Modeling the Dynamics of Oral Poliovirus Vaccine Cessation

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Background. Oral poliovirus vaccine (OPV) results in an ongoing burden of poliomyelitis due to vaccine-associated paralytic poliomyelitis and circulating vaccine-derived polioviruses (cVDPVs). This motivates globally coordinated OPV cessation after wild poliovirus eradication.

Methods. We modeled poliovirus transmission and OPV evolution to characterize the interaction between population immunity, OPV-related virus prevalence, and the emergence of cVDPVs after OPV cessation. We explored strategies to prevent and manage cVDPVs for countries that currently use OPV for immunization and characterized cVDPV emergence risks and OPV use for outbreak response.

Results. Continued intense supplemental immunization activities until OPV cessation represent the best strategy to prevent cVDPV emergence after OPV cessation in areas with insufficient routine immunization coverage. Policy makers must actively manage population immunity before OPV cessation to prevent cVDPVs and aggressively respond if prevention fails. Sufficiently aggressive response with OPV to interrupt transmission of the cVDPV outbreak virus will lead to die-out of OPV-related viruses used for response in the outbreak population. Further analyses should consider the risk of exportation to other populations of the outbreak virus and any OPV used for outbreak response.

Conclusions. OPV cessation can successfully eliminate all circulating live polioviruses in a population. The polio end game requires active risk management.

Keywords. polio eradication; dynamic modeling; disease outbreaks; oral poliovirus vaccine.

The Global Polio Eradication Initiative (GPEI) continues to make progress toward ending the circulation of all wild polioviruses (WPVs) [1–3]. Aggressive activities to end the circulation of type 1 WPV (WPV1) and any remaining WPV3 [4] motivate efforts to plan for the polio end game, which includes coordinated (ie, synchronized) global cessation of oral poliovirus vaccine (OPV) to eliminate the risks of circulating vaccine-derived polioviruses (cVDPV) and vaccine-associated paralytic polio [5–8]. Intuitively, one country cannot stop vaccinating if any other countries that may export viruses continue using OPV, because as its population becomes more susceptible, imported OPV-related viruses can more easily establish sustained circulation to develop into cVDPVs [8]. The World Health Assembly recognized the need for coordinated OPV cessation after WPV eradication [9], but uncertainties remain about when and how to implement OPV cessation because of cVDPV risks.

Once a country disrupts indigenous WPV transmission, if it subsequently fails to sustain sufficiently high population immunity, then imported WPVs can cause outbreaks and cVDPVs can emerge if OPV-related viruses circulate long enough to evolve [6, 10]. Maintaining high population immunity reduces the effective number of individuals available to participate in viral transmission and limits circulating OPV-related viruses to those genetically close to the original attenuated Sabin strains. Because cVDPVs behave like WPVs and cause outbreaks, countries respond to a cVDPV by conducting outbreak response vaccination campaigns, often with support from GPEI partners. The outbreak response...
dynamics matter, with faster and higher quality campaigns leading to fewer cases, more rapid disruption of viral transmission, and thus less chance for spread of the outbreak virus outside the initial outbreak area [11].

Given delays associated with achieving the eradication of all WPVs and the emergence of many type 2 cVDPVs (cVDPV2s), the GPEI currently plans to pursue a strategy of global type 2 OPV (OPV2) cessation before OPV1 and/or OPV3 cessation [12]. An economic analysis showed that continued trivalent OPV (tOPV) use after successful global eradication of all WPVs represents a worse option than OPV cessation [7], and this insight extends to each serotype: continued OPV2 use more than a decade after interruption of WPV2 transmission led to ongoing cases of type 2 vaccine-associated paralytic polio and cases from cVDPV2s [6, 12]. Consideration of OPV2 cessation raises questions about the risks of cVDPV2s during the transition (eg, what happens when countries stop using OPV2?) and after outbreak response (eg, what happens if we use monovalent OPV type 2 to respond to cVDPV2 outbreaks detected after global OPV2 cessation?) This article explores these questions to help support decisions [13]. We focus on the dynamics of OPV cessation, without considering changes in existing national RI schedules. We separately demonstrate the overall impacts of changing RI schedules to include the use of inactivated poliovirus vaccine (IPV) [14] and the application of various policies in high-risk areas of Nigeria [15] and India [16].

