Published in final edited form as:

Risk Anal. 2021 February ; 41(2): 320–328. doi:10.1111/risa.13555.

Updated characterization of post-OPV cessation risks: Lessons from 2019 serotype 2 outbreaks and implications for the probability of OPV restart

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Abstract

After the globally-coordinated cessation of any serotype of oral poliovirus vaccine (OPV), some risks remain from undetected, existing homotypic OPV-related transmission and/or restarting transmission due to several possible reintroduction risks. The Global Polio Eradication Initiative (GPEI) coordinated global cessation of serotype 2-containing OPV (OPV2) in 2016. Following OPV2 cessation, the GPEI and countries implemented activities to withdraw all the remaining trivalent OPV, which contains all three poliovirus serotypes (i.e., 1, 2, and 3), from the supply chain and replace it with bivalent OPV (containing only serotypes 1 and 3). However, as of early 2020, monovalent OPV2 use for outbreak response continues in many countries. In addition, outbreaks observed in 2019 demonstrated evidence of different types of risks than previously modeled. We briefly review the 2019 epidemiological experience with serotype 2 live poliovirus outbreaks and propose a new risk for unexpected OPV introduction for inclusion in global modeling of OPV cessation. Using an updated model of global poliovirus transmission and OPV evolution with and without consideration of this new risk, we explore the implications of the current global situation with respect to the likely need to restart non-outbreak response use of OPV2. Simulation results without this new risk suggest OPV2 restart will likely need to occur (81%) to manage the polio endgame based on the GPEI performance to date with existing vaccine tools, and with the new risk of unexpected OPV introduction the expected OPV2 restart probability becomes 89%. Contingency planning requires new OPV2 bulk production, including genetically stabilized OPV2 strains.

Social media summary:

Study shows increased chance of needing to restart the use of serotype 2 oral poliovirus vaccine to manage risks in the polio endgame

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Keywords

polio eradication; dynamic modeling; oral poliovirus vaccine

1. INTRODUCTION

Twenty years after the initial target date for polio eradication, the Global Polio Eradication Initiative (GPEI) is off track in the remaining endemic countries (Kalkowska, Wassilak, Cochi, Pallansch, & Thompson, 2020), with serotype 1 wild polioviruses (WPV1s) expected to continue to transmit in Pakistan and Afghanistan. Additional modeling suggests that substantial improvements in the quality of coverage achieved with oral poliovirus vaccine (OPV) immunization activities in endemic countries could stop WPV1 transmission (Kalkowska & Thompson, 2020). In addition, although the GPEI globally-coordinated the cessation of serotype 2 OPV (OPV2) in 2016, as of early 2020, outbreaks of vaccine-derived polioviruses (VDPVs), particularly serotype 2 circulating VDPVs (cVDPV2s), continue to pose challenges and necessitate the use of serotype 2 monovalent OPV (mOPV2) for outbreak response. Successful global OPV2 cessation should have ended all transmission of all live polioviruses (LPVs) of serotype 2 (LPV2s), including OPV2, all OPV2-related viruses, and VDPV2s, and all paralysis caused by OPV, including vaccine-associated paralytic polio (VAPP) and cases caused by VDPVs. Through mid-2018, reviews by modelers of the experience with OPV2 cessation showed success in the vast majority of geographies, but also highlighted some areas with limited programmatic performance and raised the potential need to restart OPV2 use beyond only outbreak response use (e.g., in routine immunization) (Blake et al., 2018; Duintjer Tebbens & Thompson, 2018; Kroiss et al., 2017; Thompson & Duintjer Tebbens, 2017). Surveillance data prior to 2019 supported the general observation of local die out of transmission of OPV2 and OPV2-related viruses even with some inadvertent OPV2 use in the weeks to months after the coordinated OPV2 cessation (Diop et al., 2017; PTI, 2018), consistent with the expectations from prior modeling (Duintjer Tebbens, Hampton, & Thompson, 2016a, 2016b).

