***Classification: Biological Sciences, Population Biology***

**The risk of Type 2 oral polio vaccine use in post-cessation outbreak response**

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**Abstract**

Wild type two poliovirus (WPV2) was last observed in 1999. The Sabin-strain oral polio vaccine type two (OPV2) was critical to eradication, but is known to revert to a neurovirulent phenotype, causing vaccine-associated paralytic poliomyelitis (VAPP). OPV2 is also transmissible and can establish circulating lineages, called circulating vaccine-derived polioviruses (cVDPVs), which can also cause paralytic outbreaks. Thus, in April 2016, OPV2 was removed from immunization activities worldwide. Interrupting transmission of cVDPV2 lineages that survive cessation will require OPV2 in outbreak response, which risks seeding new cVDPVs; this potential cascade of outbreak responses seeding new vaccine-derived lineages, thus necessitating further outbreak responses, presents a critical risk to the polio eradication effort.

The EMOD individual-based disease transmission model was used to investigate the risk of cVDPV2 establishment following OPV2 use in outbreak response in West African populations**.** Under a broad range of scenarios, the probability that OPV2 use in outbreak response establishes new cVDPV2 lineages in this model exceeds 50% in as little as 18 months and no later than four years post-cessation. The risk of a cycle in which outbreak responses seed new cVDPV2 lineages suggests that OPV2 use should be managed carefully as time from cessation increases. Key approaches to mitigating the risk that OPV2 use will be needed in the far future focus on extinguishing existing cVDPV2 lineages soon: maintaining high-quality surveillance, conducting aggressive near-term outbreak responses, strengthening IPV in routine immunization, and gaining access to currently inaccessible areas of the world to conduct surveillance.

**Significance Statement**

Wild type two poliovirus (WPV2) was last observed in 1999, and the type 2 oral polio vaccine (OPV2) was a critical tool in eradication. However, OPV2 is a live attenuated virus, which is able to spread in human populations and regain neurovirulence (becoming circulating vaccine-derived poliovirus, or cVDPV). Ending the use of OPV2 is therefore critical to global poliovirus eradication, and in April 2016, OPV2 was removed from immunization activities worldwide. However, interrupting transmission of any extant cVDPVs will require local use of OPV2, which risks seeding new cVDPVs; the potential for this cycle presents a critical risk to the polio eradication effort. This work investigates the conditions under which OPV2 immunization activities risk seeding new cVDPV lineages.

**Background**

April 2016 marks the global cessation of the use of the Sabin-strain oral polio vaccine type two (OPV2) in routine and campaign immunization, with all 155 OPV-using countries switching from the trivalent to the bivalent form of OPV, which contains only vaccine types 1 and 3 (1). The last case of wild type 2 poliovirus (WPV2) was observed in India, in 1999 (2). OPV2 is a live, attenuated virus, capable of genetic reversion to a neurovirulent phenotype that imposes a health burden due to vaccine-associated paralytic polio (VAPP). The Sabin-strain viruses are also capable of transmission, and in low-immunity settings can establish circulation; these established lineages are termed circulating vaccine-derived polioviruses (cVDPVs) (3–6). Among the three OPV serotypes, OPV2 is estimated to cause 40% of all VAPP cases, and 90% of all cVDPV cases (7). The successful removal of OPV2 from elective use therefore presents clear public health benefits. However, the cessation of OPV2 immunization carries the implicit risk that Sabin-strain lineages will survive to become cVDPV2s in the future, necessitating outbreak response with OPV2, thereby potentially seeding new lineages (8, 9). Historical experience has established that Sabin-strain polioviruses (and other live, attenuated polioviruses) are able to broadly circulate within populations when introduced after relatively brief (1-3 year) interruptions in OPV use (10–13). The possibility of a cycle in which OPV2 use in outbreak response seeds new cVDPV2 lineages, necessitating further outbreak response, represents a fundamental risk to the cessation of OPV2 immunization.

This manuscript addresses the conditions under which OPV2 use in outbreak response could establish new chains of Sabin 2 transmission, and how this risk evolves as population immunity declines post-cessation. Many factors affect an outbreak response activity’s propensity to establish new VDPV2 lineages: population immunity at the time of outbreak response, the base reproductive rate R0 of the Sabin type 2 virus (which may change during genetic reversion), and the epidemiological connectedness of spatially separated populations. Each of these factors is also highly uncertain, and varies with the geographical/societal context under consideration. In this work, a variety of potential scenarios are considered (see Table 1), and in each scenario, a Separatrix algorithm (14). is used to quantify the risk that an outbreak response conducted according to existing protocol will seed a new VDPV2 as a function of the time since cessation and the mean per-person per-day migration rate between provinces.