**METHODS**

**Model**

We use a poliovirus transmission model that characterizes OPV transmission and evolution [17, 18] to explore the interaction of population immunity, OPV-related poliovirus prevalence, and cVDPV emergence around the time of OPV cessation and in the event of a post-cessation outbreak. We focus on behavior within closed, hypothetical populations representing a diverse range of possible settings to explore the impact of vaccination policies before OPV cessation on cVDPV emergence risk and different OPV outbreak response strategies to control a post-OPV cessation cVDPV. Given the plans for OPV2 cessation, we use model inputs for type 2 [14, 17], although the concepts of this analysis extend to the other 2 serotypes.

The differential equation-based model includes 8 recent and 24 historic immunity states associated with live poliovirus (LPV) infections (eg, WPV, OPV, OPV-related, and cVDPV infections) and/or successful IPV vaccinations. We model the process of OPV virus evolution using 20 discrete stages, which increase in neurovirulence and transmissibility from OPV-like properties in the first stage to fully reverted WPV-like properties in the last stage [6, 17]. The model includes age-heterogeneous mixing and forces die-out of WPV and OPV-related virus in each reversion stage by setting the strain-specific force of infection to 0 once the effective proportion infectious with the strain drops below a transmission threshold level calibrated across a wide range of situations. We capture the possibility that supplemental immunization activities (SIAs) repeatedly miss the same children and model both the true coverage of each round and the conditional probability of targeted fully susceptible or maternally immune individuals not receiving a dose given that they did not receive a dose in the previous round [18].

We characterize population immunity to poliovirus in the model by the mixing-adjusted effective immune proportion (EIPM), which accounts for partial immunity to poliovirus transmission of individuals in each immunity state and heterogeneous mixing between age groups and/or subpopulations [15]. EIPM equals $1 - R_{net}/R_0$, where $R_{net}$ represents the net reproductive number, defined as the average number of secondary infections caused by a single infection introduced into a population with a given immunity level, and $R_0$ represents the basic reproductive number (ie, the average number of secondary infections caused by a single infection introduced into a fully susceptible population) [19]. If population immunity remains high enough ($R_{net} < 1$), then each new infection generates <1 new infection on average, and the virus eventually dies out, whereas $R_{net} > 1$ allows the virus to “take off.” Consequently, we define the threshold $EIP^* = 1 - 1/R_0$ above which the virus will eventually die out and below which virus sustained transmission can occur. $EIP^*$ also represents the population immunity level corresponding to the equilibrium state of the system for any given vaccination intensity that remains insufficient to eventually prevent circulation. For high enough vaccination intensity, the EIPM will remain above $EIP^*$. In this article, $R_0$ and $R_{net}$ refer to the reproductive numbers of WPV, which we assume equal those of fully reverted cVDPVs. Thus, in our analyses of cVDPVs, $EIP^*$ and $R_{net}$ refer to cVDPVs (which behave like WPVs) and not to the lower threshold $EIP^*$ and $R_{net}$ values for the lower reversion stages characterized by lower $R_0$

We characterize the prevalence of OPV-related viruses as the effective proportion infectious with OPV-related viruses (EPI-ORV) in any reversion stage, which weighs all infected individuals according to their combined fecal-oral and oropharyngeal relative infectiousness compared with fully susceptible individuals [17]. We use all previously developed generic model inputs that remain the same for all populations (ie, inputs to characterize immunity states, paralysis-to-infection ratios, infection process, waning process, and OPV evolution process) [17, 18]. We start the model with the steady-state age distribution corresponding to the assumed constant, age-independent and equal birth and mortality rate and run the model up to a WPV-free state by letting the population go through epidemiological modes of endemic transmission without vaccination, only RI, and finally elimination after initiating regular SIAs [10]. We keep the RI coverage before SIAs
Table 1. Fixed Model Inputs Across All Runs*

