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# Evaluation of Response Scenarios to Potential Polio Outbreaks Using Mathematical Models

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Appropriate response to polio outbreaks represents an important prerequisite for achieving and maintaining global polio eradication. We use an existing dynamic disease transmission model to evaluate the impact of different aspects of immunization campaigns in response to polio outbreaks occurring in previously polio-free areas. This analysis yields several important insights about response strategies. We find that delay in response represents a crucial risk factor for occurrence of large outbreaks and we characterize the tradeoffs associated with delaying the initial response to achieve better population coverage. We also demonstrate that controlling most potential outbreaks will likely require at least three immunization rounds, although the impact of the optimal interval between rounds varies. Finally, long after oral poliovirus vaccine cessation the choice of target age groups during a response represents an important consideration.

**KEY WORDS:** Epidemic modeling; optimization; outbreak response; polio

## 1. INTRODUCTION

The Global Polio Eradication Initiative (GPEI) successfully reduced the annual global burden of paralytic poliomyelitis caused by wild polioviruses (polio cases) from an estimated 350,000 at its launch in 1988 to less than 2,000 annual cases in recent years.(1) Due to the absence of circulating wild polioviruses and difficulties sustaining high vaccination coverage, many countries that recently achieved polio-free status proved vulnerable to the risk of poliovirus reintroductions. From 2002 to 2005, 21 previously polio-free countries experienced outbreaks due to reintroductions of the virus, causing over 1,000 polio cases in 2005 alone.(1,2) Successfully and rapidly controlling these outbreaks represents a key factor in the achievement of global polio eradication. Immediately after global wild poliovirus eradication, a high probability still exists for transmissible vaccine-derived polioviruses (VDPVs) to cause one or more outbreaks. A lesser possibility also exists of reintroduction of wild poliovirus through an unintentional release of virus from a laboratory or from an inactivated poliovirus vaccine (IPV) manufacturing facility, or an unpredictable risk from an intentional release of the virus.(3) With the cessation of routine oral poliovirus vaccine (OPV) use emerging as a likely component of posteradication policy,(4) containing potential post-OPV cessation outbreaks represents the most prominent challenge for the post-OPV cessation era. Failure to plan for and manage these events could potentially result

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in spread of the virus across large geographic areas,[5] and could possibly culminate in the need to restart routine vaccination and a likely return to higher endemic disease levels in developing countries.

Following the confirmation of polio cases in a previously polio-free country (or region), current immunization response strategies typically include a rapid mop-up immunization campaign in the affected communities, followed by large-scale campaigns in the form of national immunization days (NIDs) or sub-NIDs (sNIDs) as appropriate.[6] These campaigns typically consist of two or more rounds and each aims to administer a dose of monovalent OPV (mOPV) or trivalent OPV (tOPV) to all children younger than five years of age, regardless of immunization history, in a short period of time (i.e., two to seven days). The GPEI increasingly relies on mOPV type 1 and type 3 for stopping transmission of remaining types 1 and 3 wild polioviruses because of its superior single-dose seroconversion ("take") rates, although tOPV remains a viable option for responding in situations where several serotypes circulate or mOPV is not readily available,[7] or in the event of type 2 VDPV outbreaks. The interval between tOPV response rounds commonly ranges between four and six weeks to avoid interference of serotypes that would result in lower primary take rates. However, depending on logistical constraints, responding with mOPV rounds at shorter intervals may not affect take rates among seronegative recipients and may more quickly raise population immunity.

This analysis uses an existing mathematical model for polio outbreaks[8] to evaluate the impact of different response scenarios on the number of polio cases in the outbreak. We emphasize that the endpoint in this analysis is not outbreak control but the number of polio cases occurring in the two years following virus introduction. This model assumes predefined, closed, and homogeneously mixing populations.[8] Consequently, it does not address the possibility of exportations of the virus to other populations that would amplify the size of the total outbreak scenario or that could imply that the occurrence of cases beyond the two years following virus introduction remains possible. Nevertheless, we expect that evaluation of the partially controllable aspects of the outbreak response (e.g., the delay between detection and response of the outbreak, number of vaccination rounds and their coverage, choice of vaccine used for the response, interval between rounds, and target age groups of the response) will focus attention on priorities and tradeoffs and prove helpful in informing response plans.

Fig. 1 illustrates the multiple steps that occur between virus introduction and initiation of the first

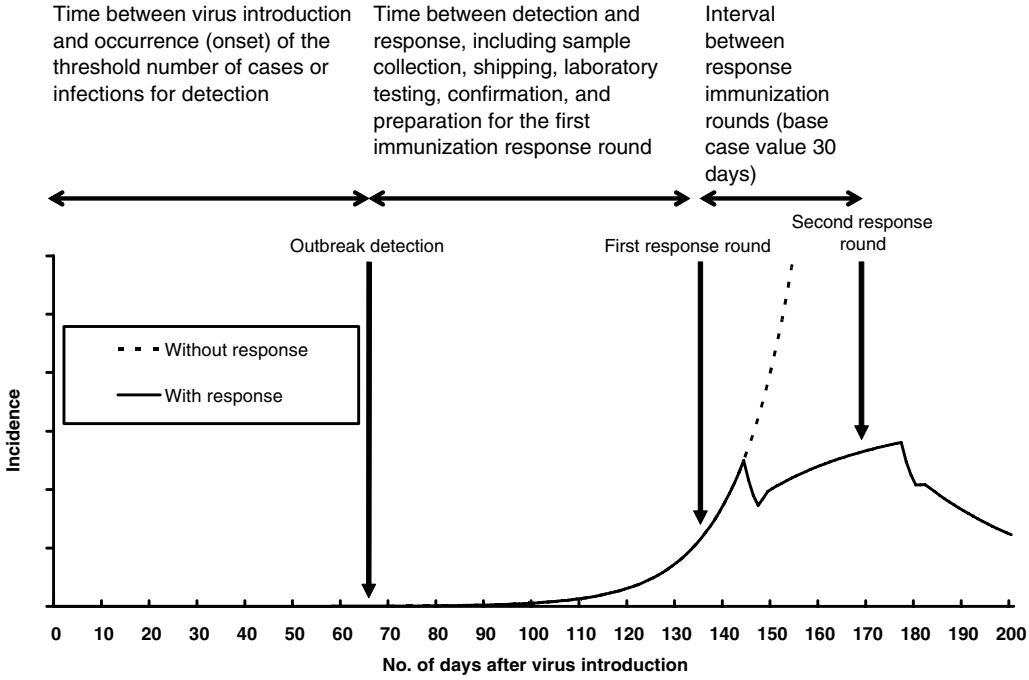


**Fig. 1.** Time intervals in an outbreak response.

round of response for a hypothetical outbreak. The time between virus introduction and detection depends on the conditions in the population (immunity and the basic reproductive number $R_0$) that determines the initial rise in incidence, and on the type of surveillance, which determines the threshold of detection (e.g., onset of the first clinical case, onset of the $n$th clinical case, or a signal of a certain number of cumulative infections circulating found with environmental surveillance). The time between detection and response includes the time from the recognition of the threshold case or infection through the preparation of the logistics for response. This includes the time required for logistics of specimen transport, virus isolation, confirmation, and notification, which depend in part on the laboratory network methods and proximity. It also includes any communications between governments and health officials and others who collectively share responsibility for response. For brevity, we refer to the time between initial detection and the actual response as the response *delay*. Besides the delay in response, we recognize that immunity does not occur immediately after vaccine administration (i.e., if successful, vaccination provides partial immunity from infection and full disease immunity in approximately seven days).[8] A delay of approximately 10 days also occurs between infection and onset of paralysis.[8]

In the next section, we describe the methodology and framework for this analysis. In the subsequent section, we present the results organized into model output analyses that yield specific insights. Finally, we discuss the results and limitations and identify potential areas of future work on response strategies. An Appendix provides complementary results and lists the full set of scenarios that we considered and discussed.

