Original Articles

The Case for Cooperation in Managing and Maintaining the End of Poliomyelitis: Stockpile Needs and Coordinated OPV Cessation

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Abstract

Context: Achieving successful eradication of a disease requires global cooperation to obtain a shared goal. Coordination of the endgame may seem an obvious requirement for success, but that does not ensure that cooperation will occur.
Objective: To analytically explore the need for cooperation to maintain global polio eradication specifically related to creation of a global polio vaccine stockpile and coordination of oral poliovirus vaccine (OPV) cessation.
Design: Using risk and decision analysis and game theoretical concepts, we modeled the importance of global cooperation in managing the risks associated with polioviruses for a time horizon of 20 years after successful global disruption of circulation of wild polioviruses.
Results: Countries may wish to avoid the financial costs of vaccination and risks for vaccine-associated paralytic polio following eradication of wild polioviruses, which may lead them to reduce their use of OPV. However, reducing or stopping vaccination too soon and without coordination poses serious risks, including the possibility of reimportation of wild polioviruses and the possibility of vaccine-derived polioviruses. Analysis of the risks for potential outbreaks suggests the need for creation and maintenance of a global stockpile of vaccine for outbreak response. Game theoretical considerations show that coordination of OPV cessation optimizes expected costs and risks globally, despite the potential perceived incentives for countries to stop OPV earlier or later than other countries, or to continue OPV use indefinitely.
Conclusions: This article makes the strong case for global cooperation on risk management and suggests that even though individual countries may perceive their own risks as small, risks at the global level warrant cooperative action and coordination of OPV cessation.

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Introduction

Many studies have considered the generic decision to eradicate a vaccine-preventable infectious disease.[1-6] Geoffard and Philipson[3] explored the dynamics of disease eradication and suggested that eradication efforts could fail if the demand for vaccines depends on prevalence of the disease (ie, if the perceived benefit of vaccination drops as prevalence decreases). Although the consequence of such a failure may lead to a control policy, maintaining a very high level of control for an eradicable disease can never be optimal.[4] Barrett[5] explored eradication as an economic game, with individual countries as the players making interdependent decisions, and identified differences in national net costs and benefits of eradication that can lead to several potentially stable equilibria. Barrett[6] recently discussed the economics of policies for control or eradication and demonstrated the potentially greater economic incentives for international cooperation for eradication.

Focusing specifically on polio, Thompson and Duintjer Tebbens[7] presented the economic and humanitarian case for completion of eradication compared with control. The World Health Organization (WHO) continues to work toward completion of eradication and a global commitment to a world free of circulating wild polioviruses.[8] The approach of this goal appropriately motivates considerable discussion about the endgame policies.

Studies have suggested that policies for managing risks following global eradication will play a critical role in maintaining a world free of circulating wild polioviruses, and possibly free of poliomyelitis due to poliovirus altogether if countries agree to stop use of the live oral poliovirus vaccine OPV.[9-16] Although OPV cessation implies lower numbers of expected cases of paralytic polio and costs,[15] national and global health leaders will face many complex choices[9] with real costs[10] and risks.[11] In the past decade, outbreaks occurred when OPV began to circulate through populations with low vaccine coverage, mutate back toward wild poliovirus, and cause paralysis.[17] The risks for outbreaks from circulating vaccine-derived polioviruses (cVDPVs) clearly demonstrate that as countries succeed in nationally disrupting wild poliovirus transmission, they must continue to keep vaccination coverage relatively high. However, following global disruption of wild poliovirus circulation, the continued use of OPV will mean both continued cases of vaccine-associated paralytic polio (VAPP) and potential outbreaks from cVDPVs,[11,15] and many countries expect to stop using OPV after certification of the world as free of circulating wild polioviruses. The Global Polio Eradication Initiative currently recommends coordinated global OPV cessation,[18,19] and in anticipation of discussions and negotiations about this recommendation and its implementation, this article explores the analytic case for global cooperation on a vaccine stockpile, coordinated OPV cessation, and subsequent risk management.