<table>
<thead>
<tr>
<th>Model Inputs</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age groups</td>
<td>0–2, 3–11 mo; 1–4, 5–9, 10–14, 15–39, ≥40 yearsa</td>
</tr>
<tr>
<td>Interval, years</td>
<td></td>
</tr>
<tr>
<td>Before $R_0$ seasonality starts</td>
<td>5</td>
</tr>
<tr>
<td>Before RI starts</td>
<td>15</td>
</tr>
<tr>
<td>Before regular SIAs start</td>
<td>25</td>
</tr>
<tr>
<td>Before regular SIAs end</td>
<td>35</td>
</tr>
<tr>
<td>Duration of each regular SIA, days</td>
<td>5</td>
</tr>
<tr>
<td>Timing of regular SIAs during year</td>
<td>Days 0, 60, 120, . . .</td>
</tr>
<tr>
<td>Proportion of transmissions via oropharyngeal route ($p^o_{\text{oro}}$)</td>
<td>0.3</td>
</tr>
<tr>
<td>RI coverageb before SIAs start</td>
<td>Linear ramp from 0 (at start of RI) to 0.5 (at start of regular SIAs)</td>
</tr>
</tbody>
</table>

* This table supplements generic model inputs reported elsewhere [14, 17, 18] and analysis-specific model inputs (Table 2).

Abbreviations: mo, months; $R_0$, basic reproductive number; RI, routine immunization; SIAs, supplemental immunization activities.

a Age groups for which the fraction immune determines the fraction of children entering the maternally immune state at birth [17].
b Coverage with exactly 3 RI doses, assuming no partial coverage, birth doses, or booster doses.

and timing of modes during the run-up fixed for all runs, which speeds up the run time without significantly affecting the results, and we fix the proportion of transmissions via the oropharyngeal route at a typical value for developing countries [14, 17, 20]. Tables 1 and 2 show the model inputs we used for the 3 analyses we performed.

OPV Cessation Behavior
We considered a single hypothetical population to explore effects of OPV2 cessation on the behavior of population immunity (ie, EIPM), the effective prevalence of OPV-related viruses (ie, EPIORV), and the paralytic poliomyelitis incidence due to cVDPVs using serotype 2 input values. We used random population-specific model values (ie, variability inputs), except for assuming a high-end value for $R_0$ to increase the possibility of cVDPVs and no seasonality to avoid oscillations around the steady-state for more visual clarity of the behavior. We varied RI coverage to generate different constant steady-state population immunity levels without SIAs at OPV cessation. We investigated RI coverage levels that lead to population immunity well above, just above, and just below the threshold EIP*. For the former, we iteratively determined the lowest RI coverage level for which no cVDPVs emerge, using trial and error of RI coverage values at 1% increments.

OPV Cessation Policies
We explored the impact of various policy options on the postcessation cVDPV emergence risk across a random sample of hypothetical populations to represent a simplified characterization of the variability that exists in real countries. We characterized variability in the inputs between populations as a distribution to represent real differences that may affect the impacts of policy choices. We recognize that policy options represent model inputs that decision makers can control completely (eg, time without SIAs before OPV cessation) or partially (eg, RI coverage and SIA impact), and they therefore differ from variability in the conditions between populations. Thus, we drew a random sample of 500 points from the variability space to obtain a representative sample of populations. For some inputs, we sampled from different ranges depending on the sampled $R_0$ value, higher values of which we use as a proxy for conditions that correlate with less seasonality, more age-homogeneous mixing (due to more intense transmission and larger household sizes), and lower OPV take rates. We use ranges consistent with model input combinations we previously used across different situations. For WPV1 $R_0$, we sample from the range 5–13, which the model multiplies by 0.9 to reflect WPV2 values (ie, 4.5–11.7) [17], with more weight given to the middle part of the range than to the extremes (see Supplementary Appendix). After sampling the variability space, we ran the model for each of the 500 points from the variability space for the different policy options to explore relationships between policy choices and post-cessation cVDPVs risks. We approximated the post-cessation cVDPV risk as the fraction of 500 runs with a cVDPV emergence. We defined cVDPV emergence as the occurrence of cVDPV prevalence above the transmission threshold for nonzero force of infection at any point in time after OPV cessation.