## 2. METHODS

For all response rounds, we assume the use of mOPV or tOPV live virus vaccine, which excludes potential use of IPV to control importations and outbreaks. With the use of OPV, in addition to reducing the susceptibility of individuals who receive vaccine directly, response rounds also reduce susceptibility of between 20 and 60% of all remaining susceptibles (depending on the income level) through secondary OPV infections.[8] We use our previously developed polio outbreak model to evaluate response scenarios by varying inputs in the model.[Ref.8,Table3] including the time from detection to the first response round, number of immunization rounds and their coverage, interval between rounds, and choice of vaccine. We held the duration of immunization rounds fixed at its base case value of three days.[8] The target age groups include all cohorts born since cessation of vaccination, rounded to the next multiple of 5 (i.e., 0–4 year olds during the first five years after cessation, 0–9 year olds during the next five years, although we note that for large populations this would imply important cost implications and present logistical challenges). Unless noted otherwise, we assume the response targets only children younger than five years of age in the event of continued routine vaccination (OPV or IPV). For purposes of this analysis, we define the size of an outbreak as the total number of paralytic polio cases occurring in the two years following the virus introduction.[8]

While we adopt all base case values from Tables 1 and 3 from Duintjer Tebbens *et al.*,[8] this model requires further assumptions about conditions and policies in the affected population, including the population size, value of $R_0$, income level, detection threshold (which follows from the surveillance policy), and population immunity profile at the beginning of the outbreak. The model computes the latter from assumptions about the vaccination policy, number of years since OPV cessation, number of years since a country conducted supplemental immunization activities (SIAs, i.e., NIDs, SNIDs, or mop-up campaigns) prior to OPV cessation, and routine vaccination coverage since the last year with SIAs. For pre-OPV cessation outbreaks, we ran response scenarios that varied delay from 15 to 75 days in 10-day increments ($n = 7$), coverage of the first round from 30% to 90% in 15% increments ($n = 5$), and vaccine use options of mOPV for all three rounds, tOPV for all three rounds, and tOPV for one round followed by two rounds of mOPV ($n = 3$). This led to a total of 105 scenarios (i.e., $7 \times 5 \times 3$), which we ran for 72 different permutations of conditions that varied income level (low or lower-middle), population size (10 or 100 million), number of years since last regular SIAs (0, 3, or 5), $R_0$ (low medium or high medium[8]), and routine vaccination coverage (25%, 50%, and 75%) (i.e., $2 \times 2 \times 3 \times 2 \times 3$ permutations). For post-OPV cessation outbreaks, we ran 47 response scenarios, including 35 scenarios that varied delay ($n = 7$) and coverage of the first round ($n = 5$) (i.e., $7 \times 5$ scenarios) and 12 scenarios that held the delay at 25 days while varying the interval between rounds (15 or 30 days), coverage of the second round (70%, 80%, or 90%), and the number of rounds (two or three) (i.e., $2 \times 3 \times 2$ scenarios). We

**Table I.** Outbreak Size as a Function of the Delay Between Outbreak Detection and Initiation of the First Response Round for Different Income Levels, Routine Vaccination, and Years Since OPV Cessation

| Income Level | Routine Vaccination | Year[c] | Number of Cases Assuming Low-Medium $R_0$s[a] | | | | Number of Cases Assuming High-Medium $R_0$s[b] | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Delay of 15 Days | Delay of 35 Days | Delay of 55 Days | Delay of 75 Days | Delay of 15 Days | Delay of 35 Days | Delay of 55 Days | Delay of 75 Days |
| LOW | IPV | 1st | 3.5 | 6.1 | 10 | 18 | 11 | 30 | 79 | 200 |
| LOW | IPV | 5th | 11 | 27 | 67 | 160 | 47 | 190 | 610 | 1,500 |
| LOW | IPV | 20th | 160 | 690 | 2,100 | 4,200 | 1,100 | 3,200 | 5,900 | 7,600 |
| LOW | No routine | 1st | 3.8 | 6.9 | 12 | 23 | 12 | 34 | 92 | 240 |
| LOW | No routine | 5th | 14 | 42 | 120 | 360 | 64 | 300 | 1,100 | 2,900 |
| LOW | No routine | 20th | 93 | 670 | 3,600 | 11,000 | 450 | 3,800 | 13,000 | 19,000 |
| LMI | IPV | 1st | <1 | <1 | <1 | <1 | 4.4 | 7.2 | 12 | 19 |
| LMI | IPV | 5th | 2.5 | 3.4 | 4.6 | 6.3 | 15 | 32 | 68 | 140 |
| LMI | IPV | 20th | 18 | 39 | 79 | 150 | 300 | 610 | 1,100 | 1,600 |
| LMI | No routine | 1st | <1 | <1 | <1 | <1 | 4.8 | 8.2 | 14 | 25 |
| LMI | No routine | 5th | 3.3 | 5.4 | 8.7 | 14 | 16 | 43 | 110 | 270 |
| LMI | No routine | 20th | 12 | 41 | 130 | 410 | 60 | 340 | 1,600 | 5,000 |
| UMI | IPV | 1st | <1 | <1 | <1 | <1 | 2.1 | 2.6 | 3.3 | 4 |
| UMI | IPV | 5th | <1 | <1 | <1 | <1 | 5.2 | 8.4 | 14 | 22 |
| UMI | IPV | 20th | 4.2 | 6.0 | 8.6 | 12 | 110 | 230 | 410 | 690 |
| UMI | No routine | 1st | <1 | <1 | <1 | <1 | 2.3 | 3.2 | 4.5 | 6.2 |
| UMI | No routine | 5th | 1.7 | 2.1 | 2.7 | 3.3 | 6.6 | 13 | 26 | 52 |
| UMI | No routine | 20th | 5.1 | 11 | 24 | 53 | 26 | 110 | 440 | 1,600 |

[a]The low-medium $R_0$ value equals 10 in low-income countries, 8 in lower-middle-income countries, and 6 in upper-middle-income countries.
[b]The high-medium $R_0$ value equals 13 in low-income countries, 11 in lower-middle-income countries, and 9 in upper-middle-income countries.
[c]Year after OPV cessation. Conditions assume absence of supplemental immunization activities for three or five years prior to OPV cessation for low- and middle-income countries, respectively. Response rounds cover 90% of children younger than five years of age, except for the case of no routine vaccination 20 years after OPV cessation, in which case they cover everyone younger than 20 years of age.
IPV = inactivated poliovirus vaccine; LMI = lower-middle-income country; LOW = low-income country; OPV = oral poliovirus vaccine; UMI = upper-middle-income country.

tested these scenarios on 216 different permutations of conditions that varied income level, routine vaccination policy, population size, number of years since OPV cessation, surveillance policy, and $R_0$ (i.e., $3 \times 2 \times 3 \times 3 \times 2 \times 2$ permutations). The post-OPV cessation conditions further assume absence of regular SIAs for three or five years before OPV cessation for low- and middle-income countries, respectively (see Tables A1 and A2 in the Appendix for details).

We characterized our results using a number of different metrics. To quantify the impact of a change in one characteristic of a response scenario (e.g., delay, coverage, choice of vaccine in each round), we focus on what we call the *average effect*. Given one permutation of the conditions (i.e., an outbreak in a country with a particular income level, population size, $R_0$, surveillance policy, immunization policy, and routine coverage occurring a certain number of years after OPV cessation), we define the average effect as the average size of the outbreak (i.e., $C$ paralytic polio cases) for all possible scenarios with one specific characteristic ($j$) set at the value that typically yields larger outbreaks ($\underline{C}_{j=\text{High}}$) minus the average size of the outbreak for all possible scenarios with the same specific characteristic set at the value that yields smaller outbreaks ($\underline{C}_{j=\text{Low}}$) as shown in Equation (1):

$$\text{Average effect (for a change in } j) = \underline{C}_{j=\text{High}} - \underline{C}_{j=\text{Low}}, \quad (1)$$

where the underscore ($\underline{C}$) indicates averaging over all possible scenarios. For example, to find the average effect of delay, we would first specify the permutation of the conditions and then find the average size of outbreaks for all of the scenarios with the delay set at 75 days minus the average size of outbreaks for all of the scenarios with the delay set at 15 days:

$$\text{Average effect (for a change in delay from 75 to 15 days)} = \underline{C}_{j=75} - \underline{C}_{j=15}. \quad (2)$$