A recent review identified atypical epidemiology associated with some VDPV2 outbreaks that occurred in 2019 (Macklin et al., 2020). Notably, the phylodynamics of the cVDV2 outbreaks in Angola, Central African Republic (CAR), and Pakistan suggested broad exposure to Sabin OPV2 in populations for which no OPV2 use should have occurred, with unknown sources of origin (Macklin et al., 2020). These areas continue to use bivalent OPV (bOPV), which contains serotypes 1 and 3 OPV, for both routine immunization (RI) and supplemental immunization activities (SIAs). With many birth cohorts born since April 2016 with no exposure to any LPV2, however, the combined atypical appearance of LPV2 viruses in 2019 and continued mOPV2 use for cVDPV2 outbreak response resulting in new emergences of VDPV2 cases in other areas, suggest a high probability of unstoppable transmission and thus an increased probability of needing to restart OPV2 vaccine production and use.

We recently updated our earlier global poliovirus transmission and evolution model to account for the global experience through the end of 2019 (e.g., including outbreaks in

Nigeria, the Democratic Republic of the Congo (DRC), and CAR) (Kalkowska et al., 2020). For that analysis, we assumed importation events in 2019 that reproduced the cVDPV2 outbreaks in the blocks in our model that include conditions representative of Angola and Pakistan in the reference case (RC) (Macklin et al., 2020). However, as more epidemiological and virological information about these 2019 outbreaks emerges, the associated viruses appeared more like re-introductions due to the use of OPV2-containing vaccine (i.e., tOPV or mOPV2) in unexpected areas and/or the use of bOPV contaminated with mOPV2, similar to the 2018 event reported by India (PTI, 2018).

The experience with LPV2s in 2020 will likely determine whether and how the GPEI and some countries will need to restart OPV2 use in national immunization programs to stop and prevent cVDPV2 outbreaks (Thompson & Kalkowska, 2019). In 2019, the GPEI released a 2019–2023 strategic plan with a budget estimate of $4.2 billion, which focused on completing the eradication of WPV1 and did not include explicit plans for ending the transmission of VDPV2s and all mOPV2 use (i.e., ending verifying, and ensuring the end of all LPV2 transmission by removal of all OPV2 from the supply chain) (World Health Organization Global Polio Eradication Initiative, 2019). To deal specifically with the continued transmission of cVDPV2s, now 4 years after coordinated OPV2 cessation, the GPEI recently issued an amendment to the plan (World Health Organization Global Polio Eradication Initiative, 2020b). The amendment to the 2019–2023 strategic plan places significant confidence in successful use of a novel genetically-stabilized OPV2 strain (nOPV2) (World Health Organization Global Polio Eradication Initiative, 2020b). Although some clinical trials provide limited experience with nOPV2 candidates (Van Damme et al., 2019), the effectiveness and other properties of a new nOPV2 strain remain unevaluated in the field to date.

The nature of the Angola, CAR, and Pakistan experience with LPV2s in 2019 and the reported use of contaminated bOPV in India in 2018, suggest the need to update our characterization of the introductions in 2019 and post-OPV cessation risks for use in prospective global modeling (Kalkowska et al., 2020). The application of the updated risks in global modeling can provide a baseline for the global risks of OPV2 restart in the absence of nOPV2, or if the unknown behavior of nOPV2 matches the behavior of mOPV2. Prior to OPV2 cessation, we made optimistic assumptions about GPEI and national programmatic performance (Thompson & Kalkowska, 2020), and estimated a global risk of any OPV restart (for any serotype) on the order of approximately 5–6% for 2013–2052 (Duintjer Tebbens, Pallansch, Wassalik, Cochi, & Thompson, 2015). Because of the risks of using mOPV2 in populations that would increasingly become vulnerable to the introductions of mOPV2 leading to unstoppable transmission (Duintjer Tebbens, Hampton, & Thompson, 2016a), our earlier modeling also demonstrated the importance of achieving and maintaining high quality surveillance to quickly detect any transmission, managing global OPV2 cessation to end all LPV2 infections as quickly as possible by aggressively responding to and shutting down any outbreaks using mOPV2, and developing of a global stockpile of mOPV2 to enable rapid and aggressive response (Duintjer Tebbens, Pallansch, Alexander, & Thompson, 2010; Duintjer Tebbens, Pallansch, Wassilak, Cochi, & Thompson, 2016; Duintjer Tebbens & Thompson, 2017, 2018; Thompson & Duintjer Tebbens, 2008).