**Results**

Figure 1 presents the output of a single run of the Separatrix algorithm, with R0f = 2·0, *f* = 0·5, *λ*= 60 days, N­IPV= 1, *c*= 1 (see Table 1 for definition of symbols). Figures 1-3 all present comparisons at the moderate immunity profile (defined in Table 1) in the pre-cessation birth cohort. The color surface shows the imputed risk throughout a 2D space of mean migration rate and time since cessation; the gray crosses and circles indicate simulations in which a new lineage succeeds or fails, respectively, to establish long-term circulation (defined for the purposes of this study as continued viral transmission, outside of the response provinces, 9 months after the outbreak response); the thin black dashed box outlines a space of migration rates preferred by a calibration to a previous travelling outbreak of WPV1 in the region (Supplement); and the black line represents the 50% separatrix line, the imputed contour in parameter space along which the VDPV2 risk is 50%. In this scenario, this line indicates that this risk reaches 50% around 2·5-3·5 years post-cessation, depending on the migration rate.

**Scenario comparison –dependence of VDPV2 risk on infectivity profile**

It is difficult to visually compare the full risk surfaces of multiple scenarios, so the 50% separatrix contours derived in different scenarios are used to compare the relative risks. Figure 2 illustrates how the risk profile depends on R0f and *f,* with other parameters held constant (*λ*= 60 days, N­IPV= 1, *c*= 1)*.* As expected, the risk of continued circulation rises earlier with increasing R0 of fully reverted OPV2; the lowest tested value, 1·2, presents minimal risk even five years post-cessation in the preferred migration rate region, while the highest value, 3·0, presents high risk just 18 months post-cessation. At a given R0f, changing *f* from 0·5 to 0·25 induces a small but non-negligible shift of the separatrix to later times/higher migration rates.

**Scenario comparison – dependence of VDPV2 risk on IPV use in routine immunization post-cessation**

Figure 3 illustrates how the inclusion of IPV in routine immunization (RI) affects the risk of OPV2 survival in this model. The coverage of routine immunization is assumed to be 80%. While the herd immunity effects of IPV are evident in developed nations, where the oral-oral transmission route likely dominates (15, 16). they are poorly characterized in developing countries where the fecal-oral transmission route dominates. At the individual level, recent mOPV2 challenge studies comparing a variety of mixed IPV-bOPV schedules have found that mixed IPV-bOPV schedules provide heterotypic mucosal immunity to Type 2 that appears superior to bOPV or IPV alone but inferior to mOPV2 or tOPV (17, 18). It is not immediately apparent from literature whether additional IPV doses beyond the first induce a dose-dependent increase in this heterotypic immunity, or whether this incremental effect depends on the ordering of bOPV and IPV in the schedule (17, 18). The observed induced immunity reduces both the probability of acquisition upon mOPV2 challenge and the duration and amount of Sabin 2 shedding in stool. At the population scale, it is unclear how this reduction in acquisition at challenge doses translates to protection at natural exposure levels, and how the reduction in shedding translates to reduced infectiousness in close-contact and community settings in regions of poor sanitation (19, 20). In this model, it is assumed that children born post-cessation will be bOPV-exposed, and that a dose of IPV in RI will confer some degree of heterotypic protection – a 10% reduction in the recipient’s effective exposure and a 10% reduction in a recipient’s onward infectivity are assumed; given the uncertainties around incremental effects of additional doses, a 2xIPV RI schedule is not compared here. In the model, the IPV distributed during outbreak response will have similar effects on the OPV2-naïve, but induce a boosting response in the OPV2-exposed. Under these assumptions about bOPV+IPV immunization, Figure 3 shows that even the limited mucosal protection that a dose of IPV in RI provides can substantially mitigate OPV2 survival if the reverted Sabin R0,f is low, but this mitigating effect declines as R0,f increases.

**Scenario comparison – dependence of VDPV2 risk on immunity profile at OPV2 cessation**

Finally, Figure 4 presents a comparison of the two potential pictures of immunity at the time of cessation. The solid lines indicate simulations with pre-cessation population immunity in zero-to-five year olds induced by three OPV campaigns at 80% coverage, 50% take; the dashed lines indicate sims with 100% coverage, 100% take (essentially, perfect immunity within this cohort). The dashed lines essentially indicate the time at which the cohort of children born after OPV2 cessation will be able to sustain circulation of OPV2 in the absence of any transmission through the older cohort. The duration of the additional protection from perfect pre-cessation immunity increases as R0,f increases, as the virus is increasingly able to recruit the partially immune older children into the transmission chain. The additional protection against cVDPV2 establishment provided by perfect immunity in the older cohort is modest given the extreme nature of this assumption, as the naïve cohort of children born post-cessation eventually grows sufficiently large to sustain transmission.