Thus, the average effect depends on the range for the characteristic considered. We also compute *average reductions* in the form of ratios of the average effect of a specific characteristic $j$ divided by the average size

of outbreak at the low value ($\underline{C}_{j=\text{Low}}$), or equivalently as

$$\text{Average reduction (for a change in } j) = (\underline{C}_{j=\text{High}} - \underline{C}_{j=\text{Low}})/\underline{C}_{j=\text{High}}. \quad (3)$$

To quantify the relative importance of a characteristic $A$ compared to another characteristic $B$, we focus on the *effect ratio of A to B*, defined as the average effect of changing characteristic $A$ divided by the average effect of changing characteristic $B$ such that

$$\text{Effect ratio of } A \text{ to } B = (\underline{C}_{A=\text{High}} - \underline{C}_{A=\text{Low}})/(\underline{C}_{B=\text{High}} - \underline{C}_{B=\text{Low}}). \quad (4)$$

To graphically illustrate the two-way interactions of effect ratios, we use contour plots that present *isocase* lines showing values of the two characteristics ($A$ and $B$) for which the outbreak size remains invariant, comparable to isobar lines on a weather map or contour lines on a topographical map. As described above, the average effects, reductions, and effect ratios all average the outbreak sizes over response scenarios and not over permutations of conditions. To explore the impact of different permutations of conditions, we also considered the distributions of average effects across the evaluated permutations of conditions and provide quantitative information about these distributions in the form of basic statistics (i.e., the mean, 5th quantile, and 95th quantile). We note that the probabilistic interpretation of the quantiles holds only if the assumption of equal likelihood for each permutation holds. We performed all analyses using Mathematica™ (Wolfram Research, Inc., Champaign, IL).

## 3. RESULTS

Our analysis demonstrates that the response delay impacts the outbreak size substantially. Table I shows selected results obtained by varying the delay across the different permutations of post-OPV cessation conditions for low-medium and high-medium values of $R_0$. The results in Table I correspond to a hypothetical outbreak in a population of 10 million people with acute flaccid paralysis surveillance with response scenarios involving three mOPV rounds achieving 90% coverage at 30-day intervals. The table demonstrates the importance of the response delay, revealing substantial differences between the extremes in many cases. Table I also shows that high-medium $R_0$ values lead to a larger number of cases and to a smaller relative difference between the extremes of the response delay. We observed a similar pattern when modifying assumptions about surveillance or population size. Averaging across all of the 288 permutations evaluated we found that reducing the delay from 75 to 15 days led to an approximately 68% reduction in the number of cases. Excluding the (39) permutations for which no significant outbreak occurred (i.e., no detection within two years minus the shortest delay of 15 days), the average reduction increased to 79%.

Given the importance of a relatively rapid response, we explored the tradeoffs associated with conducting the first response round earlier but with lower coverage, which represents a real dilemma for managing an outbreak response. Fig. 2 compares pre-OPV cessation response scenarios assuming that the first round occurs either 45 days after detection with 90% coverage or 15 days after detection with 75% coverage. The conditions represent a hypothetical low-income country of 10 million people that conducts routine OPV immunization with 50% coverage. In either response scenario, the coverage of the subsequent two rounds remains 90%. The figure demonstrates that even with the reduced coverage of the first round in the rapid scenario the early response appears strong enough to substantially limit the growth of the outbreak that would otherwise occur in the 45-day scenario. For this permutation, we observed a reduction in total outbreak cases from approximately 11 in the 45-day response scenario to approximately 5 in the 15-day response scenario. More generally, among the 288 permutations of post-OPV cessation conditions we observed a reduction in outbreak size between the two scenarios averaging 58% and ranging as high as 96% (excluding 39 permutations in which we observed no reduction because the outbreaks died out naturally).

Fig. 3 shows a post-OPV cessation example with the number of outbreak cases as a function of coverage of the first round (ranging from 30% to 90%) and the response delay (ranging from 15 to 75 days) in the form of a contour plot. Each different shade of gray represents 1/10th of the range in number of cases (in this figure the range goes from 14 to 537 cases, so each change in shade corresponds to an increment of approximately 52 cases). The narrowness of the shades at high delays illustrates that the number of cases rapidly increases in that range. The *isocase* lines between shades indicate values of the coverage and delay for which the outbreak size remains invariant. For example, the combination of coverage of 30% and a delay of 25 days produces approximately the same number of outbreak cases as the combination of coverage of 90% with a delay of 33 days. For this

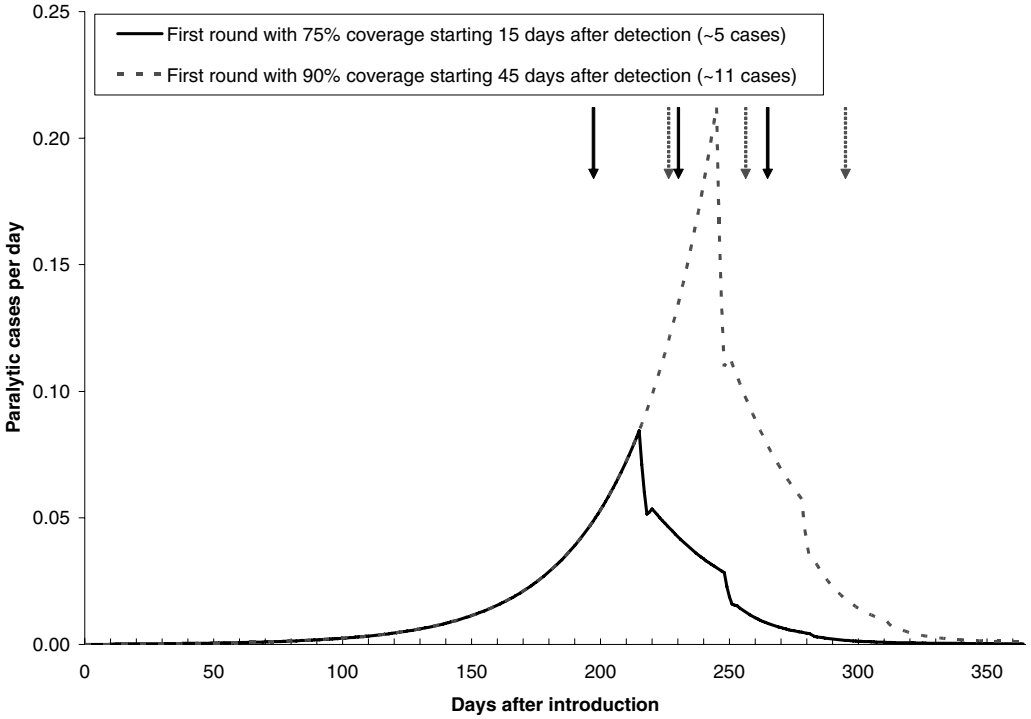


**Fig. 2.** Impact of a pre-OPV cessation response scenario with rapid first round in a low-income country with 10 million people, 50% routine OPV vaccination coverage, acute flaccid paralysis surveillance, and low-medium $R_0$ (=10), which conducted no supplemental immunization activities in the three years prior to the outbreak. Both response scenarios target children less than five years of age with mOPV and occur at 30-day intervals with the second and third rounds achieving 90% coverage. Arrows indicate the timing of response rounds.

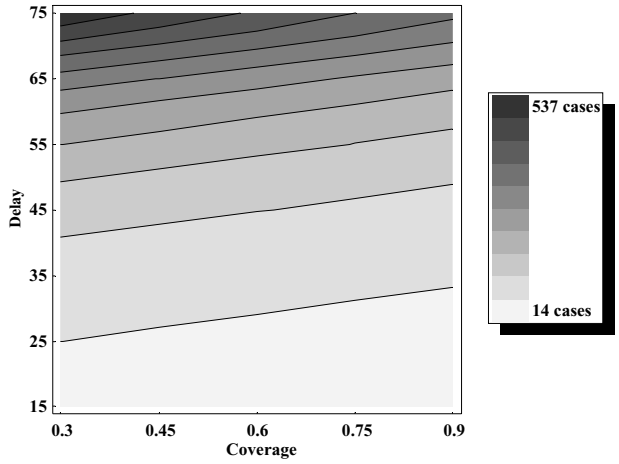


**Fig. 3.** Outbreak size as a function of response delay and coverage in a low-income country with 10 million people, no routine immunization for five years after OPV cessation, acute flaccid paralysis surveillance, and low-medium $R_0$ (=10). All response scenarios target children less than five years of age with mOPV and occur at 30-day intervals with the second and third rounds achieving 90% coverage.

permutation of conditions, the average effect of reducing the delay from 75 to 15 days equals approximately 425 cases and that of increasing the coverage from 30% to 90% equals approximately 63 cases. This implies that the reduction in delay prevents on average approximately seven times more cases than the coverage increase (i.e., the effect ratio of delay to coverage equals approximately 7 for this permutation). We emphasize that the number of cases depends on the conditions. For example, Fig. 4 shows that if we assume population immunity based on routine IPV immunization, we see different widths between the isocase lines and fewer polio cases, although each day of reduction in delay "buys" an even greater percentage of increased coverage of the first round (i.e., the effect ratio of delay to coverage equals approximately 9 for the permutation shown in Fig. 4).