We recognize the need to provide an updated estimate of the probability of the need to restart OPV2 using evidence of actual GPEI and national performance through 2019, more realistic assumptions about prospective performance, and assuming no nOPV2 to provide context for comparison to future analyses. For this analysis, we do not constrain vaccine supply, which like prior similar analyses allows us to explore vaccine needs without constraints (Duintjer Tebbens et al., 2015; Duintjer Tebbens, Pallansch, et al., 2016) to provide context for analyses that include constraints (e.g., (Duintjer Tebbens & Thompson, 2017)).

2. METHODS

We apply an updated global poliovirus transmission and OPV evolution model (Kalkowska et al., 2020) to explore the probability of OPV2 restart. Since most poliovirus infections occur asymptomatically (e.g., only approximately 1 in 2,000 cVDPV2 infections results in acute flaccid paralysis (AFP)), the model tracks infections (Kalkowska et al., 2020). The model groups the global population into 72 blocks (Kalkowska et al., 2020). Each block consists of 10 subpopulations, and thus, each subpopulation includes approximately 10.7 million people in 2019 (Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat, 2017). Within a block, the people mix homogeneously with a subpopulations with some heterogeneity by age, while between block mixing occurs according to a preferential mixing structure of 9 varying preferential mixing areas (PMAs) of different size, which in abstract represent larger geographical regions (e.g., Africa, Australasia, Europe) (Kalkowska et al., 2020). We differentiate the blocks by their World Bank Income Level (low-income, LI; lower middle-income, LMI; upper middle-income, UMI; high-income, HI (World Bank, 2019)) and current vaccine use (OPV+IPV, IPV/OPV, IPV-only (World Health Organization, 2019)), aiming to characterize the global variability in conditions, costs, and preferences. Notably, as of 2019, all countries include at least one dose of IPV in their RI schedules. We distinguish the use of sequential schedules that give IPV first followed by OPV at later scheduled contacts as IPV/OPV. For countries that used OPV-only in RI prior to OPV2 cessation, and who added one dose of IPV given to children simultaneously with the third OPV dose (i.e., adding IPV to their OPV-only RI schedule around the time of OPV2 cessation), we refer to the RI schedules as OPV+IPV. The use of IPV can protect individual children who receive IPV only (e.g., for serotype 2) from becoming paralyzed if they subsequently become infected by community spread of an LPV (e.g., a cVDPV2). Notably, IPV use can effectively reduce the ability of the AFP surveillance system to detect transmission by reducing cases, while not stopping transmission (Thompson & Duintjer Tebbens, 2012). Populations that can stop transmission with IPV need to achieve and maintain very high coverage rates (Thompson, Kalkowska, & Duintjer Tebbens, 2015). Even with very high IPV coverage, not all populations can stop the transmission of all LPVs, and in these cases the LPV transmission may occur without AFP detection (i.e., asymptomatically), although sensitive environmental surveillance (ES) systems can detect transmission (Kalkowska et al., 2015). The updated global model includes detection through AFP and/or ES consistent with the current global poliovirus surveillance system design and quality (Kalkowska et al., 2020). At the beginning of the analytical time horizon (T_0=January 1, 2019), the epidemiological, demographic, and

transmission assumptions of the model represent global conditions that existed as of the end of 2018. We apply assumptions for 2019 that allow us to match the 2019 experience (Kalkowska et al., 2020), and for this analysis we update these to account for additional information now available.

The model tracks the cVDPV cases following serotype-specific OPV cessation and uses a serotype-specific threshold of 5,000 cumulative global cVDPV cases since the time of OPV cessation of the serotype as a trigger for serotype-specific OPV restart (Kalkowska et al., 2020). When that case count reaches the threshold, the model triggers a restart of homotypic OPV use in RI schedules for all countries with OPV in their schedule (Kalkowska et al., 2020; Thompson & Kalkowska, 2019). The restart occurs with an assumed delay associated with producing, relicensing, and distributing the vaccine, national immunization program financing, and/or other operational delays post global OPV cessation (Kalkowska et al., 2020; Thompson & Kalkowska, 2019). In addition to cVDPVs occurring endogenously in the model associated with OPV transmission and evolution in under-vaccinated populations (Duintjer Tebbens et al., 2013), we also include other stochastic risks that may influence the occurrence and speed of a potential OPV restart (Kalkowska et al., 2020). These risks (Kalkowska et al., 2020) include: (i) the introductions of VDPVs excreted by individuals with prolonged or chronic infections due to rare B-cell related primary immunodeficiency diseases (iVDPVs) (Duintjer Tebbens, Kalkowska, & Thompson, 2019), (ii) the use of unreturned OPV after vaccine withdrawal from serotype-specific coordinated OPV cessation or after any post-cessation outbreak response SIAs (oSIAs), (iii) unintentional release from: IPV production sites, non-vaccine producing polio essential facilities (PEFs), and/or facilities holding potentially infectious materials (PIMs), and/or (iv) intentional releases (Duintjer Tebbens, Kalkowska, & Thompson, 2018).