Understanding the Risks: Variability, Uncertainty, and Time

We previously characterized the uncertain and variable dynamic risks associated with posteradication polio risk management policies over time[11] to support our efforts to evaluate the risks, costs, and benefits of posteradication policy options at the global level.[15,16] These analyses recognized the large differences in risks that exist between countries by stratifying countries into groups according to the World Bank income levels (ie, low-income, lower middle-income, upper middle-income, and high-income).[9] Although we did not characterize the risks for each individual country, stratification at the income level allowed us to capture important differences between nations at the global level with respect to costs, hygiene, and other risk factors. The analyses consider the risks over a 20-year period from the time when the world is certified as free of circulating wild polioviruses (T_0) and assume that at T_0 no wild polioviruses are circulating -- otherwise wild polioviruses would not be truly eradicated. Of importance, the analyses assume for policies that involve OPV cessation that this would occur in a globally coordinated and synchronized fashion.

Table 1 provides point estimates of the probability of at least 1 outbreak (defined as 1 or more cases of paralytic polio) in the first 6 years and first 20 years after T_0 in a hypothetical country with a population of 100 million people by income level. The outbreak probabilities depend on routine immunization policies, which for OPV may include increasing coverage with supplemental immunization activities (SIAs), and policies related to maintaining and enforcing containment.[20,21] For the condition of continued OPV use, cVDPV risks dominate such that we obtain the same results with either option for containment. The probability estimates also depend on assumptions about which historical VDPV risk cases we include in the extrapolation for estimation of future risks (ie, based only on cVDPVs confirmed by more than 1 case of paralytic polio or on cVDPVs plus ambiguous VDPVs [aVDPVs], events that suggest circulation of vaccine strains, but which did not result in multiple confirmed paralytic cases[11]). The probabilities shown in Table 1 include all of the events that could lead to outbreaks (ie, those from cVDPVs and aVDPVs, unintentional and intentional releases, and any VDPVs that occur in individuals with rare immunocompromised conditions that lead to prolonged or chronic excretion of live polioviruses [iVDPVs][11]), assuming complete interruption of all wild poliovirus circulation (ie, no continued, undetected wild poliovirus circulation). Finally, the probability estimates also depend on assumptions about the population immunity at T_0, which affect the probability of cVDPVs. We include 2 possibilities: realistic population immunity (the base case), which assumes countries stop conducting SIAs or maintaining high population immunity 3-5 years prior to T_0, and maximum population immunity, which assumes a coordinated pulse or efforts that bring coverage in all areas up to more than 90% prior to T_0.[15,16]

The estimates in Table 1 are intended to provide the context for national policy makers about the relative probabilities of future outbreaks under different conditions. They do not provide the actual estimates for any individual identified country. The estimates of the probability of at least 1 outbreak during the first 6 years and first 20 years, assuming a country with a population of 100 million, can be scaled linearly to some degree to get an idea of the probabilities for other population sizes. However, linear scaling is not appropriate for relatively larger annual outbreak rates and population sizes because clearly the probabilities cannot exceed 1. Table 1 shows that low-income and lower middle-income countries face the highest probabilities of future outbreaks, and high-income countries, which we assume will continue vaccination for the foreseeable future using inactivated poliovirus vaccine (IPV), face the lowest probabilities while paying the highest costs.[10,11]

The outbreak probabilities and costs look very different from a national perspective than when combined into global estimates. Table 2 summarizes the net present value of the expected costs (and fifth and 95th percentiles) aggregated by income group for the vaccination options.[10] The results suggest costs on the order of billions for continued vaccination with OPV or IPV in the 20-year time period. Table 2 also shows that most of the policy options and different income group-dependent outbreak rates that change over time lead to an expected value of 1 or more outbreaks in the future.[11] Although such results may seem counterintuitive, whereas individual nations face what may seem like relatively small risks (Table 1), at the global level we expect an approximately 50% to 100% chance of at least 1 outbreak during the first 20 years after global OPV cessation.[11] Of course, we do not and cannot know where or when the statistically expected outbreak(s) will occur, and we hope that no future outbreaks would in fact ever happen. However, this result is not surprising, particularly given experience with the only disease successfully

eradicated to date (smallpox). Although few people realize it, 1 fatal laboratory-acquired case (an outbreak by our definition) occurred after eradication of smallpox.[22] For context, if we fail to eradicate wild polioviruses, then polio outbreaks will continue in the future for certain.

