**Risks of Type 2 Oral Polio Vaccine use in post-cessation outbreak response**

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**Abstract**

**Background**

In April 2016, the Sabin-strain Oral Polio Vaccine Type two (OPV2) was removed from routine and campaign immunization worldwide. Wild Type Two poliovirus (WPV2) was last observed in 1999 in India; since then, all Type Two paralytic poliomyelitis has been caused by the attenuated OPV strain, through vaccine-associated paralytic polio (VAPP) or circulating vaccine-derived polioviruses (cVDPV). Interrupting any transmission that continues post-cessation may require OPV2 in outbreak response, risking the seeding of new VDPV strains. The possibility of a vicious cycle, of outbreak responses seeding new cVDPV2 lineages, presents a fundamental risk to the success of OPV2 cessation.

**Methods**

The EMOD individual-based disease transmission model was used to investigate the risk of OPV2 use in outbreak response post-cessation, in a model of West African populations. Modeling begins with a hypothetical outbreak response in northwest Nigeria, and a new cVDPV2 lineage was considered to have established if the OPV2 virus escaped the response region and continued to circulate nine months post-response. The probability of this event is investigated in a variety of possible scenarios.

**Findings**

Under a broad range of realistic scenarios, the probability of OPV2 use in outbreak response establishing new cVDPV2 lineages in this model exceeds 50% in as little as 18 months or as long as four years post-cessation.

**Interpretation**

The risk of a vicious cycle of outbreak responses implies a need to focus programmatic activities towards the goal of mitigating the probability 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, and continuing the push for a new polio vaccine that can induce mucosal immunity without the attendant risks of transmission or reversion.

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**Background**

April 2016 marks a global cessation of the use of Oral Polio Vaccine Type Two (OPV2) in routine and campaign immunization, with all 155 OPV-using countries switching from the trivalent form to the bivalent form of OPV.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 transmission and genetic reversion to a more pathogenic phenotype (vaccine-derived poliovirus, or VDPV).3–6 In the years since the last paralytic WPV2 case, all Type 2 paralytic poliomyelitis has been caused by the genetic reversion of the attenuated OPV2 strain, through vaccine-associated paralytic polio (VAPP) or circulating vaccine-derived poliovirus (cVDPV). 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 use therefore presents clear public health benefits. However, the cessation of OPV2 use carries the implicit risk that some OPV2 transmission lineages will survive, necessitating the use of OPV2 in outbreak response and 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 in populations when introduced after relatively brief (1-3 year) interruptions in OPV use.10–13 The possibility of this vicious cycle represents a fundamental risk to the cessation of OPV2 use (this risk will also be present in future cessations of OPV types one and three, though likely smaller as their relative shares of historical cVDPV outbreaks are smaller).

This manuscript addresses the conditions under which OPV2 use in outbreak response could establish new chains of OPV2 transmission, and how this risk evolves as population immunity declines post-cessation. The manuscript proceeds as follows: a description of the model employed, calibration of the model, utilization of the model to investigate the risk of OPV2 use in a variety of scenarios, and a discussion of the findings with related policy implications.

**Methods**

**Model specification**

The generic disease branch of the individual-based disease modeling software EMOD DTK v2.8 was used to model polio transmission;14 a complete specification of the 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 (all polio paralysis data from POLIS),15 the model tracks only infection and transmission in the under-5 cohort.

**Modeling scenarios**

Many factors affect the risk of an outbreak response activity establishing new VDPV lineages, including population immunity at the time of outbreak response, the base reproductive rate R0 of OPV2, which may change during genetic reversion to a more pathogenic phenotype, and connectedness of the provinces. 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, the risk of seeding VDPV2 is investigated as a function of the time since cessation and the mean per-person per-day migration rate.

For simplicity, initial population immunity is treated as constant across the provinces. The cohort of children old enough to have been alive at cessation has one of two immunity profiles: one consistent with having experienced three rounds of OPV2 distribution, at 80% population coverage (independent in each 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 OPV-naïve, but depending on the scenario, they may receive zero, one, or two doses of the inactivated polio vaccine (IPV), which induces strong protection from paralysis (humoral immunity) but little protection against acquisition and onward transmission (mucosal immunity). No waning of immunity over time is assumed.