We modeled multiple scenarios to demonstrate the impact of these stochastic risks for overall OPV2 restart probabilities. We code the model using the general-purpose programming language JAVA™ and the integrated development environment Eclipse™, and we run stochastic simulations on the Amazon Elastic Compute Cloud (Amazon EC2). We performed 100 stochastic simulations for each scenario for the time horizon of 2019–2029. We use the same 100 sets of stochastic events for each scenario (e.g., we randomly draw 100 sets of importation event time and location inputs prior to the simulation and use those same sets for each scenario), which controls some of the stochastic variability across the scenarios. The RC, for which we previously reported a single iteration of the model only through 2023 without considering the stochastic nature of the risks, included single point introductions of cVDPV2 in 2019 into the blocks in the model representing conditions like Angola and Pakistan based on the information available at the time (Kalkowska et al., 2020).

Following the unexpected and atypical epidemiological VDPV2 outbreaks in Angola and Pakistan in 2019, we updated our characterization of those outbreaks in a new reference case (RC1) in the blocks in the model representing conditions like these countries as multiple manual deterministic point introductions occurring 10 days apart in the first half of 2019. Table 1 provides the details of all manual introductions included in RC1. For these introductions, we introduced the OPV-related virus at model OPV reversion stages consistent with Sabin (stage 0) and partially reverted (stage 6) as appropriate for these

blocks in all stochastic realizations of the model (see Table 1). The block that includes characteristics for the relatively small population of CAR also includes DRC, for which our earlier assumptions of importations of cVDPV2 appear sufficient (Kalkowska et al., 2020), and consequently we did not change our assumptions for this block. Finally, due to the detection of cases in the Philippines of unknown origin in 2019, we added a point introduction of cVDPV2 to the block in the model like the Philippines, although we expect that future studies may need to update the assumptions about these introductions as more evidence becomes available.

Learning from the 2019 experience (as well as the observed OPV contamination reported in India in 2018 (PTI, 2018)) and consistent with the changes we made in RC1, we recognized the need to update the types of prospective risks to add the risk of unexpected/contaminated OPV use, which we apply from 2020 onward in reference case 2 (RC2). Specifically, for RC2, we assume the same conditions as RC1 up through 2019, and then add a yearly global Poisson rate of 0.25 (1 per 4 years) for unexpected use of a withdrawn OPV serotype in OPV-using blocks for as long as the blocks continue scheduled OPV use in RI. The model determines the location and time of simulated events randomly, and we model each introduction event as a random number of point introductions drawn from the uniform distribution, U(1–10) occurring 10 days apart at reversion stage 0 (keeping these consistent across the scenarios). With respect to mOPV2 use for outbreak response, the RC1 and RC2 scenarios allow the model to use mOPV2 for outbreak response through April 2024 and then to use IPV after that time for outbreak response with lower intensity (Kalkowska et al., 2020). In both scenarios, the GPEI maintains a strategy of high control for WPV1 (no WPV1 eradication) (Kalkowska et al., 2020) and the analyses do not include nOPV2 use.

We also run a final scenario (RC2*) that combines the assumptions in RC2 with the alternative reference case (RC*) from another paper (Kalkowska & Thompson, 2020), in which the WPV1 endemic countries improve the quality of planned, preventive SIAs (pSIAs) with bOPV such that global WPV1 eradication occurs before 2023. RC2* also assumes that all OPV+IPV using countries maintain bOPV pSIAs until globally-coordinated bOPV cessation on January 1, 2025. For the RC2* scenario, we assume that mOPV2 use can occur in outbreak response throughout the time horizon and do not include nOPV2 use. The assumptions in RC2* represent a situation in which nOPV2 either behaves identically to mOPV2 or nOPV2 use does not materialize and the GPEI needs to continue using mOPV2.