The probabilities associated with OPV cessation policy options change over the 20-year time period.[11] The most probable outbreaks expected under a policy of coordinated OPV cessation result from cVDPVs that occur only during the first few years after cessation, provided that they are successfully controlled through adequate response measures. Switching to IPV reduces the risks, but it does not eliminate them. According to Table 2 , continued use of OPV for routine vaccination, particularly without SIAs, leads to a relatively large number of expected outbreaks over the 20-year time period. These results strongly support the case for OPV cessation following the successful eradication of wild polioviruses, because after successful eradication of wild polioviruses, either stopping polio vaccination altogether or switching to IPV reduces the numbers of expected outbreaks and paralytic polio cases.[15,16] Although national leaders will face difficult choices about whether to stop all polio vaccinations or switch to IPV, we expect that stopping the use of OPV will save both money and lives.[15] However, in order to stop OPV use and minimize the risks for even more cVDPVs, we will need a global stockpile of vaccine to respond to any cVDPV outbreaks that occur, and all countries will need to stop using OPV at essentially the same time.

Stockpiling Polio Vaccines for Outbreak Response

Given the relatively low probabilities of an outbreak after OPV cessation in any single country, it seems unlikely that individual countries will want to invest significant financial resources in developing their own stockpiles of OPV. However, given the relatively high chance of at least 1 outbreak somewhere in the world, and uncertainty about the location and timing of such outbreak(s), all countries will most likely want some form of insurance. Considered independently from the national perspective, we expect that countries would most likely consider 3 general options:

1. Invest in building and maintaining a national stockpile that meets the national needs for the worst-case scenario (most expensive option, because the worst-case scenario will generally assume that the country itself will experience an outbreak and need to respond);
2. Invest in building and maintaining a national stockpile that meets the expected national needs, which would include consideration of the low probability of an outbreak occurring (economically preferred option, because it considers the likelihood of needing the stockpile); and
3. Do not invest in a national stockpile.

From an economic perspective, if all countries chose option 1, then globally the amount of vaccine in stockpiles would far exceed expected global needs. Similarly, if all countries chose option 3, the amount of vaccine available would not meet global needs. If all countries chose option 2, then globally the right amounts of vaccine would be available in stockpiles, but the issue would arise that an individual country may not have the vaccine that it needs, whereas other countries would have the vaccine that they will not use. In addition, if countries prefer different options, then this creates the possibility of numerous types of "gaming" behaviors.[6, 23-26]

The situation represents a classic insurance problem. We have a population (in this case, the world) whose individual members (in this case, individual countries) face an uncertain risk for expected events, but the time of these events and the individuals who will experience them cannot be known a priori. The consequences of the event to the "unlucky" individual members who experience the event (in this case, a cVDPV outbreak) are significant enough that all individual members will see potential value in purchasing insurance that will compensate them if they are unlucky or provide them with peace of mind knowing that they would have been protected if they were the "lucky" ones who do not experience the event. As in most classic insurance problems, the risks differ for individual members, which may affect their individual preferences for participation in an insurance program. However, we can reasonably assume that all countries would want to participate in access to a global vaccine stockpile insurance program if it were free, because in theory it would eliminate the need for them to spend national resources for their own stockpiles. Even if it were not free, the global stockpile would protect unlucky countries from the worst-case scenario, whereas countries would invest no more than for option 2 above. In fact, the costs per country would most likely be lower due to economies of scale and pooling of resources for development and maintenance of the stockpile. Thus, we suggest that global health leaders will need to develop a global polio vaccine stockpile and determine an appropriate strategy for financing it and ensuring rapid access to any country that needs it, and we expect that this will obviate the need for individual countries to struggle with difficult choices about building national stockpiles.