Post-cessation Outbreak Response
We focused on a single hypothetical population to explore EIPM, EPIORV, and the resulting paralytic poliomyelitis incidence for various OPV response scenarios. For this analysis, we selected 1 point from the random sample of the variability space that led to a cVDPV after OPV cessation. This point involves the maximum $R_0$ value from the range (WPV1 $R_0 = 11.7$), with a policy scenario of median RI coverage and OPV cessation 1 year after conducting the last annual SIA with medium impact. Using assumptions about outbreak detection and response (Table 2), we varied the number of outbreak response SIA (oSIA) rounds to determine the number of rounds that controls the cVDPV outbreak and to investigate the persistence of introduced OPV-related viruses. We also explored whether conducting an additional oSIA round with low impact long after the initial oSIA rounds can reintroduce cVDPVs into the population.

RESULTS

OPV Cessation Behavior
Figure 1 illustrates the relationship between population immunity (ie, EIPM), OPV-related virus prevalence (ie, EPIORV),
and indigenous cVDPV emergence in the model. We allow a very long time (ie, 15 years) between the last regular SIAs and OPV cessation so that the system reaches a steady-state before OPV cessation, with constant EIPM and EPIORV due to constant RI coverage. At OPV cessation (without IPV use), the EPIORV immediately starts to decay toward 0 in the absence of new introduction of OPV into the population. At the same time, the EIPM decreases due to births of children that remain unvaccinated and decreasing exposure to OPV-related viruses for unvaccinated children or individuals with waned immunity. More OPV use up until OPV cessation implies higher prevalence of OPV at OPV cessation, which may suggest a longer time until the prevalence of OPV decays below the transmission threshold for nonzero force of infection once the supply of new OPV stops. However, because more OPV use up until OPV cessation leads to higher EIPM at OPV cessation, the net effect of more OPV use just before OPV cessation can result in faster die-out of OPV-related viruses. Thus, the interplay of these dynamically interrelated trends determines the emergence of cVDPVs.

Figure 1A shows the lowest EIPM at OPV cessation that does not lead to post-cessation cVDPV emergence for the hypothetical population modeled. The lower $R_0$ of OPV-related viruses in lower reversion stages than cVDPVs imply higher thresholds.
than the EIP* shown for cVDPVs, which suggests that OPV-related viruses in lower reversion stages cannot sustain transmission at the time of OPV cessation for an EIPM at or below the threshold (EIP*). However, the relatively rapid decrease in EIPM after OPV cessation takes it below the EIP* while OPV-related viruses still linger in the population. Therefore, preventing post-cessation cVDPVs requires slightly higher population immunity than the EIP* at OPV cessation. In the example in Figure 1A, with minimally sufficient EIPM at OPV cessation, we observe a rapid decay in EPIORV, with die-out approximately 9 months after OPV cessation. In the absence of any LPVs or RI IPV vaccination, EIPM initially decreases rapidly due to waning and the introduction of new susceptible individuals and then the decline toward 0 slows down due to relatively slow population turnover (see Supplementary Appendix).

Figure 1B shows that with lower EIPM at OPV cessation than in Figure 1A, but still higher EIPM than the threshold EIP*, the decrease of the EIPM below the EIP* soon after OPV cessation allows the OPV-related viruses to sustain transmission and develop into cVDPVs approximately 8 months after OPV cessation. If they emerge, the cVDPVs develop epidemic behavior at some point, similar to typical epidemic behavior of WPVs or precessation cVDPV outbreaks (i.e., in the absence of a response, the cVDPVs eventually establish a new endemic equilibrium of cVDPV transmission). Figure 1C shows that with an initial EIPM below the EIP*, cVDPVs emerge somewhat earlier (i.e., a little more than 6 months after OPV cessation) but reach a lower peak because fewer effective susceptible individuals build up before emergence. Figure 1B and 1C tend to the same equilibrium state, given that they both involve no vaccination after OPV cessation. Even lower RI coverage than in Figure 1C leads to emergence of cVDPVs before OPV cessation, which, owing to the self-correcting behavior of the system leads to higher EIPM at OPV cessation.