The other scenario parameters (the distance-dependence in the gravity model of migration, the reversion rate of OPV2 infectivity) are both found to have comparatively small effects on the position of the separatrix line; the figures illustrating the comparisons between these scenarios can be found in the supplemental materials.

**Discussion**

The population immunity conditions in the upcoming years will be unprecedented; little to no immunity will be acquired through natural infection as in the pre-vaccine era, and Type 2 immunity will be provided solely through IPV, with little ability to induce strong intestinal mucosal immunity. Any observed cVDPV2 must be extinguished, and OPV2 is the best currently available tool for doing so, but outbreak response activities post-cessation will infect a sizable population with the OPV2 virus in a world with an ever-growing young cohort lacking intestinal mucosal immunity. While uncertainty in immunity, transmission, and migration conditions prevent a strongly constrained estimate of this risk vs. time in a particular context, the results of this study indicate that under a wide range of conditions, outbreak responses as currently outlined could potentially create a cascade of new outbreaks within 18 months to four years post-cessation.

Once population immunity becomes low enough to support circulation, it is unclear whether this risk can be mitigated without new vaccines that induce mucosal immunity without transmitting efficiently or reverting to neurovirulence. In the near-term, minimizing the risk of cascading cVDPV2 outbreaks requires strategies that minimize the risk that OPV2 use will be required at all in the future.

1. **Strengthen both paralysis-based and environmental poliovirus surveillance.** In the absence of OPV2 use, the emergence of cVDPV2 relies on the unobserved survival of lineages seeded before cessation. Detecting and interrupting any cVDPV2 lineages currently circulating, while global population immunity is high, minimizes the risk of cascading cVDPV2 outbreaks in the future. Environmental surveillance provides the ability to detect poliovirus in a population in the absence of paralytic cases, and could be used to track Sabin 2 survival in the near-term to identify places of concern early.
2. **Aggressive outbreak response in the near-term.** The emergence of VDPV2 in the near-term will be an effective indicator of locally low population immunity in a world in which immunity remains high. Near-term OPV2 use does not present substantially more risk than did its use immediately pre-cessation. Widespread cVDPV2 circulation has been observed in the past (21, 22), and immunity conditions post-cessation will be unprecedented due to a lack of both natural and vaccine-derived immunity. These facts argue for outbreak responses soon after cessation to be geographically broad, both to ensure interruption of the observed transmission chain and to raise population immunity in regions surrounding the emergence. It may be advantageous to heighten surveillance in neighboring districts or countries known to have imported polioviruses in the past from the emergence region.
3. **IPV in routine immunization**. Under the (admittedly uncertain) assumptions about IPV-induced intestinal mucosal immunity used in this study, high-coverage IPV immunization in RI could mitigate the OPV2 survival risk for a short time. Even if these results overestimate the herd effect of cross-protection from bOPV+IPV exposure in the post-cessation cohort, scaling up the coverage and number of doses of IPV in RI would provide valuable individual protection against paralysis, reducing the burden of VDPV2 outbreaks or VAPP caused by OPV2 response.
4. **IPV in immunization campaigns**. A second crucial feature of IPV in the post-cessation world is its ability to boost mucosal immunity against Type 2 in OPV2-exposed children. While the use of IPV in outbreak response campaigns is already a piece of the outbreak response protocol, IPV immunization campaigns targeting both the pre- and post-cessation cohort of children could serve two purposes. First, filling gaps in routine immunization, which are quite large in much of the developing world. Second, boosting Type 2 immunity in the older, OPV2-exposed cohort. This work has not addressed the question of waning mucosal immunity, but if mucosal immunity wanes on relatively short timescales, this waning could be counteracted through IPV boosting.
5. **Obtain access to currently inaccessible areas**. Regions of the world that are currently inaccessible to effective surveillance or outbreak response due to violence, instability, or local resistance, present significant risks where VDPV2 lineages could circulate unobserved. In Borno state, Nigeria, many areas have been inaccessible for years due to Boko Haram activity. In this state, both cVDPV2 (environmental isolation March 2016, most recent observed relative from May 2014) and WPV1 (paralysis onsets in July 2016, most recent observed relatives from 2011) have been recently observed.(23, 24) These discoveries highlight the critical risk that inaccessible areas present the polio eradication and OPV cessation efforts.