The WHO currently appears to be on this path, and it received initial resources to fund development of the stockpile. Although preliminary efforts to estimate needs for vaccine from the stockpile exist,[27] additional research is needed to optimize the design of the stockpile and outbreak response strategies.[13]

In the context of our earlier modeling of the risks, costs, and benefits of various posteradication policies,[15] we assumed that a global vaccine stockpile would exist and that it would be used to respond to outbreaks. Using that model, we can probabilistically characterize the uncertain demand forecast. Although the overall model disaggregates the world by income groups and evaluates many different permutations of assumptions and policies, we focus here on the base case and aggregate global totals for either a policy of cessation of all routine vaccination in low- and middle-income countries (assuming high-income countries will continue to

use IPV) or universal IPV. Table 3 provides a list of the key assumptions in the model that generated these results.

Figures 1a-b show the probability distributions of the number of doses administered (excluding wastage) in the first 6 and 20 years following cessation of routine vaccination, with IPV continuing in high-income countries, respectively. The demand in the first 6 years drives the total demand, consistent with the expectation of a decrease in outbreak probabilities.[11] As shown in the figure, we observed long tails in the distributions of the total demand over 20 years. Looking more closely at the occurrences of extremely high demand, particularly those toward the end of the time period, we found 2 iterations (out of 10,000) with very high vaccine demands (ie, approximately 5.5 billion and 10 billion doses). Further inspection revealed that these iterations corresponded to iterations (or scenarios) with a very high risk for intentional virus releases (eg, the highest was based on a risk of 0.62 intentional virus releases per year per 100 million people, which represents a clear extreme in the tail of the lognormal uncertainty distribution specified for this model input).[16] For reference, the forecasted global population younger than 20 years of age in 2030 equals only approximately 2.5 billion people,[28] so 10 billion doses translates into about 4 OPV doses for each child under 20 years of age (ie, similar to the number of doses that continued routine OPV use would administer during 20 years). Clearly, if the probability of intentional introductions indeed turned out this high, then it would be visible very early on in the 20-year time period, and this would imply a recognized failure to sustain polio eradication due to sabotage. This would represent a tragic failure, which we expect would lead to a decision to restart routine immunization everywhere that would make a stockpile irrelevant.