If detected, cVDPV outbreaks within 6 months of planned OPV cessation would delay the global implementation of OPV.
cessation and restart planning efforts due to an expectation of interruption of all known cVDPV transmission 6 months before OPV cessation [12], which would most likely imply significant programmatic costs. Lowering the initial EIPM delays die-out of OPV-related virus, up to the point when OPV-related viruses survive long enough to develop into cVDPVs and establish continued circulation. For this particular hypothetical population, policy permutation, and point in the variability input space, the minimum EIPM to avoid post-cessation cVDPVs corresponds to RI coverage of 94%, but the value will vary by population (eg, for higher OPV take rate, the RI coverage to avoid post-cessation cVDPVs becomes lower).

**OPV Cessation Policies**

We explored 16 different policy permutations, each sampled across 500 points of the variability input space (Table 2), for a total of 8000 model runs. Overall, we found cVDPV emergence in 766 runs (approximately 10% of all runs). For 226 runs (approximately 3% of all runs and 30% of those with a cVDPV emergence) the cVDPV emerged some time after the last regular SIA but before planned OPV cessation, which may or may not be detected and lead to delay in planned OPV cessation. Among the 7234 runs with no post-cessation cVDPVs, the mean time until OPV-related virus die-out equaled 3.7 months (range, 2–12 months). Among the 540 runs with post- but not precessation cVDPV emergence, we found a mean time to OPV-related virus die-out of approximately 6 months (range, 0.05–12 months).

Figure 2 shows the relationship of the most important policy and variability inputs plotted against the post-cessation cVDPV risk (Figure 2A). Figure 2A reveals an important interaction of the time without SIAs before OPV cessation and RI coverage. It shows no impact of RI coverage if the time without SIAs before OPV cessation equals 0 years (ie, an SIA occurs just before OPV cessation, then no post-cessation cVDPVs emerge regardless of RI coverage level), but an increase from 0.01 to 0.71 in the post-cessation cVDPV risk between low and high RI coverage if the time without SIAs before OPV cessation equals 2 years. Consistent with the exploration of the OPV cessation behavior, the increase in cVDPV risk associated with a longer time without SIAs before OPV cessation and with less RI coverage confirms that more OPV use just before OPV cessation significantly lowers the post-cessation cVDPV risk. With a short time between the last SIA and OPV cessation, cVDPVs emerge very rarely before OPV cessation (ie, in 5 of 4500 runs [0.1%] with ≤1 year without SIAs before OPV cessation), whereas this occurs much more frequently with a longer time between the last SIA and OPV cessation (ie, in 221 of 1500 runs [15%] with 2 years without SIAs before OPV cessation). This finding remains consistent with the current experience of frequent cVDPV2 emergence in the context of limited poor quality SIAs with tOPV in many countries [6].

Figure 2B illustrates the important effect of 0 on post-cessation risk of cVDPVs, with a clear increase from 0 probability across all policy permutations to a probability of 0.26 at a base 0 of 13 for WPV1 (ie, 0 of 13 for WPV2 of 11.7). The influence of 0 interacts with other variability and policy inputs, including the duration of time without SIAs before OPV cessation (Figure 2B).

