alert to the global community of the continuing risk of cVDPV2 outbreaks as a consequence of the 2016 switch, gaps in tOPV coverage prior to the switch, and the concomitant IPV shortage that resulted in cohorts of infants not receiving 1–2 doses of IPV to provide adequate protective immunity against type 2.

Another study in this issue documents the limitations of using only IPV to develop intestinal immunity against type 2 polioviruses [15]. In this study, exclusively IPV-vaccinated Lithuanian children 1–5 years of age were administered mOPV2; 1 or 2 mOPV2 challenge doses were given 28 days apart, and viral shedding in stool was measured 28 days after each dose. After the first mOPV2 dose, 34 of 68 (50%) children were shedding virus, and 9 of 37 (24%) were shedding after the second challenge dose, comparable to immunologically naive children. The study reaffirms very limited, if any, impact of IPV-only schedules in generating intestinal mucosal immunity that would have limited viral shedding upon mOPV2 challenge, once again demonstrating that IPV alone does not limit person-to-person transmission and community spread of live polioviruses in communities with significant fecal-oral spread.

These 2 articles highlight some of the vulnerabilities that have allowed an unexpected and alarming resurgence of cVDPV2s since the 2016 global switch [5, 6] accounting for > 90% of all recent cVDPV outbreaks. During 2018–2019, the number and geographic breadth of cVDPV2 outbreaks increased markedly [5, 6] and predictably were focused on areas with low poliovirus immunity. Several factors have contributed to both expansion of outbreaks and emergence of new outbreaks, including suboptimal mOPV2 coverage within outbreak vaccination response areas, limited response scope because of global mOPV2 stockpile depletion, seeding of new outbreaks within response areas by mOPV2 use, and new emergences outside of areas of vaccine use. The spread of these recent outbreaks has been exacerbated by the large number of unvaccinated children born after the global switch who are fully susceptible to type 2 poliovirus transmission [6]. During July 2019 to February 2020 there were 31 active cVDPV2 outbreaks and 373 paralytic polio cases due to cVDPV2. To address these challenges, the GPEI adopted the 2020–2021 Strategy for the Response to Type 2 Circulating Vaccine-Derived Poliovirus as an addendum to the Polio Endgame Strategy 2019–2023 [6, 16].

The persistence of cVDPV2 outbreaks despite aggressive outbreak control measures using mOPV2 has raised questions regarding whether mOPV2 can successfully eradicate cVDPV2 under current operational conditions. To increase vaccine options, the GPEI partners have recognized the need for genetically more stable OPVs, and have accelerated the development and clinical testing of a novel OPV2 vaccine (nOPV2) [17] that has a substantially lower risk of reversion to neurovirulence. A consensus has been reached among GPEI partners that nOPV2 offers the best alternative to, and replacement for, continued use of Sabin mOPV2 with all its now-recognized shortcomings. Supplies of this nOPV2 are expected to be available in September 2020 for outbreak responses under emergency use listing requirements [6, 18]. If nOPV2 performs as expected, larger-scale outbreak response use is allowed and, as further supplies become available, nOPV2 will replace Sabin mOPV2

in outbreak response to prevent seeding of new cVDPV2 emergences and will be used more broadly [6]. Genetically more stable nOPV1 and nOPV3 vaccines are also under accelerated development. At this advanced stage in the polio eradication initiative and with the end of all polio due to live polioviruses tantalizingly in sight, this latest challenge to the success of GPEI is formidable, and success or failure may rest on how well genetically more stable nOPVs will perform.

Financial support.

This work was supported by the Centers for Disease Control and Prevention.

Disclaimer.

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

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