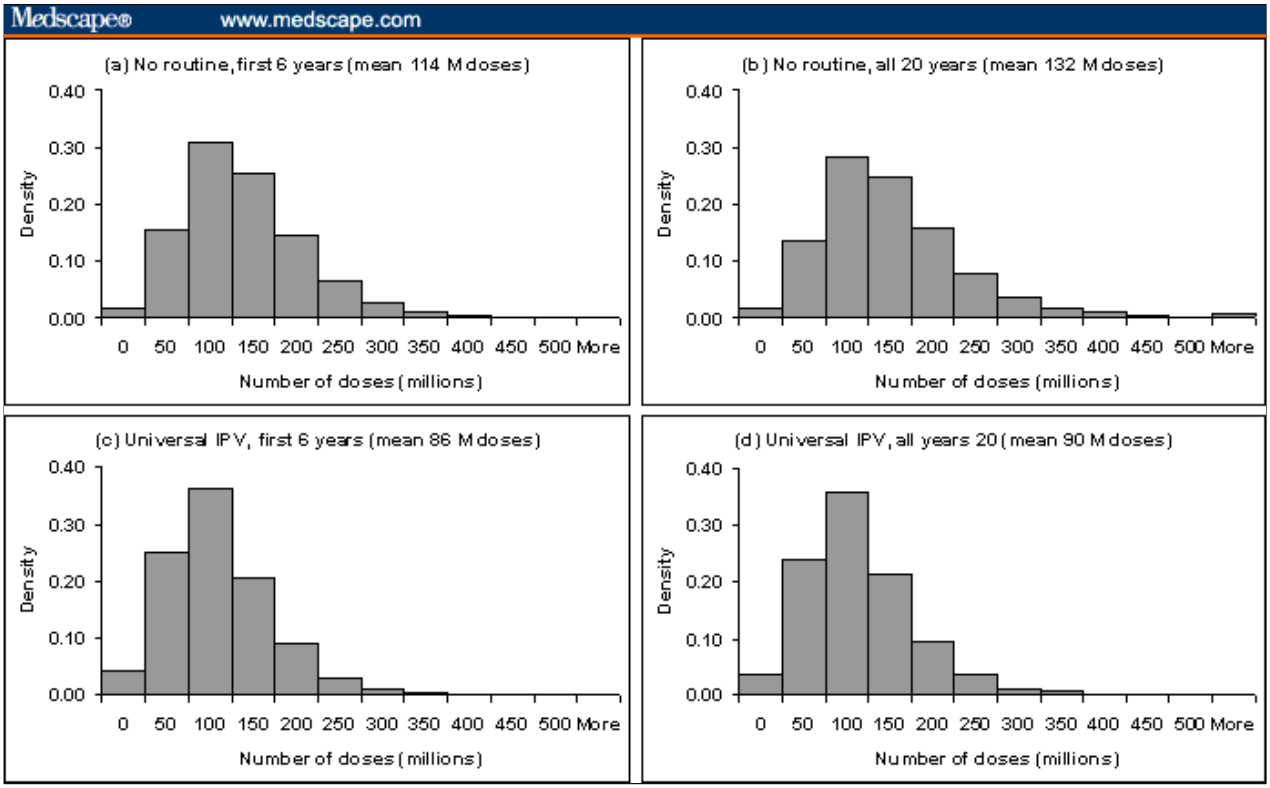

Figure 1.

The distribution of monovalent oral poliovirus vaccine (mOPV) doses used for outbreak response aggregated for (a) the first 6 years after OPV cessation with inactivated poliovirus vaccine (IPV) in high-income countries and no routine immunization elsewhere, (b) the first 20 years after OPV cessation with IPV in high-income countries and no routine immunization elsewhere, (c) the first 6 years after OPV cessation with universal IPV, and (d) the first 20 years after OPV cessation with universal IPV.

Figures 1c-d show a similar picture if the posteradication immunization policy is universal IPV. Compared with Figures 1a-b, this curve shows less density in the tail of the demand distribution because of lower risks and fewer age cohorts targeted in any outbreak response long after OPV cessation. Consistent with expectations, these figures suggest a lower probability of needing more doses with universal IPV vaccination compared with cessation of routine vaccination in most countries. However, switching from OPV to IPV still implies the need for a significant amount of vaccine in the global stockpile to deal with cVDPVs. This may seem counterintuitive, because countries may implicitly assume that paying the relatively large costs to switch to IPV will protect them completely from cVDPV outbreaks. Such an assumption is misguided, because during the first few years after OPV cessation, when cVDPV risks are highest, outbreak response would probably target children younger than 5 years of age regardless of IPV history (consistent with assumptions made to generate Figure 1). During that time period, cVDPVs that occur would have been initiated prior to OPV cessation (ie, it takes time for cVDPVs to develop and emerge). Furthermore, only a few birth cohorts would receive IPV, likely with less than 100% coverage, particularly in areas at high risk for cVDPVs, with an uncertain but probably

limited effect on providing protection against emergence of cVDPVs at the population level (Table 1). In addition, due to handling of large quantities of live poliovirus for IPV production,[20] domestically produced IPV without costly containment may lead to increased risk in the long term compared with no routine vaccination (Table 1). These results provide additional support for the WHO's containment policy efforts and ongoing discussions about IPV production using safer seed strains (ie, safer than the wild poliovirus strains currently used) and requirements for countries that produce IPV (particularly if low-income and lower middle-income countries wish to begin IPV production, which would also change the results in Table 1 because we assume that they will not produce IPV). Thus, given the reality of cVDPV risks following OPV cessation, a stockpile will most likely be needed no matter what countries decide to do with respect to stopping all polio vaccination or switching to IPV.