We leave it to future analyses to explore the important question of how using nOPV2 may change the risks of OPV2 restarts, since information about the properties, acceptability, and behavior of nOPV2 in populations may likely become available within the next year. We also leave it to future analyses to explore the implications of constrained vaccine supply. We report the results of expected OPV2 restarts triggered (i.e., iterations that reach the 5,000-case cumulative threshold) and implemented (i.e., triggered iterations that reintroduce OPV2-containing vaccine in RI) during the time horizon. We also report the expected value and range of cVDPV2 cases from the 100 iterations for each scenario. Consistent with assuming unconstrained vaccine supply for each iteration, we track the number of polio vaccine doses used for outbreak response and we report the expected value and range of mOPV2 and IPV doses used for outbreak response.

3. RESULTS

Table 2 summarizes the results for all scenarios. For the 100 stochastic realizations of RC1, 81 iterations trigger an OPV2 restart for use in RI within the time horizon (2019–2029), of which 31 restart OPV2 use in RI by the end of 2029, with the others scheduled to start after 2029. This implies that OPV2 restart appears more likely than not, and adds strong support to the GPEI efforts to obtain more OPV2 vaccine (World Health Organization Global Polio Eradication Initiative, 2020b). Adding in the new risk (to RC1), Table 2 shows that RC2 leads to an 89% probability of OPV2 restart, with 34% of iterations implementing OPV2 use in RI within the model time horizon. Finally, for RC2*, Table 2 shows 44% of iterations trigger OPV2 restart within the time horizon and 14 OPV2 restarts in RI begin by 2029. The lower fraction of OPV2 restarts in RC2* compared to RC2 largely reflects the assumption of allowing for ongoing use of mOPV2 for outbreak response (see (Thompson & Duintjer Tebbens, 2017) for context), but also includes the impacts of higher immunization coverage in blocks with conditions like Pakistan and Afghanistan.

Looking more closely at the variability that exists in the model, within the stochastic iterations that resulted in OPV2 restart, 5 out of 72 modeled blocks contributed an average of 71% (range, 19 −100%) of the cases accumulated toward the OPV2 restart trigger under RC2, and 64% (range 11 −100%) under RC2*. These blocks in the model represented conditions similar to those in DRC, Somalia, Angola, CAR, Yemen, Nigeria, Pakistan, and Afghanistan, which the GPEI recognizes as challenging based on historical experience. Uncertainty exists about how performance might change over time, for example due to disruptions that lead to inaccessibility (war, as occurred in Syria) and/or change transmission dynamics (like the coronavirus disease 2019 (COVID-19) pandemic).

As illustrated by Fig. 1 (dotted line) and Table 2, the model estimates an average of over 23,000 expected cVDPV2 cases for the RC1 over the 10-year time horizon. For RC1, outbreak responses use an average of 396M mOPV2 doses before May 2024, at which point the model assumes that mOPV2 use stops for outbreak response, which leads to outbreak responses that use an average of 511M IPV doses from May 2024 through 2029. For RC2 (Fig. 1, dashed line), the model estimates an average of over 26,000 expected cVDPV2 cases over the time horizon. For RC2, outbreak responses use an average of 401M mOPV2 doses before May 2024 and then use an average of 615M IPV doses from May 2024 through 2029. For the RC2* (Fig. 1, dot-dashed line), the model estimates an average of over 6,000 expected cVDPV2 cases over the time horizon, with average use of 704M mOPV2 doses. The RC2* outbreak responses use an average of 0.3M IPV doses in response to introductions of LPVs into the HI IPV-only using blocks, but does not use IPV in outbreak response in any other countries throughout the time horizon. Fig. 1 also includes the reported cases for 2019 and 2020 (as of June 16) (World Health Organization Global Polio Eradication Initiative, 2020a).