Overall, the average reduction resulting from decreasing the delay from 75 to 15 days equaled 77% for 185 post-OPV cessation conditions (this excludes 31 permutations for which no significant

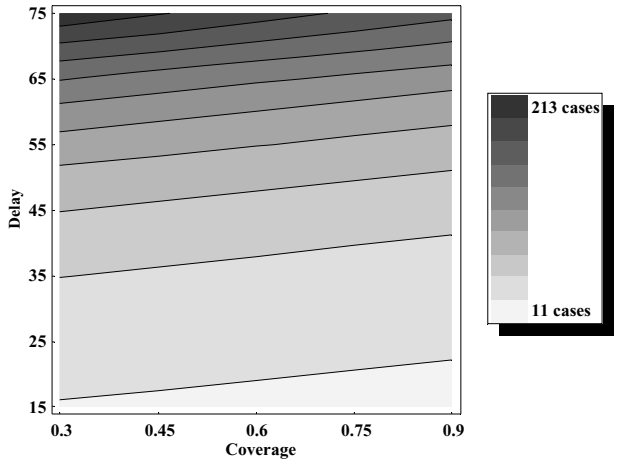


**Fig. 4.** Outbreak size as a function of response delay and coverage in a low-income country with 10 million people, IPV routine immunization (68% coverage) for five years after OPV cessation, acute flaccid paralysis surveillance, and low-medium $R_0(=10)$. All response scenarios target children less than five years of age with mOPV and occur at 30-day intervals with the second and third rounds achieving 90% coverage.

outbreak occurred) and 81% for 64 pre-OPV cessation permutations (excluding 8 permutations without significant outbreaks). We found an average relative effect of increasing coverage from 30% to 90% of approximately 22% for post-OPV cessation permutations and 24% for pre-OPV cessation permutations. In general, we observed comparably high effect ratios of delay to coverage among the 185 permutations of post-OPV cessation conditions averaging approximately 8 (range 3–20). For pre-OPV cessation outbreaks, we also found high ratios averaging approximately 7 (range 5–9) across 64 permutations with significant outbreaks (see Fig. A1).

Ideally, responders would achieve both rapid response and high coverage with multiple rounds. Given that we assumed three response immunization rounds above, we considered the impact of omitting the third round. To quantify the impact of the third response round for post-OPV cessation outbreaks, we considered the average reduction for six response scenarios with three rounds compared to two rounds (we did not test the impact of the third immunization round for pre-OPV cessation outbreaks). Across the 216 permutations of post-OPV cessation conditions, the reduction averaged 10% (12% if we omit permutations without a significant outbreak), indicating that the third round generally prevented few cases compared to the first two rounds. However, we observed an important skew in the distribution of the ratios, with outliers as high as 89% (see Fig. A2). Thus, for some conditions the third round represented an essential step in controlling the modeled outbreak. Fig. 5a shows an example of a typical outbreak for which the third round yielded little impact and Fig. 5b shows an atypical outbreak for which omitting the third round substantially increased the size of the outbreak. The conditions in Fig. 5a correspond to a low-income country five years after cessation (i.e., the same conditions as in Fig. 3), while those in Fig. 5b represent an upper-middle-income country 20 years after switching to IPV. Based on the 216 permutations of conditions we performed, the factors that make the average reduction for three versus two rounds high include a long time since OPV cessation, low secondary OPV rates due to the response rounds (correlating with high income), large populations, high $R_0$s, and routine IPV immunization. Routine IPV immunization represents a factor due to the way we modeled the target group of the response, which includes only children younger than five years of age, while the response with no routine would target everyone born since cessation. Given practical difficulties in determining in real time whether the conditions of an outbreak require two or more rounds, response planners should prepare to conduct at least three response rounds from the outset in a post-OPV cessation world.

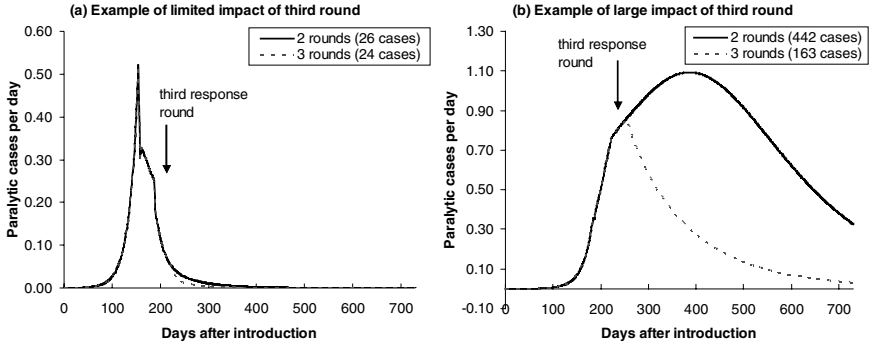


**Fig. 5.** Impact of the third immunization round. Panel (a) shows an outbreak with the conditions as in Fig. 3, while panel (b) shows an outbreak in an upper-middle-income country with 10 million people, with acute flaccid paralysis surveillance, 20 years after the switch from OPV to IPV, and high-medium $R_0$ $(=9)$. Both response scenarios assume a delay of 25 days and cover 90% of children younger than five years of age with OPV with each round occurring at 30-day intervals.

| Delay (Days) | Mean Outbreak Size If the Response Targets Only Children Younger Than 5 Years of Age (Range, Polio Cases) | Mean Outbreak Size If the Response Targets Everyone Born Since Since OPV Cessation (Range, Polio Cases) | Mean Reduction in Outbreak Size Size (Range, %) |
|---|---|---|---|
| 25 | 1,033 (5–13, 878) | 227 (3–2, 575) | 62 (16–94) |
| 45 | 2,747 (6–37, 064) | 1,003 (4–15, 398) | 53 (3–91) |
| 75 | 6,725 (10–72, 989) | 4,467 (6–63, 692) | 37 (0–88) |

**Table II.** Impact of the Target Age Groups on Outbreak Size for Different Delays, Averaged Over 36 Permutations of Conditions with Routine IPV Immunization Yielding Significant Outbreaks (Assuming 20 Years Since OPV Cessation)

We noted the importance of the assumption that the response strategy targets only children younger than five years of age in routine IPV immunization settings, regardless of the time since OPV cessation. We explored this by comparing the number of outbreak cases with this assumption to the number of cases that occur with a response strategy that targets all individuals born since OPV cessation. Table II shows the average impact of the choice of target age groups based on 36 permutations of conditions with routine IPV immunization yielding significant outbreaks and assuming 20 years since OPV cessation. Clearly, choosing the target groups plays an important role in the estimated outbreak sizes, with the relative impact increasing as the response delay decreases.

We emphasize that interpreting the impact of successive response rounds in the outbreak model requires caution because we assume a uniform coverage distribution among the target population. Consequently, each round moves a proportion of the *remaining* infectibles to groups of lesser potential to transmit infection (and full immunity to polio disease) through successful vaccinations and secondary OPV infections.[8] However, if in a real response the second and third rounds (and beyond) only reach the same children and communities again and again (i.e., leaving pockets of susceptibles untouched), then the incremental impact of these subsequent rounds diminishes depending on the number of inaccessible susceptibles (see Fig. A3). Ensuring that vaccine reaches previously unvaccinated children remains critical to effective outbreak control.