Several limitations exist in this analysis. First, 3 types of polio exist, and given the reality that we cannot predict a priori the type of virus involved in future outbreaks, the curves shown in Figure 1 should be interpreted to reflect the potential demands for each type of monovalent OPV (mOPV). We assume that mOPV represents the preferred choice for the stockpile because it offers relatively higher seroconversion rates than trivalent OPV (tOPV) and avoids the introduction of unneeded poliovirus strains into a previously poliovirus-free population.[27] This conservatively implies that all of the outbreaks would occur with the same type, but that we do not know which type, and that the design and procurement of vaccine for the stockpile must occur prior to T_0. Further consideration of these assumptions could lead to discussions about opportunities for dynamically designing the actual stockpile. Also, the assumption that response will successfully disrupt circulation of live viruses and that live viruses will not be exported from outbreaks may lead to an underestimate of stockpile needs. However, if such efforts are not successful, then similar to the sabotage scenario mentioned above, this would represent a tragic failure that would be detected relatively early in the 20 years after T_0, and would make a stockpile irrelevant due to resumption of routine vaccination. We note that in the context of recent presumed eradication of rinderpest, cessation of vaccination represents a critical step in ensuring that the virus has actually been eradicated.[29] Under a universal IPV strategy, the possibility of greater IPV use, which protects vaccine recipients from disease but provides less reduction in fecal excretion of poliovirus after (asymptomatic) reinfection than OPV,[30] raises interesting issues with respect to our ability to detect circulating live viruses. For example, virus detection depends on seeing acute flaccid paralysis cases, and greater use of IPV could potentially "mask" circulating live viruses from detection, which may necessitate investment in widespread environmental surveillance to detect live polioviruses in the absence of outbreaks. Environmental surveillance could potentially greatly increase detection of any circulating wild polioviruses and cVDPVs as eradication nears and following OPV cessation, independent of whether countries opt to use IPV.

Regardless of these limitations, we believe that this analysis provides useful context about the potential size of stockpile needed, and we hope that it will help policy makers in their initial discussions about the potential vaccine demands from a global stockpile. As this analysis shows, the choice of any finite stockpile size will imply some chance of insufficient vaccine doses available, but by showing the full distributions policy makers can make more informed decisions.

Coordinated OPV Cessation

Although the WHO assumes that global coordination of OPV cessation will occur,[20] we expect that additional analytic support for the case for coordination would be useful for policy makers.

Considered independently and from the national perspective, countries currently using OPV have the following options (note that these are independent of whether they decide to switch to IPV):

1. Stop using OPV before the coordinated cessation date;
2. Stop using OPV on the coordinated cessation date;
3. Stop using OPV after the coordinated cessation date; and
4. Keep using OPV indefinitely, even if other countries stop.

Prior analyses[15,16] make the strong analytic case that continued use of OPV implies both greater financial costs and cases of paralytic polio than stopping OPV. Given this, we anticipate that national policy makers will not independently prefer to continue to use OPV. The experience of cVDPV events following reductions in OPV use in some countries provides some evidence that countries would like to cease OPV use as soon as possible to avoid both polio vaccination costs and VAPP. Indeed, the global commitment to polio eradication included the expectation that after eradication countries could stop vaccination and save the associated future stream of polio vaccination costs while benefiting from no paralytic polio cases.[31] Thus, we expect that some countries may prefer option 1, and that the WHO will need to create incentives -- including conducting SIAs and providing vaccine financed by donors -- for some countries to continue OPV as long as is required to ensure that transmission of wild polioviruses has been disrupted. Stopping OPV before regional certification neglects the risks for importations[32] and/or outbreaks from undetected circulation.[33,34] With respect to the option of switching to IPV, which we assume would only be considered as an option in combination with OPV cessation options (1-3 above), we anticipate that national preferences about switching to IPV will depend heavily on vaccine values and costs (ie, if IPV is cheap and readily available, then some countries may prefer to continue to maintain some level of population immunity, at least for some period of time, and to forego other opportunities for using scarce health resources).