The survival of a VDPV2 lineage from pre-cessation OPV2 use is not modeled here; rather, it is simply assumed that an outbreak response has been triggered after some time has passed since cessation. The recent discovery in Borno State, Nigeria of cVDPV2 and WPV1 viruses from lineages unobserved for two and five years, respectively, indicates that prolonged unobserved circulation is feasible under suboptimal surveillance conditions.8,16,17 In the model, an initial rapid response campaign with OPV2 first takes place in Zamfara Province, Nigeria. 16 days later, an OPV2 campaign takes place in Zamfara Province plus the bordering provinces Sokoto, Katsina, Kaduna, and Kebbi, followed by a joint OPV2\IPV campaign and a third OPV campaign in the same provinces at four-week intervals.

It is unclear how (or whether) the transmissibility of the OPV2 virus changes during its genetic reversion. In this work, the infectivity of OPV2 virus is assumed to begin at some fraction *f* of the final infectivity, and to follow an exponential approach to a final, limiting infectivity; Eq. 2 in the Supplement provides the functional form employed. The values of the initial and final infectivities, as well as the timescale of the exponential approach, are varied in the modeling scenarios.

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| Quantity varied | Values |
| Final base reproductive rate of reverted VDPV2 (R0f) | {1·2, 1·5, 2·0, 3·0} |
| Initial reproductive rate of OPV2 as fraction of final R0 (*f*) | {0·25, 0·5} |
| Exponential timescale of R0 reversion (*λ*) | {60, 150} |
| IPV doses in children born post-cessation (NIPV) | {0, 1, 2} |
| Distance-dependence of migration rates (*c*) | Inverse-linear, inverse-square |
| Immunity profile of pre-cessation child cohort | Three OPV campaigns at 80% coverage and 50% take, or three OPV campaigns at 100% coverage and 100% take |

Table 1: Description of parameters varied in the different simulation scenarios.

**Post-cessation simulations**

A Separatrix algorithm18 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.

**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 1-4 all present comparisons at the more moderate immunity profile in the pre-cessation birth cohort. The color surface shows the imputed risk throughout the space of mean migration rate and time since cessation; the gray crosses and circles represent simulations in which a new lineage did or did not arise, respectively, as defined above; the blue 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 OPV2 survival risk is 50%. In this scenario, this line indicates that the risk reaches 50% around 2·5-3·5 years post-cessation, depending on the migration rate.

It is difficult to visually compare the full risk surfaces of multiple scenarios, so the 50% separatrix lines are used to compare the relative risk in the various scenarios. 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.

Figure 3 illustrates how the number of IPV doses in routine immunization (RI) affects the risk of OPV2 survival in this model, with dotted, solid, and dashed lines indicating zero, one, and two doses of RI in IPV, respectively. Coverage of routine immunization is assumed to be 80%. Gray and black lines indicate R0f values of three and two, respectively. While herd immunity effects of IPV are evident in developed nations, where the oral-oral transmission route likely dominates,19,20 they are poorly characterized in developing countries where the fecal-oral transmission route likely dominates. While challenge studies find that IPV-immunized children exhibit a small reduction in acquisition of mOPV, it is unclear how this reduction translates to natural exposure levels.21,22 Similarly, IPV-immunized children are observed to shed less poliovirus than naïve children upon OPV challenge, but it is unclear how or if this reduction translates to transmission in close-contact and community settings in regions of poor sanitation.21,22 In this study, each dose of IPV (in the absence of prior OPV exposure) is assumed to confer a 10% reduction in the recipient’s effective exposure and a 10% reduction in an infected recipient’s onward infectivity in the natural transmission setting (Supplement). Under these assumptions about IPV-only immunization, Figure 3 shows that each dose provides substantial protection against OPV2 survival, shifting the 50% separatrix line by as much as a year per dose at a fixed migration rate.

Changing the distance-dependence in the gravity model of migration or the reversion rate of OPV2 transmissibility 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.