We also explored the impact of potentially reducing the interval between response rounds. We analyzed the average reduction in outbreak size of going from a 30-day to a 15-day interval for six response scenarios for post-OPV cessation conditions (we did not test the impact of the interval between rounds for pre-OPV cessation conditions). The average reduction ranged from −30% (i.e., an increase in cases of approximately 30%) to +45% across the 216 permutations of conditions we ran, and we observed a relatively symmetric distribution with a mean of –3%, a 5th quantile of –15%, and a 95th quantile of 12% (see Fig. A4). Thus, the length of the interval between rounds does not generally impact the size of the outbreak substantially and neither the 15- nor 30-day interval appears superior in all situations. The optimal interval depends on the kinetics of the specific outbreak, and in particular on whether or when the outbreak reaches its natural peak relative to the response rounds and on whether the response leads to outbreak control at the end of the two-year analytical time horizon (see Appendix).

Recognizing that vaccine availability may constrain the choice of vaccine used for response, we explored the impacts of using mOPV versus tOPV. We assume that mOPV clearly represents the vaccine of choice for post-OPV cessation outbreaks given that: (1) it does not unnecessarily reintroduce nonoutbreak-related live virus serotypes that increase the risk of new VDPV outbreaks caused by the immunization response,[9] and (2) it offers better primary seroconversion rates than tOPV.[10] In a pre-OPV cessation setting, the first advantage does not apply given continued routine OPV immunization, and only the second advantage remains. Note that a lower take rate effectively implies a lower coverage, and that consequently the same tradeoffs observed above related to delay and coverage apply (Fig. 6). Consistent with our earlier findings,[Ref.8,Fig.2] Table III shows that mOPV clearly provides more efficient response than tOPV in 64 permutations of conditions representative of the pre-OPV cessation world (Table A1).

## 4. DISCUSSION

This study highlights several important insights about outbreak response planning. It identifies the response delay as the most important factor affecting outbreak size. Minimizing the delay implies not only rapidly responding after detection of an outbreak, but

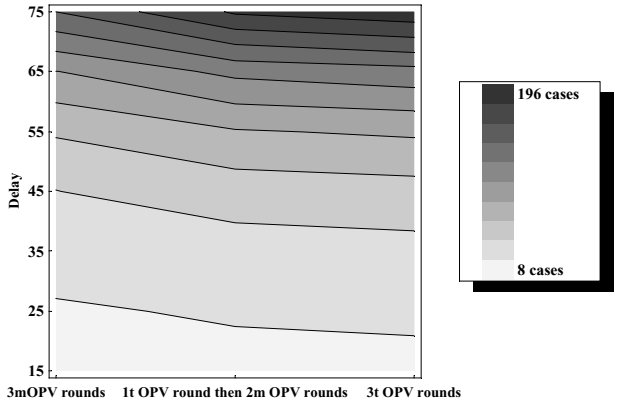


**Fig. 6.** Tradeoff between vaccine choice and delay, based on average outbreak size observed across 64 permutations of pre-OPV cessation conditions with significant outbreaks. Response scenarios all assume three rounds with 90% coverage at 30-day intervals.

also rapid detection and confirmation of the outbreak by virtue of the highest achievable surveillance quality. With the possible decline of acute flaccid paralysis surveillance as currently implemented after eradication, policymakers need to include future surveillance systems and timeliness of detection in considerations of post-OPV cessation era surveillance strategies. These results clearly suggest that in terms of reducing the logistical part of the delay in response, sacrificing the quality of the first round (i.e., with respect to coverage and/or mOPV vs. tOPV) in order to act more rapidly may result in more efficient outbreak control and fewer overall cases.

We also explored the impact of planning to conduct two rounds instead of three rounds for post-OPV cessation response. Although we generally found that the third round prevented relatively few cases compared to the first two rounds, for some conditions the third round represented an essential step in controlling the modeled outbreak. Consequently, we believe that given the practical difficulties of making a real-time determination about the sufficiency of two rounds, response plans should expect to conduct at least three response rounds in response to an outbreak detected in the post-OPV cessation world.

IPV provides immunity from paralytic disease, but those immunized with IPV may still participate in the circulation of infection.[11–13] Given that the existence of people susceptible to infection and disease in a population covered with routine IPV might mean that outbreaks could still possibly occur, we explored the impact of using a response strategy that targeted all individuals born since OPV cessation instead of the base case of a response strategy that targets only children younger than five years of age, regardless of the time since OPV cessation. Our results demonstrate that the choice of the target groups plays an important role in the estimated outbreak sizes.

We also demonstrated that the choice of vaccine used for each round represents an important determinant in the number of cases; our results show that mOPV clearly provides more efficient response than tOPV. However, we also demonstrated the real tradeoffs associated with waiting for mOPV instead of responding sooner with tOPV and found that postponing the first response round by more than five days to wait for mOPV generally results in more cases.

Our reliance on an established dynamic infection transmission model designed for polio outbreaks implies that all of the limitations of that model apply to this analysis.[8] Most notably, the model does not address exportation of an outbreak virus due to the assumption of a predefined, homogeneously mixed population. Modifying the model to characterize multiple subpopulations could provide a means to model exportation, but this remains challenging for future outbreaks that could occur in any place

**Table III.** Average Effects and Average Reductions for Different Response Vaccine Use for Permutations of pre-OPV Cessation Conditions[a]

| Change in Response Vaccine Scenario | Mean[b] Average Effect (Range, Polio Cases) | Mean Average Reduction in Outbreak Size (Range, %) |
|---|---|---|
| 3 rounds with mOPV vs. 3 rounds with tOPV | 16.1 (0.06–188.08) | 14 (3–26) |
| 3 rounds with mOPV vs. 1 round with tOPV then 2 rounds with mOPV | 10.12 (0.04–112.88) | 9 (2–18) |
| 1 round with tOPV then 2 rounds with mOPV vs. 3 rounds with tOPV | 5.99 (0.02–75.2) | 5 (1–10) |

[a]Response scenarios all assume 3 rounds with 90% coverage at 30-day intervals.
[b]Includes only those permutations of conditions for which we observed significant outbreaks ($n = 64$).

with a wide variety of diverse contact populations. The model also relies on income level and serotype averages with substantial uncertainty and variability (e.g., $R_0$ and the relative infectious and susceptibility of IPV vaccinees). In interpreting the results, readers must appreciate that each response round comes with a substantial and uncertain amount of secondary OPV infection, which we modeled using an input that represents the proportion of susceptibles eventually infected after each round.[8,14] Given our previously assumed high coverage of response rounds, this input does not depend on the coverage of the response round in these scenarios (although we relaxed this assumption in the Appendix).

Given practical constraints, we did not test all of the possibly relevant permutations of conditions that exist. For example, we did not vary the routine immunization coverage for permutations involving routine IPV use, but we used 68%, 90%, 92%, and 94% as the base case for low-, lower-middle-, upper-middle-, and high-income countries, respectively.[8] Similarly, we did not evaluate the full set of possible response scenarios. Consequently, the average effects and effect ratios only consider a limited region of the enormous space of possible combinations. However, we performed a relatively large and reasonably comprehensive set of analyses to consider a significant part of this space and demonstrate important insights. Analyzing the full space would involve an exponentially increasing number of model evaluations (as a function of the number of characteristics varied). For example, in reality, outbreak responses often include more than three rounds and also continue for periods of many months after the last confirmed case of an outbreak due to limitations on surveillance information and lack of certainty about the extent of geographic spread of an outbreak virus. In most outbreaks evaluated in this analysis, the incidence reduced substantially by the end of the two-year analytical time horizon, with few exceptions (see Appendix). We note that a stochastic model would provide a more suitable tool to address the probability of complete outbreak control (i.e., reextinction of the virus) within a given time frame.[15]

Our model also assumes an unlimited supply of vaccine for response, but in some circumstances with multiple large outbreaks this assumption may emerge as too simplistic. If future analyses strive for a fully comprehensive analysis of all response options, they might consider a limited set of policy permutations and use design-of-experiment concepts to infer effects and interactions across the entire input space of interest.[16] We believe that this analysis provides valuable insights that may help policymakers responsible for developing future polio outbreak response strategies understand the implications of different choices and improve the effectiveness of response. We believe that future studies should explore the actual experience with response activities so that response plans can begin with a clear understanding of current expectations. We expect that by combining this experience with models such as the one presented here, analysts and field workers can work together to identify opportunities for improving response strategies and optimally using limited resources for response.