Most of these items are already priorities of the Global Polio Eradication Initiative, and the idea that OPV use in a post-cessation world presents a risk of seeding new cVDPVs is not new (9). The results of this study emphasize the immediacy of this risk, highlighting that the “honeymoon period”, during which the risks associated with OPV2 use remain low, is transient and could be quite brief. Near-term cVDPV2 outbreak responses must therefore serve the dual purposes of interrupting an observed chain of transmission and preventing the emergence of new ones, and all tools available should be applied during this honeymoon period to minimizing the chances that OPV2 use in outbreak response will become necessary in 2018 or beyond.

In the long-term, in the event that all VDPV2 lineages are extinguished, the polio-free world will remain at risk of reintroduction from accidental release of VDPV2, bioterrorism, and long-term poliovirus shedding from immunocompromised individuals (25, 26). Preclinical development of stabilized, live attenuated polio vaccines, aiming to provide mucosal immunity with reduced risk of causing cVDPV, is underway (27–29). Successful development of such a tool would provide a safer tool for outbreak elimination and immunity maintenance in the post-cessation world.

In conclusion, as population immunity to Type 2 poliovirus transmission declines in upcoming years, the use of OPV2 in outbreak response will present an increasing risk of seeding new cVDPV2 lineages, putting the entire cessation effort at risk. While exact transmission conditions are uncertain and vary across geographic contexts, and the probability of observing new VDPV lineages from pre-cessation OPV use should decline over time, this risk may grow to alarming levels within as little as 18 months. Without new tools to induce strong mucosal immunity, it is unclear whether this risk can be mitigated in the long term. In the short-term, this potential outcome implies a need for strategies that minimize the risk that OPV2 use will be needed in the future: maintaining high-quality surveillance systems, broadening near-term outbreak responses, strengthening access to IPV in routine immunization, negotiating access to currently inaccessible areas. In the long-term, continuing the push for new polio vaccines that can induce mucosal immunity with reduced risks of transmission or reversion is important in the event of accidental or intentional Type 2 poliovirus release into a highly susceptible population.

**Methods**

**Model specification**

The generic disease branch of the individual-based disease modeling software EMOD DTK v2.8 was used to model polio transmission (30); a complete specification of the employed model can be found in the supplemental material. Transmission takes place on a network of populations representing Level One administrative divisions (provinces) throughout 16 countries in West Africa (details in Supplement). Within a province, disease transmission dynamics are governed by a susceptible-exposed-infectious-susceptible equation system with partial immunity, and transmission between the provinces proceeds through individual-level migration. As ~98% of all cVDPV2 paralysis cases in the AFRO region have arisen in the cohort of children under 5 years of age (polio paralysis data from POLIS) (31), the model tracks only infection and transmission in the under-5 cohort.

**Modeling scenarios**

For simplicity, initial population immunity is treated as constant across the provinces. The cohort of children old enough to have been alive at cessation is initialized with one of two immunity profiles: one consistent with having experienced three rounds of OPV2 distribution, at 80% population coverage (independent coverage per round) and 50% vaccine take, and one with three rounds at 100% coverage and take (an unrealistic assumption, but useful for comparison). The cohort born since cessation is assumed to be OPV2-naïve, but depending on the scenario, they may receive zero or one doses of the inactivated polio vaccine (IPV), which induces strong protection from paralysis (humoral immunity), little protection against acquisition and onward transmission (intestinal mucosal immunity) in OPV2-naïve individuals, and a strong intestinal mucosal boosting response in OPV2-exposed individuals (details in Supplement) (17, 18, 20, 32, 33). No waning of immunity over time is modeled.

The survival of VDPV2 lineages from pre-cessation OPV2 use is not modeled here; it is simply assumed that an outbreak response has been triggered at a given time since cessation. The recent discovery in Borno State, Nigeria of cVDPV2 and WPV1 viruses from lineages unobserved for two and five years, respectively, demonstrates that prolonged unobserved circulation is feasible under suboptimal surveillance (8, 24, 34). In the model, an initial rapid-response OPV2 campaign targets Zamfara Province, Nigeria. Sixteen days later, an OPV2 campaign targets Zamfara and the bordering provinces Sokoto, Katsina, Kaduna, and Kebbi, followed by a joint OPV2\IPV campaign (taking advantage of IPV’s mucosal boosting effect in OPV-exposed individuals) and a third OPV2 campaign in the same provinces at four-week intervals.