Although countries will look at their choices about stopping or continuing OPV independently, these choices clearly will also depend on the actions of other countries, particularly neighbors. In this regard, we must also consider the options in the context of a simple economic game.[6, 23-26] Here, we can take the perspective of each country (self) vs any or all other relevant countries considered (others). For any game, we need to consider the actions for self and the expected consequences for both self and others as a function of actions of others.

Table 4 shows a consequence table for the coordination of OPV cessation game. If a country chooses to stop all OPV use at T_0, which we assume would also be the point of coordinated OPV cessation, and if all others make the same choice, then this yields the minimum expected costs, which we assign as C_{min}. Finding the optimal T_0 implies balancing the risk for continued undetected wild poliovirus transmission after apparent eradication against the cost savings of earlier OPV cessation. This is symmetric for self and others. If a country chooses to stop OPV prior to T_0 (and thus before some or all of its neighbors), then it may avoid costs of vaccinating for some time (C_{vac1}). We assume that one country's decision to stop early does not impose additional vaccination costs on others (ie, no increased demand for vaccination from people crossing borders from countries that stopped into countries continuing to vaccinate). However, if self chooses to stop OPV prior to others, this leads to the convergence of 2 major risk factors for emergence of cVDPVs: decreasing population immunity and continued risk for exposure to OPV viruses from neighboring countries.[11,15] This leads to a higher probability of either substantial outbreak response costs or larger numbers of paralytic cases, or both, with the probability and the costs depending on many factors, including the length of time that the countries choose different options. Thus, the option of stopping early implies substantial expected health and financial costs associated with an increased risk for cVDPVs due to OPV viruses imported from its neighbors (C_{imp}), and we reasonably assume that these exceed expected avoided vaccination costs (ie, $C_{imp} > C_{vac1}$). The costs of stopping OPV early (before T_0) always exceed C_{min} by at least ($C_{imp} - C_{vac1}$), and we define the costs of stopping early for the country that does so as $C_{pre} = C_{min} + C_{imp} - C_{vac1}$. Note that if all countries (self and others) choose to coordinate stopping at an earlier T_0 than originally expected, then this simply implies a shift of T_0 to a new time (second column and row of Table 4). If, however, countries choose to stop early in an uncoordinated way (first column and row of Table 4), then any country stopping early should expect to impose a cost on itself of C_{pre}, because it must assume a higher probability that it will not be the last country to stop. In this simple formulation, we assume that choosing to stop early does not impose additional risks or costs on others.

As shown in Table 4 , countries may also consider the option of stopping OPV late (after T_0) or not stopping at all. Continued use of OPV indefinitely by self (or symmetrically by others) implies the maximum expected costs (both financial and health),[15,16] so we assign this a value of C_{max}. Unlike stopping early or at T_0, any country continuing to use OPV after T_0 will impose expected additional costs on its neighbors associated with continued and increased exported cVDPV outbreak risks. We define C_{exp} to refer to the expected costs of increased risk for cVDPVs exported to other countries due to delayed OPV cessation (ie, after T_0) and C_{inf} as the expected costs of increased risk for cVDPVs exported to other countries indefinitely ($C_{inf} > C_{exp}$).

Although the magnitudes of C_{exp} and C_{imp} arguably may be similar, the latter results from a choice by self, whereas the former results from a choice by others, so for emphasis we indicate the costs using different symbols in Table 4 . For example, if self chooses to stop at T_0 and others choose to stop later than T_0, then we add C_{exp} to self's costs and we emphasize that the country exporting the cVDPVs does not pay these costs. However, the country continuing to use OPV after T_0 will continue to pay vaccination costs (C_{vac2}), and it will also incur an increased risk of creating a cVDPV outbreak within its own borders (C_{own}). Although the country's cVDPV risks will depend on many factors, we anticipate an expected lowered public acceptance of OPV at T_0 if others stop OPV use, which would reduce coverage below levels required to prevent a cVDPV. The cost of continuing vaccination after T_0 will exceed C_{min}, and we define $C_{post} = C_{min} + C_{own} + C_{vac2}$. As noted in Table 4 , if any country truly chooses to continue OPV use indefinitely (C_{max}), then other countries would most likely incur costs between those shown and C_{max} (Table 4 shows the lower bound).