## ACKNOWLEDGMENTS

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## APPENDIX

Table A1 shows the response scenarios we ran for pre-OPV cessation importation outbreaks using previously developed response inputs and conditions.[8,17] While the selected permutations do not represent the full set of possible permutations, we believe they form a representative set that supports general insights. We ran 105 response scenarios that varied delay, coverage of the first round, and vaccine by round (i.e., $7 \times 5 \times 3$ scenarios). We ran these scenarios for 72 different permutations of conditions that varied income level, population size, number of years since last regular SIAs, $R_0$, and routine vaccination coverage (i.e., $2 \times 2 \times 3 \times 2 \times 3$ permutations).

Table A2 similarly shows the response scenarios we ran for post-OPV cessation outbreaks using previously developed response inputs and conditions.[8,17] For post-OPV cessation outbreaks, we ran 47 response scenarios, including 35 that varied delay and coverage of the first round (i.e., $7 \times 5$ scenarios) and 12 that varied the number of rounds, the interval between rounds, and the coverage of the second

**Table A1.** Combinations of Values Run for Response Scenarios and Permutations of Conditions for Pre-OPV Cessation Outbreaks[a]

| Values for Response Scenarios (Number) | | | | | | |
|---|---|---|---|---|---|---|
| Delay (Days)[b] ($n = 7$) | Number of Rounds ($n = 1$) | Interval Between Rounds (Days) ($n = 1$) | Coverage of First Response Round ($n = 5$) | Coverage of Second Response Round ($n = 1$) | Coverage of Third Response Round ($n = 1$) | Vaccine Used ($n = 3$) |
| 15–75 at 10-day increments | 3 | 30 | 30–90% at 15% increments | 90% | 90% | 3 rounds of mOPV<br>3 rounds of tOPV<br>1 round tOPV + 2 rounds of mOPV |

| Values for Permutations of Conditions for Each Response Scenario (Number) | | | | | | |
|---|---|---|---|---|---|---|
| Income Level ($n = 2$) | Routine Vaccination ($n = 1$) | Population Size ($n = 2$) | Years After Last SIAs ($n = 3$) | Surveillance[c] ($n = 1$) | $R_0$ Case[d] ($n = 2$) | Routine Vaccination Coverage ($n = 3$) |
| Low | OPV | 10 million | 0 | AFP | Low medium | 25% |
| Lower middle | | 100 million | 3 | | High medium | 50% |
| | | | 5 | | | 75% |

[a]All response scenarios assume response rounds target children younger than five years of age.
[b]Delay between outbreak detection and initiation of the first response round.
[c]AFP surveillance assumes detection occurs after onset of the first paralytic case.
[d]The low-medium $R_0$ value equals 10 in low-income countries and 8 in lower-middle-income countries; the high-medium $R_0$ value equals 13 in low-income countries and 11 in lower-middle-income countries.
AFP = acute flaccid paralysis; mOPV = monovalent OPV; OPV = oral poliovirus vaccine; SIAs = supplemental immunization activities; tOPV = trivalent OPV.

round (i.e., $2 \times 3 \times 2$ scenarios). We tested these 47 scenarios on 216 different permutations of conditions that varied income level, routine vaccination policy, population size, number of years since OPV cessation, surveillance policy, and $R_0$ (i.e., $3 \times 2 \times 3 \times 3 \times 2 \times 2$ permutations). The post-OPV cessation conditions further assume absence of regular SIAs for three years prior to OPV cessation for low-income countries (and similarly for five years prior for middle-income countries).

In addition to the scenarios shown in Tables A1 and A2, we considered three scenarios with delays of 25, 45, and 75 days for all 36 permutations of post-OPV cessation conditions with routine IPV immunization and at a time 20 years after OPV cessation to investigate the impact of the target age groups in an outbreak on a largely IPV-immunized population. These additional scenarios assumed a response targeting all individuals younger than 20 years of age instead of only those younger than five years of age.

Fig. A1 shows the distributions of the effect ratios for the pre- and post-OPV cessation permutations we performed. In general, we observed comparably high effect ratios of delay to coverage among the 185 permutations of post-OPV cessation conditions averaging approximately 8 (range 3–20). For pre-OPV cessation outbreaks, we also found high ratios averaging approximately 7 (range 5–9) across 64 permutations with significant outbreaks.

Fig. A2 shows the distribution of the reduction in outbreak size with three versus two response rounds. Across the 216 permutations of post-OPV cessation conditions, the reduction averaged 10% (12% if we omit permutations without a significant outbreak), indicating that the third round generally prevented few cases compared to the first two rounds. However, we observed an important skew in the distribution of the ratios, with outliers as high as 89%. Thus, for some conditions the third round represented an essential step in controlling the modeled outbreak.

Fig. A3 demonstrates the impact of the assumptions about successive rounds. The uniform coverage scenario (used in all analyses throughout this article) assumes that each round reaches all *remaining* susceptibles at the same rate. For example, this implies that if the first round vaccinates 75% of unvaccinated children, then the second round vaccinates 75% of the remaining 25% of unvaccinated children,

**Table A2.** Combinations of Values Run for Response Scenarios and Permutations of Conditions for Post-OPV Cessation Outbreaks[a]

| Values for Response Scenario Inputs (Number) | | | | | | |
|---|---|---|---|---|---|---|
| Delay (Days)[b] ($n = 7$) | Number of Rounds ($n = 1$) | Interval Between Rounds (Days) ($n = 1$) | Coverage of First Response Round ($n = 5$) | Coverage of Second Response Round ($n = 1$) | Coverage of Third Response Round ($n = 1$) | Vaccine Used ($n = 1$) |
| 15–75 at 10-day increments | 3 | 30 | 30–90% at 15% increments | 90% | 90% | mOPV |
| Delay (Days)[b] ($n = 1$) | Number of Rounds ($n = 2$) | Interval Between Rounds (Days) ($n = 2$) | Coverage of First Response Round ($n = 1$) | Coverage of Second Response Round ($n = 3$) | Coverage of Third Response Round ($n = 1$) | Vaccine Used ($n = 1$) |
| 25 | 2<br>3 | 15<br>30 | 90% | 70%<br>80%<br>90% | 90% | mOPV |

| Values for Permutations of Conditions for Each Response Scenario (Number) | | | | | | |
|---|---|---|---|---|---|---|
| Income Level ($n = 3$) | Routine Vaccination ($n = 2$) | Population Size ($n = 3$) | Year After Cessation ($n = 3$) | Surveillance[c] ($n = 2$) | $R_0$ Case[d] ($n = 2$) | Routine Vaccination Coverage ($n = 1$) |
| Low<br>Lower middle<br>Upper middle | IPV<br>No routine | 0.5 million<br>10 million<br>100 million | First<br>Fifth<br>Twentieth | AFP<br>Passive only | Low medium<br>High medium | Projected averages[e] |

[a]All response scenarios assume response rounds target children younger than five years of age if routine IPV vaccination continued, or all children born since cessation if all routine vaccination ceased. Conditions assume absence of supplemental immunization activities for three years prior to OPV cessation in low-income countries and five years in middle-income countries.
[b]Delay between outbreak detection and initiation of the first response round.
[c]AFP surveillance assumes detection occurs after onset of the first paralytic case, passive surveillance assumes detection occurs after onset of the fifth paralytic case.
[d]The low-medium $R_0$ value equals 10 in low-income countries, 8 in lower-middle income countries, and 6 in upper-middle income countries; the high-medium $R_0$ value equals 13 in low-income countries, 11 in lower-middle income countries, and 9 in upper-middle income countries.
[e]Projected routine immunization coverage equals 68% in low-income countries, 90% in lower-middle income countries, and 92% in upper-middle income countries.[18]
AFP = acute flaccid paralysis; IPV = inactivated poliovirus vaccine; mOPV= monovalent OPV; OPV = oral poliovirus vaccine.

and the third round vaccinates 75% of the 6.25% unvaccinated children remaining after two rounds, which leaves only approximately 1.6% of children unvaccinated after three rounds. However, the proportion of children who did not seroconvert remains greater and depends on the take rate. Similarly, each round moves a fixed proportion (e.g., 30% in upper-middle-income countries[8]) of remaining susceptible