Due to the GPEI planned scale back of the scheduled bOPV SIAs and the resulting modeled decline in population immunity to transmission, for the 100 stochastic iterations of the RC2*, 19 iterations trigger a restart of serotype 1-containing OPV (OPV1) within the time horizon, of which none restart OPV1 use in RI by the end of 2029. Thus, efforts to scale up

(or intensify) bOPV pSIAs to achieve WPV1 eradication in endemic countries should also motivate maintaining high population immunity to transmission in all countries prior to any globally-coordinated bOPV cessation (Duintjer Tebbens, Hampton, & Thompson, 2018; Duintjer Tebbens, Hampton, Wassilak, et al., 2016). Unless the GPEI and countries continue to perform a sufficient number of high-quality SIAs prior to bOPV cessation or perform highly-effective bOPV intensification SIAs to increase population immunity to transmission prior to bOPV cessation, the cessation of bOPV may result in problems similar to those that OPV2 cessation presents now.

4. DISCUSSION

With the changing cVDPV2 epidemiology in 2019, compared to earlier modeling (Duintjer Tebbens et al., 2015), the results from this updated global modeling suggest much higher OPV2 restart risks and OPV2 vaccine demands, and a much higher probability of failure of OPV2 cessation as a global strategy. The risk of vaccine-associated paralytic poliomyelitis (VAPP) in OPV recipients and close contacts (Duintjer Tebbens et al., 2006; Platt, Estivariz, & Sutter, 2014) helps to motivate OPV cessation after WPV eradication. In addition, following the first recognized cVDPV1 outbreak in 2000 in Hispaniola (Kew et al., 2002) and the retrospective identification of a prolonged cVDPV2 outbreak in Egypt originating in the 1980s (Centers for Disease Control and Prevention, 2001), the GPEI recognized that the continued use of OPV after WPV eradication was not compatible with the 1988 World Health Assembly resolution to end all poliomyelitis (World Health Assembly, 1988). This conclusion led to a 2008 World Health Assembly resolution to implement OPV cessation after WPV eradication (World Health Assembly, 2008). The 2015 declaration of the global eradication of indigenous transmission of serotype 2 WPV (Global Polio Eradication Initiative, 2015) led to the coordinated switch from tOPV to bOPV in 2016. Part of the OPV2 cessation strategy included the creation of an mOPV2 stockpile and procedures for its careful management to facilitate rapid response to shut down any cVDPV2 outbreaks detected in the first few years after OPV2 cessation (Duintjer Tebbens et al., 2010; Duintjer Tebbens, Pallansch, et al., 2016; Duintjer Tebbens & Thompson, 2017, 2018; Thompson & Duintjer Tebbens, 2008).

Overall, the continued need to use mOPV2 after OPV2 cessation reflects a combination of programmatic performance issues, including insufficient/ineffective pSIAs with tOPV prior to OPV2 cessation and slow and low-quality outbreak response after the detection of cVDPV2s (Blake et al., 2018; Duintjer Tebbens & Thompson, 2018). This situation is now compounded by the risk of unexpected OPV2 use in RI and/or pSIAs (Macklin et al., 2020). The probability of OPV restarts is high in the context of ongoing efforts to stop outbreaks that started prior to 2019 and the continued need to use mOPV2 in increasingly vulnerable populations, in which the mOPV2 itself can restart transmission. Adding this new risk increases the probability of OPV2 restart (Duintjer Tebbens, Hampton, & Thompson, 2016a), and will likely imply greater risks associated with future efforts to stop OPV use of other serotypes.

This analysis reflects the polio endgame experience prior to 2020 and suggests that the GPEI and the world need to urgently develop options for restarting OPV2 production and its use in

RI in OPV-using countries. The GPEI partners have already committed to ordering the bulk production of more OPV2 for oSIA use only, and have indicated a continued commitment to pursue OPV cessation as the polio endgame strategy (World Health Organization Global Polio Eradication Initiative, 2020b). While the pursuit of new bulk OPV2 production meets the criterion that we previously applied to define an OPV2 restart (Duintjer Tebbens et al., 2015; Duintjer Tebbens & Thompson, 2017, 2018), we recognize that ordering new bulk production of OPV2 represents a contingency action; committing to using it again in RI represents exercising the contingency. We also recognize that our modeling may assume greater OPV2 use than what the GPEI may have available due to constrained supplies, and that insufficient supply can lead to greater demand and the need to restart OPV2 use in RI sooner. In the absence of a genetically stabilized OPV2 strain (i.e., nOPV2) combined with more effective outbreak responses, the results in this analysis suggest that the GPEI and OPV-using countries will need to restart trivalent OPV (tOPV) for both SIAs and RI as soon as logistically possible.