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 with increasing transmissibility, as at higher R0, the virus is increasingly able to recruit partially immune children into the transmission chain. The additional protection provided by perfect immunity in the older cohort is also relatively modest given the extreme nature of this immunity assumption, adding at most about 1 year of protection in the preferred migration space within this model.

**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 mucosal immunity. Of course, any observed cVDPV must be extinguished, 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 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 within two to four years post-cessation could potentially create a cascade of new outbreaks.

It is unclear whether this risk can be mitigated without new tools that can induce mucosal immunity but cannot transmit efficiently or genetically revert. Therefore, in the near-term, the polio eradication program should aim to reduce the chance that outbreak response activities will be necessary in the future.

1. **Maintain vigilance and strengthen both paralysis-based and environmental poliovirus surveillance.** In the absence of OPV2 use post-cessation, the emergence of cVDPV2 relies on the unobserved survival of VDPV2 lineages seeded pre-cessation. The optimal way to ensure that highly risky OPV2 use will not be required in the future is to identify and extinguish all surviving lineages immediately, while population immunity remains high.
2. **Implement widespread outbreak response in the near-term.** Emergence of VDPV2 in the near-term will be an effective indicator of locally low population immunity in a world in which immunity is still high. The use of OPV2 in the near-term likely does not present substantially more risk than did its use immediately pre-cessation. Widespread cVDPV circulation has been observed in the past,23,24 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 broadly geographically targeted, both to ensure interruption of the observed transmission chain and to raise population immunity in regions surrounding the emergence. Particular attention should be paid to neighboring districts or countries known to have imported wild or vaccine-derived poliovirus in the past from the emergence region.
3. **Ensure access to IPV in routine immunization**. Under the (admittedly uncertain) assumptions about IPV-induced musical immunity used in this study, high-coverage IPV immunization can substantially mitigate the OPV2 survival risk. Even if IPV induces no herd effect, individual protection against paralysis is still valuable, reducing any burden due to VDPV outbreaks or VAPP caused by OPV response.
4. **Negotiate 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 obvious opportunities for VDPV2 lineages to circulate unobserved. Borno state, Nigeria, large sections of which have been inaccessible for years due to Boko Haram activity, has recently been found to have been harboring cVDPV2 (paralysis onset March 2016, most recent observed relative from May 2014) and WPV1 (paralysis onsets in July 2016, most recent observed relatives from 2011).17,25 These discoveries highlight the existential risk that inaccessible areas present the polio eradication and OPV cessation efforts. Obtaining access to inaccessible populations will be necessary to ensure a polio-free world.
5. **Continue research into better tools for inducing mucosal immunity**. 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.26,27 The development of a new vaccine, capable of providing mucosal immunity without the attendant risks of transmissibility and reversion, would provide a path to a polio-free world if the current cessation plan fails.

Most of these items are already programmatic priorities, 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 to the program during this honeymoon period should be applied to minimizing the chances that OPV2 use in outbreak response will become necessary in 2018 or beyond.

**Conclusions**

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 VDPV events that would trigger new outbreak response activities should decline over time, this risk may grow to alarming levels within as little as 2 years. 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 to focus programmatic activities now towards the goal of mitigating the probability 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, and continuing the push for a new polio vaccine that can induce mucosal immunity without the attendant risks of transmission or reversion.

**Declaration of Interests**

The author declares no competing interests.

**Role of the Funding Source**

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**Patient and other consents**

Permission for access to the Polio Information System (POLIS) case and campaign databases was granted to the Institute for Disease Modeling researchers through the World Health Organization.

**Authors’ contributions**

KM conceived the study, designed and ran all simulations, and drafted the manuscript.

**Availability of data and analyses**

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 supporting data not protected by data sharing agreements is available at (link to come).

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**Figures**



Figure 1: 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 2: 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 3: 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 dotted, solid, and dashed lines respectively indicate N­IPV = 0, 1, 2, while the grey, and black respectively indicate R0f values of 2 and 3. 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, with each additional dose shifting the separatrix line by a few months to as much as a year at a constant migration rate.



Figure 4: 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. 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.

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