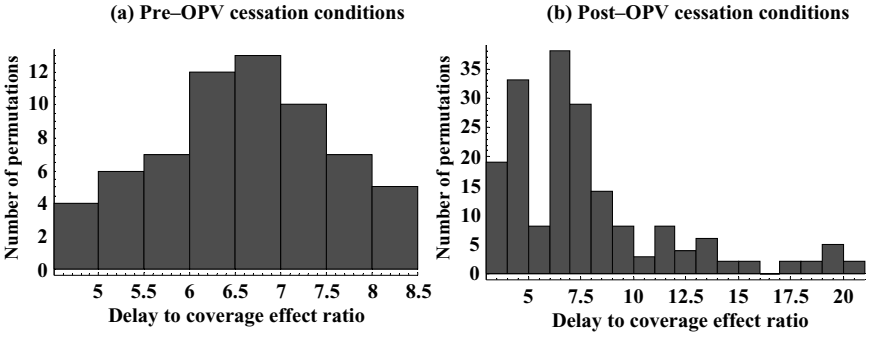


**Fig. A1.** Histograms for the delay to coverage effect ratio for 64 permutations of pre-OPV cessation conditions (panel (a) assumes routine OPV immunization) and 185 permutations of post-OPV cessation conditions (panel (b) assumes no routine or IPV immunization) for which significant outbreaks occurred.

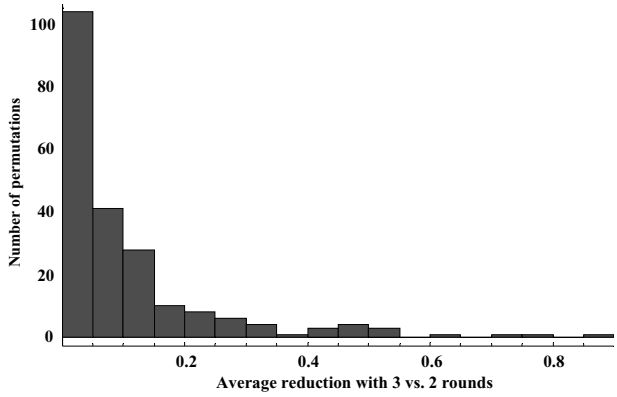


**Fig. A2.** Histogram for average reduction in outbreak size for scenarios with three rounds compared to scenarios with two rounds across the 216 post-OPV cessation condition permutations.

children to a partial infectibility group in the uniform coverage scenario. An alternative scenario reduces either the coverage or the secondary OPV proportion, or both, by 50% in each subsequent round. Clearly, the assumption of uniform (primary and secondary) coverage affects the outbreak size, although the absolute impact depends on the other conditions.

Fig. A4 shows the distribution of the average reduction (decrease, or increase when negative) in outbreak size with 30-day versus 15-day response rounds. The average reduction ranged from –30% (i.e., an increase in cases of approximately 30%) to +45% across the 216 permutations of conditions we ran, and we observed a relatively symmetric distribution with a mean of –3%, a 5th quantile of –15%, and a 95th quantile of 12%. Thus, the length of the interval between rounds does not generally impact the size of the outbreak substantially and neither the 15- nor 30-day interval appears superior in all situations.

We also investigated the impact of different levels of coverage for the second round for post-OPV cessation scenarios with two or three rounds separated by 15 or 30 days (see Table A2). Across the 216 post-OPV cessation permutations with outbreaks, we observed the average effect of increasing the coverage from 70% to 90% ranging from 0 to 695 prevented polio cases with a mean of only 12 prevented cases. Fig. A5 shows the average reduction in outbreak size with the coverage at 90% compared to 70%. This reduction ranged from 0 to 0.15 (mean = 0.021, or 0.025 if we exclude the 31 permutations where no significant outbreak occurred).

Fig. A6a and A6b show *atypical* examples of outbreaks for which the 15-day interval or the 30-day interval clearly provides the best response, respectively. Analyzing all post-OPV cessation condition permutations, we found that outbreaks where the 30-day interval proved better than the 15-day interval (in terms of lower outbreak size) coincided with outbreaks where control apparently did not occur within the two-year analytical time horizon. For permutations where the 30-day interval proved better, the incidence on day 730 equaled on average 13% of the highest recorded incidence compared to 4.2% for

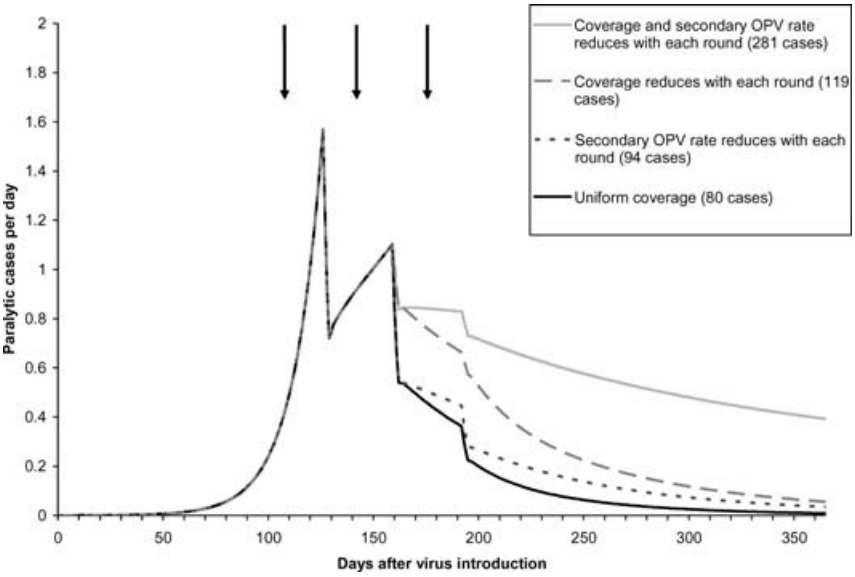


**Fig. A3.** Impact of the assumptions about uniformity of successive rounds in the response. Response scenarios assume a delay of 25 days, 75% coverage for all three rounds at 30-day intervals, and targeting children younger than five years of age. Conditions assume an outbreak in an upper-middle-income country with 10 million people and acute flaccid paralysis surveillance, occurring 20 years after the switch from OPV to IPV, and a high-medium $R_0$ (=9). Arrows indicate the timing of response rounds.

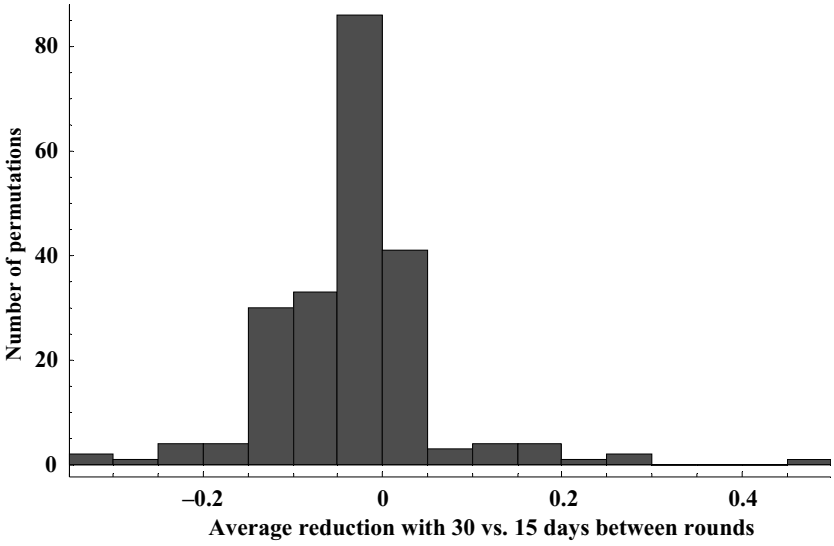


**Fig. A4.** Histogram for average reduction in outbreak size for scenarios with 30 days between rounds compared to scenarios with 15 days between rounds across the 216 post-OPV cessation condition permutations.