However, the potential of imminent nOPV2 availability leads to substantial uncertainty about the best strategy and necessitates further modeling to assess its role. The possibility of nOPV2 presenting a better vaccine option than mOPV2 (and similarly future novel strains for serotypes 1 and 3 OPV) complicates policy analysis, options, and decision making. Multiple key questions currently include: which strain of OPV2 will we use, which vaccines in what quantity should the GPEI order now with respect to mOVP2, nOPV2, and/or tOPV formulations containing mOPV2 or nOPV2, and which strategy should the GPEI apply to best manage the complex supply with multiple vaccine formulations available? Based on the results from this analysis, we can qualitatively anticipate that OPV2 restart in RI will need to occur, independent of the choice of vaccine strain, unless nOPV2 substantially alters the current dynamics of cVDPV2 outbreaks. Future analyses will need to consider the potential impacts of nOPV2.

The GPEI expects to use nOPV2 in late 2020 (World Health Organization Global Polio Eradication Initiative, 2020b), but the current COVID-19 virus pandemic could impact its use in unexpected ways. In addition, the disruptions due to the COVID-19 pandemic may drastically change poliovirus transmission dynamics and the resulting population immunity to transmission (Thompson, Pallansch, Duintjer Tebbens, Wassilak, & Cochi, 2013), and we can anticipate that the scenarios modeled may not reflect the actual global trajectory, even in the absence of nOPV2. Future modeling should quantitatively explore the consequences of: (i) physical distancing efforts made by individuals in some countries that will impact mixing, which changes poliovirus transmission, (ii) the likely reduced distribution of vaccines, particularly OPV in SIAs, and (iii) reduction in healthcare seeking behavior and/or disruption of surveillance that will lead to decreases in surveillance quality. Securing the fragile supply chain for OPV production now also represents a significant priority, and providing clear demand signals along with guaranteed purchase of OPV produced to meet GPEI orders may be required (because some countries may wish to cancel their orders due to an inability to distribute poliovirus vaccines).

Like any model, this analysis is limited by the model structure and assumptions, and by the information available (see (Kalkowska et al., 2020) and its appendix for details). In

particular, we base our results on a limited number of stochastic iterations, with many iterations required to observe relatively rare events. Our estimates of future inputs and policies come with intrinsic uncertainties associated with projection, which may significantly impact the overall results. We recognize the largest uncertainties now relate to questions about what will happen to the GPEI and national immunization programs as we face a global pandemic, and what will emerge as additional weakest links for the polio endgame, which this analysis does not address. We hope that this analysis motivates efforts to ensure that the GPEI and countries will emerge from the global COVID-19 pandemic in a better position by helping to anticipate possible futures. At the same time, we emphasize that this analysis sheds light that should provide important lessons learned from the experience as of early 2020 with the 2016 globally-coordinated OPV2 cessation and what this means for future modeling and future OPV cessation activities.

ACKNOWLEDGMENTS

This publication was supported by Cooperative Agreement Number 5NU2RGH001913-05-00 funded by the Centers for Disease Control and Prevention. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention or the Department of Health and Human Services.

