Why Have cVDPV2 Outbreaks Increased Globally After the Polio Immunization Strategy Switch: Challenges for the Polio Eradication Endgame

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Since the World Health Assembly (WHA) set the goal of polio eradication in 1988, the Global Polio Eradication Initiative (GPEI) has reduced the global incidence of polio by more than 99%, and the number of countries with endemic polio decreased from 125 countries to 3. Except for Afghanistan, Pakistan, and Nigeria, wild poliovirus (WPV) transmission has been confirmed to have been interrupted globally. Thanks to the polio eradication program, more than 10 million people are able to walk today who would have been paralyzed by polio had the initiative not been undertaken (1–2). In September 2015, WHO declared eradication of polio caused by the wild poliovirus type 2 (WPV2) (3–5), and in October 2019, WHO announced the eradication of polio caused by wild poliovirus type 3 (6). After 40 years of effort, polio eradication has made great progress; we are in the final stage towards a polio-free world (7–8).

However, eradication of polio means eradication of all polioviruses—not only wild poliovirus, but also vaccine-derived polioviruses (VDPV) and the occurrence of vaccine-associated paralytic poliomyelitis (VAPP). In 1999–2000, GPEI realized that VDPVs could cause outbreaks of polio, similar to wild virus outbreaks (1). Although the last WPV2 had been seen in 1999, more than 90% of outbreaks that were caused by circulating VDPVs (cVDPV) were caused by type 2 vaccine-derived polioviruses (1) and 40% of VAPP was caused by type 2 oral poliovirus vaccine (OPV2) (3).

Because wild type 2 poliovirus had apparently been eradicated globally, but OPV2 was causing polio, in October 2015, the WHO Strategic Advisory Group of Experts on Immunization (SAGE), reviewed the epidemiology of type 2 vaccine-derived polioviruses (VDPV2) against the criteria of OPV cessation and recommended a globally-coordinated withdrawal of OPV2 among all OPV-using countries in 2016. SAGE recommended switching from the use of trivalent OPV (tOPV) to a type 1 and type 3 bivalent OPV (bOPV) and introducing at least one dose of inactivated polio vaccine (IPV) into routine immunization schedules (4) to reduce the occurrence and ultimately eliminate all VDPV2s.

Unfortunately, rather than decreasing, the number of cVDPV2 outbreaks increased significantly after the tOPV-to-bOPV switch. Although there were only two countries with cVDPV2 outbreaks in 2017, 96 cases were reported—the largest number since 2010 (excluding 2019) (9–10). The number of countries with cVDPV2 outbreaks increased to 5 in 2018 with 71 cases reported and to 15 countries with 251 reported cases in 2019 (reported by January 14, 2020). The number of reported cases and the number of cVDPV2 virus strains isolated from people and from the environment reached the highest level in history (10). The 2017 cVDPV2 outbreak in Syria lasted for more than half a year with 74 cases reported (11); a cVDPV2 outbreak in the Democratic Republic of the Congo (DRC) was discovered in 2017 and has continued to date with 105 cases reported—63 of them in 2019 (10,12). A large outbreak in 2019 in Angola comprised 88 cVDPV2 cases (10).

In short, after the tOPV to bOPV switch, the unanticipated increase in cVDPV2 outbreaks and positive environmental samples has made the VDPV2 situation significantly more challenging than the expectation prior to OPV2 cessation.

Why is that? Based on analysis of existing data, I believe that there are seven reasons.

First, the risk of cVDPV2 outbreaks after the switch was underestimated. In October 2015, SAGE confirmed the switch date as all readiness criteria had been met. Risk assessments showed that continued use of type-2-containing tOPV posed a greater risk to public health than withdrawal of OPV2, even though introduction of a dose of IPV would be delayed in some OPV-using countries due to supply constraints (4). Although risk of cVDPV2 transmission after the tOPV-to-bOPV switch was anticipated, it was believed that this risk was greatest during the first six months

after the switch. Since 2014, risk of cVDPV2 transmission was believed to be greatest in Nigeria and Pakistan, while risk in other parts of the world was considered to be of lesser magnitude (*4,13*). According to one modelling study, cVDPV2s were predicted to be gone within a year and a half of OPV2 cessation and the number of cVDPV2 transmissions would be limited (*14*). Having to rely on underestimated modelling shows limitations and challenges for polio eradication strategy decision making.

Second, Supplementary Immunization Activities (SIAs) were not conducted in some areas that had low routine vaccination coverage before the tOPV-to-bOPV switch. Two mathematical modelling studies demonstrated that in order to reduce risk of cVDPV2 outbreaks in low-vaccine-coverage regions, it was important to establish high population immunity against type 2 polio virus through high quality tOPV SIAs conducted before the switch (*14–15*). However, pre-switch tOPV coverage in Syria was reported to be about 65% (*16*), and actual coverage before the Syrian cVDPV2 outbreak was less than 50% (*11*). Similar low-coverage situations occurred in Nigeria (*17*), Central Africa, and Somalia, where coverage ranged from 30% to 60% and cVDPV2 outbreaks occurred after the switch (*16*). Although DR Congo reported high tOPV coverage of 90% (*16*), a 2017-2018 cVDPV2 outbreak showed that children living in affected areas had not received good routine immunization services or supplementary vaccination with tOPV before switching OPVs (*18*).