**Post-cessation Outbreak Response**

Figure 3 explores the behavior of EPIM, EIPORV, and paralytic poliomyelitis incidence for different outbreak response scenarios.
In Figure 3A, EIP* oscillates because of the assumed seasonality in $R_0$. After the last SIA conducted 1 year before OPV cessation, the EIPM starts to decrease, with a faster decrease after OPV cessation. The EPIORV decreases immediately after OPV cessation, but not enough to die out because of the low EIPM, which allows a cVDPV to emerge approximately 6 months after OPV cessation. In the absence of any oSIAs, the cVDPVs settle into a new (oscillating) equilibrium after an initial large cVDPV outbreak (Figure 3B and 3C). Conducting any oSIAs after cVDPV detection increases the EIPM and EPIORV compared with no response. This depends on the timeliness of the outbreak response, with possibly a higher peak of EPIORV due to the cVDPV outbreak than from the OPV response, as shown in Figure 3B. In this example, conducting only 2 timely oSIAs of medium impact (Table 2) does not sustain higher EIPM than the EIPM that occurs from natural burn-through in the absence of oSIAs (Figure 3B), although it prevents many cases during the initial cVDPV outbreak (Figure 3C). Adding a third and fourth oSIA further increases and sustains EIPM beyond the natural burn-through level for long enough to interrupt transmission of all OPV-related viruses, including the cVDPV outbreak virus and the OPV-related viruses introduced during the response. Thus, within a closed population, if the OPV response creates high enough population immunity to interrupt the cVDPV transmission, then it will also interrupt transmission of all OPV-related viruses. The situation after the last oSIA resembles OPV cessation explored in the policy analysis above with an SIA conducted just before OPV cessation, which already leads to a very low probability of post-cessation cVDPVs (Figure 2A), but with the added benefit of high population immunity due to the transmission of the outbreak virus and aggressive enough outbreak response to control the cVDPV. More oSIAs will further increase population immunity to more rapidly interrupt cVDPV transmission and therefore also further reduce the already unlikely possibility that any introduced OPV-related viruses establish continued circulation.

Figure 3. Population immunity, OPV-related virus prevalence, and paralytic poliomyelitis incidence in the analysis of post-cessation outbreak response. A, Population immunity. B, Total OPV-related virus prevalence. C, Paralytic poliomyelitis incidence due to fully-reverted cVDPVs. Abbreviations: cVDPVs, circulating vaccine-derived polioviruses; EIP*, threshold effective immune proportion; EIPM, mixing-adjusted effective immune proportion; EPIORV, effective proportion infectious with OPV-related polioviruses; OPV, oral poliovirus vaccine; oSIAs, outbreak response SIAs; SIAs, supplemental immunization activities.
We explored whether adding a poor-quality fifth oSIA round after interruption of the cVDPV outbreak would create new cVDPVs, but for the plausible timing of this fifth round no cVDPV outbreak occurs because the round further increases the already high population immunity that interrupted the outbreak cVDPV. In Figure 3, we unrealistically delayed the fifth SIA by a full year, by which time the population immunity dropped far below the threshold and the reintroduced OPV-related viruses can create new cVDPVs. For this example, a poor-quality fifth oSIA round does not create new cVDPVs if conducted less than a half year after the previous round. The minimum time until new cVDPV creation can occur increases significantly with a better-quality last oSIA round or with more oSIAs conducted in immediate response to the initial post-cessation cVDPV outbreak.

DISCUSSION

Our analysis yields numerous important insights related to managing OPV cessation. cVDPVs may emerge after OPV cessation, but OPV cessation does not automatically lead to cVDPV emergence. The outcome depends on the dynamic race between decreasing OPV-related prevalence and decreasing population immunity after OPV cessation. Although more OPV use up until OPV cessation increases the prevalence of OPV, it implies higher population immunity, which produces a net effect of a lower cVDPV risk [5, 6]. The model demonstrates that the choices made by national, regional, and global policy makers will determine the cVDPV risks before, during, and after OPV cessation (ie, more OPV before OPV cessation represents the key to managing post-cessation cVDPV risks). Our analysis suggests that countries will need to achieve somewhat higher population immunity than the threshold level to completely prevent cVDPV outbreaks. Thus, preparations for OPV cessation should prioritize attaining the highest possible level of population immunity everywhere before the coordinated stop. In particular, countries with suboptimal RI coverage should continue to conduct as many tOPV SIAs as possible up until coordinated, synchronous global OPV2 cessation, with some rounds timed relatively shortly before planned OPV2 cessation. Manufacturers will need to play a critical role in OPV cessation by producing sufficiently large quantities of tOPV before OPV cessation.