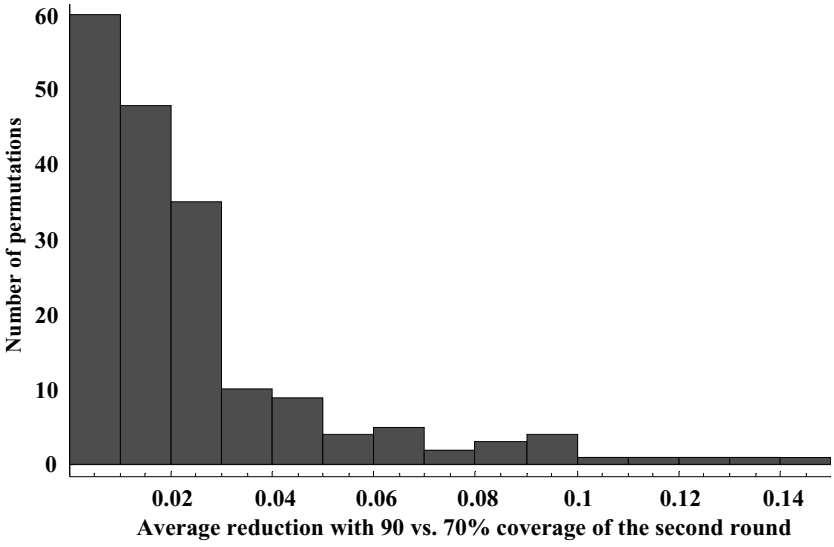


**Fig. A5.** Histogram for the average reduction in number of cases in scenarios with 90% coverage of the second round compared to scenarios with 70% coverage of the second round across the 216 post-OPV cessation condition permutations.

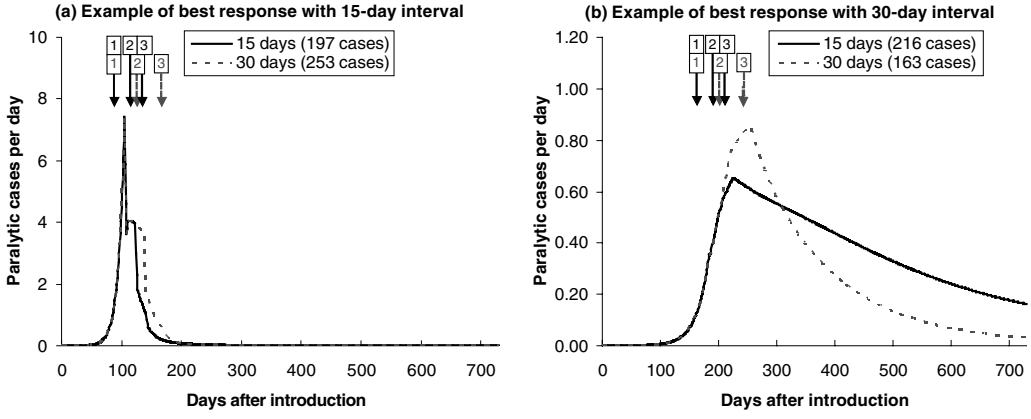


**Fig. A6.** Impact of the interval between immunization rounds. Panel (a) shows an outbreak with the same conditions as Fig. 3 except 20 years after OPV cessation. Panel (b) shows an outbreak with the same conditions as Fig. 5b. Both response scenarios assume a delay of 25 days and cover 90% of children younger than five years of age with mOPV used in each of the three rounds. The arrows with numbers on top indicate the starting days of each round.

all permutations where outbreaks occurred and 0.5% for permutations where the 15-day interval proved better (considering only the 12 response scenarios that vary the interval between rounds).

Although stochastic transmission models remain better suited to explore the probability of outbreak control, we did investigate for all of the scenarios that we ran how often apparent control occurred. In this deterministic model, a fraction of infectibles always remains (while new susceptibles continue to accumulate due to births) and therefore complete control never occurs in the model. Table A3 gives the ratio of the incidence at the end of the two-year time horizon divided by the highest recorded incidence during the outbreak across all permutations of (deterministic) conditions and response scenarios for pre- and post-OPV cessation outbreaks. For pre-OPV cessation outbreaks, the ratio never exceeded 0.05, while for post-OPV cessation outbreaks, more than 4% of permutations included outbreaks where the incidence on day 730 exceeded 10% of the highest incidence, and for 2.1% of outbreak the highest incidence occurred on day 730 (i.e., a ratio of 1). All but one outbreak in the latter category occurred in the context of settings where the detection occurred too late to see the effect of the response within the two-year time horizon (all in upper-middle-income countries). The only exception was an upper-middle-income country with routine IPV immunization, acute flaccid paralysis surveillance, 100 million people, and high-medium $R_0$. In this context, a two-round response only slowed down the incidence without stopping its increase, while the three-round response reduced the incidence but not to the point of control.

Finally, Table A4 summarizes the main findings of the response scenario analyses.

**Table A3.** Tabulated Distribution of the Ratio of the Incidence at Day 730 Compared to the Peak Incidence, Across All Permutations of Conditions and Response Scenarios

| | Pre-OPV Cessation | | Post-OPV Cessation | |
|---|---|---|---|---|
| Range of Ratio (Excluding Upper End) | Frequency | Relative Frequency | Frequency | Relative Frequency |
| 0–0.00005 | 3,861 | 57.5% | 4,445 | 51.1% |
| 0.00005–0.0001 | 602 | 9.0% | 469 | 5.4% |
| 0.0001–0.0005 | 1,464 | 21.8% | 959 | 11.0% |
| 0.0005–0.001 | 222 | 3.3% | 466 | 5.4% |
| 0.001–0.005 | 320 | 4.8% | 809 | 9.3% |
| 0.005–0.01 | 99 | 1.5% | 287 | 3.3% |
| 0.01–0.05 | 152 | 2.3% | 701 | 8.1% |
| 0.05–0.1 | 0 | 0.0% | 191 | 2.2% |
| 0.1–0.5 | 0 | 0.0% | 115 | 1.3% |
| 0.5–1 | 0 | 0.0% | 71 | 0.8% |
| 1 | 0 | 0.0% | 182 | 2.1% |
| *N* | 6,720 | – | 8,695 | |

**Table A4.** Mean Average Reductions (%) Associated with Altering Assumptions about the Response Scenarios (5th and 95th Quantiles of the Distribution of Average Reductions Across Permutations of Conditions).

| Change | Pre-OPV Cessation Permutations ($n = 185$) | Post-OPV Cessation Permutations ($n = 64$) | Combined ($n = 249$) |
|---|---|---|---|
| Reducing the delay from 75 to 15 days | 77 (45 to 98) | 81 (44 to 97) | 78 (43 to 98) |
| Reducing the delay from 75 to 45 days | 51 (8 to 83) | 60 (26 to 80) | 53 (14 to 82) |
| Reducing the delay from 45 to 15 days | 60 (28 to 91) | 60 (25 to 83) | 60 (27 to 90) |
| Increasing the coverage of the first round from 30 to 90% | 22 (4 to 53) | 24 (9 to 36) | 23 (5 to 48) |
| Increasing the coverage of the first round from 75 to 90% | 7 (1 to 19) | 7 (2 to 11) | 7 (1 to 15) |
| Adding the third response round | 12 (1 to 46) | NA[a] | 12 (1 to 46) |
| 15-day interval vs. 30-day interval | 3 (−14 to 13) | NA | 3 (−14 to 13) |
| 3 mOPV rounds vs. 3 tOPV rounds | NA | 14 (4 to 23) | 14 (4 to 23) |
| 3 mOPV rounds vs. 1 tOPV round then 2 mOPV rounds | NA | 9 (3 to 16) | 9 (3 to 16) |
| 1 tOPV round then 2 mOPV rounds vs. 3 tOPV rounds | NA | 5 (2 to 9) | 5 (2 to 9) |
| Increasing the coverage of the second round from 70 to 90% | 77 (45 to 98) | 81 (44 to 97) | 78 (43 to 98) |
| Targeting all people younger than 20 instead of 5 years of age[b] | 46 (13 to 82) | NA | 46 (13 to 82) |

[a]NA indicates that we did not perform response scenarios for given permutations.
[b]Only for 36 permutations with routine IPV immunization and assuming 20 years after OPV cessation.

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