Third, OPV2 cessation from the switch weakened population immunity against type 2 poliovirus, in part because of a global shortage of IPV, but also because of the different abilities of OPV and IPV to induce intestinal immunity. In countries that had cVDPV2 outbreaks after the switch— especially countries with many cases—preexisting type 2 poliovirus population susceptibility due to low coverage, augmented with new birth cohorts that received bOPV rather than tOPV, has resulted in sizeable populations with little intestinal immunity to stop type 2 virus transmission, leading to cVDPV2 circulation. Since IPV produces little intestinal immunity, children born after OPV2 cessation who receive all of their type 2 protection from IPV may not have sufficient intestinal mucosal immunity (*19–20*) to interrupt transmission of type 2 poliovirus (*17,21*).

Although one dose of IPV is unable to establish an effective intestinal immunity barrier to prevent the spread of cVDPV2s, it can mitigate the risk of cVDPV

infection and prevent paralysis from the poliovirus vaccine. However, a global shortage of IPV after the switch worsened the situation. WHO data show low coverage globally with one dose of IPV—about 50% in 2016, 60% in 2017, and only 72% in 2018 (*22*). Prior to the tOPV-to-bOPV switch in April 2016, only 94 of the 126 tOPV-using countries had introduced IPV. Rapidly increasing demand for IPV, with lower-than-anticipated supply, led to global shortages (*23*) to the extent that UNICEF was able to supply less than 50% of the IPV demand in 2016 and 2017 and some countries had no IPV available at all after the switch (*24–25*). At the end of 2018, there were still countries that lacked IPV (*22*).

Furthermore, one dose of IPV, either Sabin IPV or Salk IPV, produces limited immune protection. A domestic study showed that seroconversion after one dose of Sabin IPV was 62% (93% for 2 doses and 99% for 3 doses) (*26*). Similar results were also found for Salk IPV (*27–29*). OPV-only countries that introduce a single dose of IPV at 14 or 16 weeks may protect only about half of the population from type 2 polio (*29*).

Fourth, emergency use of monovalent OPV2 (mOPV2) to stop cVDPV2 outbreaks can seed type 2 virus and increase risk of transmission of VDPV2 and future resource needs. When a large cVDPV2 outbreak occurs, an mOPV2 campaign is a critical intervention to interrupt transmission. Such vaccination campaigns must be of high quality, with several rounds that yield high vaccination coverage. Low-coverage campaigns or campaign with fewer rounds may neither stop cVDPV2 transmission nor interrupt transmission of mOPV2 itself, potentially seeding additional cVDPV2 outbreaks (*15,30*). Genetic sequence analyses showed related VDPV2s occurred 1–2 years after the tOPV/bOPV switch, indicating that these VDPV2s probably came from mOPV emergency campaigns responding to VDPV2 outbreaks (*12,30–31*).

Fifth, VDPV2s can have a long-term existence and sustain transmission silently. The possibility of long-term replication and silent transmission VDPV2s after the switch has been demonstrated through genetic sequence analysis (*31*). Most have sustained transmission for 1–2 years, and a few for more than five years based on epidemiological data and laboratory evidence. Such sustained transmission raises the importance of timely identification of cVDPVs and initiation of outbreak control (*12,30*).

Sixth, the widespread existence and spread of VDPV2s have increased the difficulty of control

measures. The latest cVDPV2 outbreaks showed that VDPV2s were not only found in paralyzed patients, but were also isolated from healthy people and the environment (*10*). In addition, studies have shown that while the severity of VDPV2 paralysis is similar to that of the wild virus, the case : infection ratio appears to be lower, so that one VDPV2 patient may indicate the presence of more than a thousand infected people in the community maintaining VDPV2 transmission (*31–32*).

Seventh, before the switch, compared with type 1 and 3 VDPVs, type 2 VDPVs caused the majority of VDPV outbreaks and those with the largest scale—an observation that suggests this virus might transmit more readily and be more difficult to control and stop.

Polio eradication has a long way to go, and the increasing number of cVDPV2 outbreaks poses a great challenge to polio eradication. It is worth further reflection on the tOPV/bOPV switch to re-evaluate cVDPV2 risk and determine the effectiveness, the scientific basis, and the feasibility of the current polio eradication strategy.

Key questions are how to safely terminate existing outbreaks and how to prevent future cVDPV2 outbreaks. Regions or countries with existing VDPV2 outbreaks can introduce two doses of IPV in high-quality campaigns of emergency vaccination to increase type 2 immunity and help reduce cVDPV2 transmission. Monovalent OPV2 should be used very carefully as it increases risk of future VDPV2 outbreaks. Novel OPV2, a genetically more stable vaccine, appears to be a safer alternative to mOPV2 for stopping cVDPV2 transmission and should be considered for emergency use authorization once available later this year, as endorsed by SAGE (*33–34*). Countries and regions using bOPV, should accelerate introduction of 2 doses of IPV and catch up children who lack 2–dose protection from type 2 polioviruses. When epidemiological conditions permit, a 4-dose IPV schedule will prevent generation of cVDPVs and eliminate VAPP.

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Conflicts of Interest

No conflicts of interest were reported.

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