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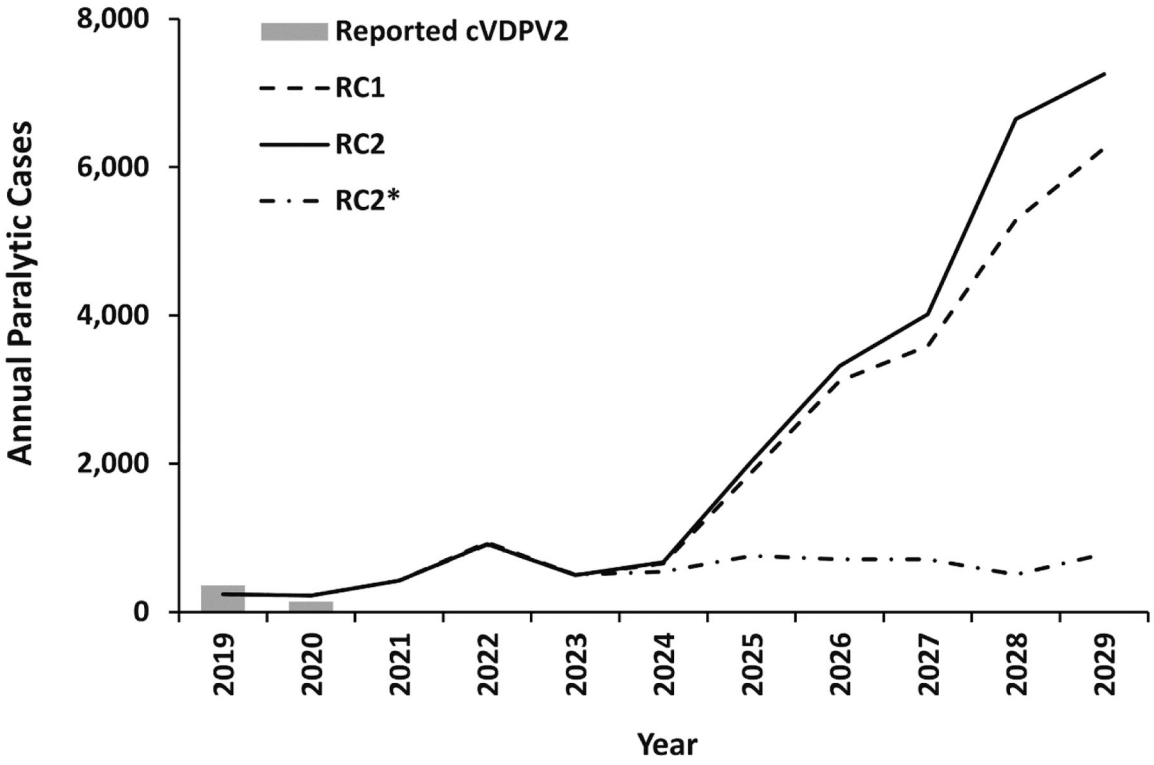

Fig. 1.

Modeled average annual cVDPV2 cases in 100 stochastic iterations for the different scenarios for 2019–2029

Abbreviations: cVDPV2, serotype 2 circulating vaccine derived polioviruses; RC, reference case

Table 1.

Assumptions for 2019 manual VDPV2 introductions

Time	Block	Subpopulation	Serotype	Reversion stage
T_0+0.14	7	0	2	6
T_0+0.16	7	0	2	6
T_0+0.19	7	0	2	6
T_0+0.22	7	0	2	6
T_0+0.25	7	0	2	6
T_0+0.27	35	0	2	0
T_0+0.30	35	0	2	0
T_0+0.33	35	0	2	0
T_0+0.36	35	0	2	0
T_0+0.38	35	0	2	0
T_0+0.41	35	0	2	0
T_0+0.44	35	0	2	0
T_0+0.47	35	0	2	0
T_0+0.49	35	0	2	0
T_0+0.49	12	0	2	19

Abbreviations: T_0, beginning of the analytical time horizon, January 1, 2019; VDPV2, serotype 2 vaccine derived polioviruses

Table 2.

Restarts triggered (and implemented), estimated expected value (and range) of cVDPV2 cases and expected value (and range) of vaccine use for outbreak response in 100 stochastic iterations for the different scenarios for 2019–2029

Scenario	Restarts triggered (implemented)	Estimated expected cVDPV2 cases (range)	Estimated expected mOPV2 doses used during years when mOPV2 use is allowed (range)	Estimated expected IPV doses used (range)
RC1	81 (31)	23,100 (721 – 111,354)	396M (177M - 735M)	511M (0M - 2241M)
RC2	89 (34)	26,226 (721 – 111,354)	401M (177M - 745M)	615M (0M - 2241M)
RC2*	44 (14)	6,292 (662 – 39,346)	704M (189M - 2041M)	0.3M (0M-8M)

Abbreviations: mOPV2, serotype 2 monovalent oral poliovirus vaccine; IPV, inactivate poliovirus vaccine; RC, reference case;