It is unclear how (or whether) the transmissibility of the OPV2 virus changes during genetic divergence from the Sabin strain. Here, the infectivity of Sabin 2 virus is assumed to be some fraction *f* of the fully-reverted infectivity, and to follow an exponential approach to a final infectivity (Supplement Eq. 2). The values of the initial and final infectivities, as well as the timescale of the exponential approach, are varied in the modeling scenarios.

**Post-cessation simulations**

A Separatrix algorithm (14) is used to explore the risk of OPV2 survival in the outbreak response described above, as a function of the time since cessation and the mean per-person per-day migration rate. A new circulating lineage is considered to have arisen whenever there are individuals infected with the virus, outside of the original response region, nine months after the outbreak response. The algorithm is terminated after only two rounds; a first round in which 500 samples are cast throughout the 2D space, and a second in which 500 additional points are targeted to map the contour in parameter space that produces a 50% probability of this outcome.

**Availability of data and analysis code**

The code developed for running the simulations and analyzing outputs is available at <https://github.com/AMUG/OPV_PostCessation_Response_Project>.

Simulation outputs and all non-confidential supporting data is available at <https://www.dropbox.com/sh/vqk8878p1ch9oog/AACyBjP96-lh6qOOU_zgBIOCa?dl=0>.

Permission for access to the Polio Information System (POLIS) case and campaign databases, and use of WHO shapefiles, was granted to the Institute for Disease Modeling researchers through the World Health Organization. The boundaries and names shown and the designations used in the maps in the supplement of this document do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city, or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

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**Figure Legends**

Figure : Example output from a single Separatrix scenario, with R0f = 2.0, f = 0.5, λ= 60 days, N­IPV= 1, c= 1. The colored surface represents the probability that the OPV2 used in outbreak response continues to circulate, outside of the response region, 9 months after the final response campaign. The black solid line represents the parameter contour along which this probability is 50%. Gray crosses represent simulations in which this exportation and survival outcome occurs, and gray circles represent those in which it does not. The thin black dashed box indicates migration rates that are preferred by a calibration to a single travelling WPV1 outbreak in the region, in 2008. The distribution of simulated points illustrates the behavior of the algorithm; the first round of the separatrix algorithm broadly explores the space, and the second concentrates simulations around the contour of interest.

Figure : Position of the 50% separatrix line as the R0 profile of OPV2 varies, at constant λ= 60 days, N­IPV= 1, c= 1. The solid and dashed lines respectively indicate f=0.5 and f=0.25, while the cyan, red, grey, and black respectively indicate R0f values of 3, 2, 1.5, and 1.2. The thin black dashed box indicates migration rates that are preferred by a calibration to a single travelling WPV1 outbreak in the region, in 2008. The final R0 is observed to have the dominant effect, with the risk at a given time point and migration rate decreasing with R0f as expected. The initial R0 multiplier has a comparatively small effect, but a lower initial R0 does also mitigate the survival risk.

Figure : Position of the 50% separatrix line as number of IPV doses in routine immunization varies, at constant λ= 60 days, f = 0.5, c= 1. The dashed and solid lines respectively indicate N­IPV = 0 or 1, and the cyan, red, grey, and black respectively indicate R0f values of 3, 2, 1.5, and 1.2. The thin black dashed box indicates migration rates that are preferred by a calibration to a single travelling WPV1 outbreak in the region, in 2008. Under the assumptions made in this model regarding the population-level effects of IPV dosing, an additional dose of IPV in routine immunization in the cohort born after cessation provides a strong mitigating effect on the risk of OPV2 survival and circulation at low R0; the mitigating effect declines as the R0 of the reverted virus increases.

Figure : Dependence of the position of the 50% separatrix line on immunity levels in the cohort of children born before cessation: 100% immunity (dashed lines) vs. immunity induced by 3 rounds of OPV at 80% coverage, 50% take (solid lines). All lines at constant f=0.5, N­IPV= 1, c= 1, λ= 60 days. The cyan, red, grey, and black respectively indicate R0f values of 3, 2, 1.5, and 1.2. The final R0 is observed to have the dominant effect. The thin black dashed box indicates migration rates that are preferred by a calibration to a single travelling WPV1 outbreak in the region, in 2008. The effect of increasing immunity in the older cohort is largest at higher R0, as higher R0 facilitates more transmission through partially immune older children. However, the additional protection is somewhat modest (considering the extreme assumption of perfect immunity in all children born pre-cessation), indicating that the cohort of children born post-cessation rapidly becomes a dominant contributor to OPV2 transmission in this model.