Our results show that the timeline for indigenous cVDPV emergence remains relatively short. Post-cessation cVDPVs either die out within about a year of OPV cessation, or emerge within less than 1.5 years. Thus, very sensitive surveillance and rapid outbreak response [11] remain imperative during the first 2 years after OPV cessation, although surveillance should remain intense beyond that period because of the risk of VDPV introductions from chronic excretors or breaches (intentional or unintentional) in LPV containment [5]. For a path of OPV2 cessation first, followed by cessation of OPV1 and OPV3, surveillance must remain intense throughout and for some time beyond the period of any OPV use.

In the event that we do not manage to prevent cVDPV2s, we must ensure preparedness to respond to all cVDPV outbreaks [8]. Responding to a cVDPV outbreak with a sufficient OPV outbreak response to interrupt the outbreak virus will not create new cVDPVs from within the same population. The feared “fire with fire” risk does not seem to represent a concern within the outbreak population; consequently, avoiding OPV use for outbreak response shortly after OPV cessation because of the perceived risk of reseeding the outbreak population with new cVDPVs does not seem justified. Aggressive response to a cVDPV outbreak after OPV cessation must stop transmission within the outbreak population as rapidly as possible. Exportation of the outbreak virus will represent the primary concern, and the outbreak response will need to be aggressive enough to stop the outbreak. An aggressive outbreak response may potentially lead to higher OPV-related prevalence than natural burn-through of the outbreak virus, which may imply a greater risk of exportation of the less-transmissible OPV-related viruses introduced by the outbreak response than the outbreak virus itself. Thus, assessing the risk of reseeding LPVs to other populations requires considering multiple interconnected populations, and the risks will depend on the population immunity in the connected populations and their risks of potentially importing either the circulating outbreak virus or OPV-related viruses. Soon after global OPV cessation, population immunity in surrounding areas should still remain high (otherwise they would generate their own cVDPVs), but alternative outbreak response strategies to OPV campaigns should remain under consideration in the event of a cVDPV emergence in a population with strong connections to other high-risk populations.

We did not consider the possibility that OPV used for outbreak response generates new chronic excretors of VDPVs in individuals with certain rare types of immunodeficiencies, which requires further study. Countries should not introduce OPV long after control of an outbreak or into a population without a circulating LPV. Long-term outbreak response after an exogenous LPV introduction represents a fundamentally different situation than managing OPV cessation because of much lower population immunity overall, which may imply more risks associated with OPV outbreak response and requires further study. For long-term outbreak response, the vaccine stockpile will most likely need to contain IPV.

Our analyses remain limited by the use of a deterministic model in closed, hypothetical populations and by some other factors. Real populations may include preferentially mixing undervaccinated subgroups that play an important role in continued WPV transmission and cVDPV emergence [15–18]. Thus, application of the analyses from this article to real populations might further inform OPV cessation risks [15, 16].
transmission and cVDPV emergence in real populations also depend on stochastic processes such as die-out, which we approximate in our deterministic model [17]. Although we expect the same dynamic interplay between population immunity, OPV-related prevalence, and cVDPV emergence in stochastic models, the inclusion of stochasticity could alter some of the quantitative results from this analysis (eg, the time until OPV die-out or cVDPV emergence). Although we base model inputs for the OPV evolution process on an extensive expert literature review and model calibration process, uncertainties remain regarding the details of OPV evolution [6, 17, 19, 20, 21]. Further empirical evidence may help bound the uncertainty about the OPV evolution process [6, 20]. We consider the role of IPV in achieving higher population immunity before OPV cessation and/or maintaining some level of population immunity after OPV cessation in a separate analysis [14]. Further studies that explore the impact of IPV on post-cessation cVDPV risks will help inform decision makers about the important trade-offs associated with the planned strategy [12, 22, 23]. The concepts of our analyses extend to other serotypes, with some notable differences (eg, OPV1 and OPV3 do not take at the same high rate as OPV2 in tOPV and do not generate as much secondary spread [17, 20, 21, 24], and OPV2 reverts relatively more quickly [6, 17, 20, 21]).

In conclusion, the polio end game requires active management of population immunity to reduce the risks of cVDPVs and preparedness to aggressively respond to any cVDPV outbreaks after cessation of each OPV type.

Supplementary Data

Supplementary materials are available at The Journal of Infectious Diseases online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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