In this simple formulation, the best option is for global coordination of OPV cessation because each country and all others will experience the minimum expected costs. Although coordinating global OPV cessation will require both trust and cooperation, it represents a stable equilibrium, because no country can do better than choosing to participate in coordinated cessation, even if others behave nonoptimally (ie, for self, the second row dominates, and for others the symmetric second column dominates). This stable equilibrium depends only on the reasonable assumption that the costs associated with the increased risk for cVDPV outbreaks due to OPV-derived virus importations from neighbors exceeds the cost savings associated with stopping vaccination earlier. Although this highly simplified game theoretical approach should motivate dynamic modeling and greater consideration of the risks across boundaries and for different specific countries, it makes clear that national and global interests should align independent of whether individual nations choose to switch to IPV (ie, because IPV use would reduce C_{vac1} to 0 at best or more likely yield a cost increase). Thus, unless countries can truly lower their costs by continuing OPV use when others stop (eg, at least until they are convinced that all other countries truly stop using OPV), nations will have no incentives to use OPV any longer than T_0, the point of coordinated cessation. The scenario that an individual country can lower its costs by continuing to use OPV seems highly unlikely (even in the short term) because global actions related to OPV cessation will most likely reduce the acceptability of OPV for individuals within all countries, which will undoubtedly reduce coverage. This means that any national leaders selecting to continue OPV use after T_0 should prepare to explain cases of VAPP, deal with any cVDPVs that they create (within their own country or by exposing neighbors), and make the case to parents and caretakers of vaccine recipients that they should accept a vaccine that the WHO and the United Nations Children's Fund (UNICEF) no longer support for routine use. Of note, we anticipate

that the WHO will face increasing pressure to compress the timing of OPV cessation because many countries are likely to want to stop using OPV as soon as they can do so. In contrast to smallpox vaccination, for which countries could stop vaccination without coordination because no comparable risk for VDPVs existed, countries will need to coordinate in order to minimize their own and the global risk for cVDPVs. That said, even with coordination, a relatively high probability exists that an outbreak (ie, 1 or more cases of paralytic polio) will occur following OPV cessation. Thus, national and global health leaders need to be prepared, but this should not be used as an argument to support nonoptimal actions.

Discussion

Although many challenges remain with respect to eradication of wild polioviruses and management of future risks, this article provides motivation for coordination of global activities for a vaccine stockpile and for synchronized OPV cessation in all countries. Other studies may need to address additional issues that may be raised (eg, related to containment, surveillance, etc), but we anticipate that this analysis may help national policy makers focus on these 2 aspects of global policy with the support of some analytic rigor.

We explicitly stated that the analysis applies independent of whether countries opt to switch to IPV, and we expect that this may lead to some discussion because others may disagree. For example, some analysts may argue that countries that may want to switch to IPV but cannot (eg, those who believe their absolute best use of incremental resources is IPV but who lack such resources) will prefer to continue to vaccinate with OPV because continuing some polio vaccination would prevent them from building up susceptible individuals while they raise the resources to make the switch. This suggestion essentially argues that countries would rather take the approach that yields the expected worst case with respect to costs and cases because they fear the consequences of a small, but nonzero probability of a reintroduction of live polioviruses after OPV cessation. Clearly, efforts to reduce the cost and increase access to IPV are needed for countries that wish to spend their resources on maintaining immunity from an eradicated disease. However, we anticipate an income gradient with respect to these preferences, with the lowest-income countries likely to prefer to spend scarce health resources on nonpolio efforts as soon as they can do so, particularly because switching to IPV does not appear cost-effective for low-income countries.[15,16] We note that switching to IPV was not considered cost-effective for high-income countries,[35] but that cost-effectiveness was (and is) not the only attribute considered by policy makers. In high-income countries, the issues associated with greater numbers of paralytic cases of VAPP than from wild polioviruses raised concerns about the potential of widespread OPV rejection by parents (ie, given the greater perceived risk associated with the live vaccine than with the wild virus). With any vaccine, the incentives of individuals to participate in vaccination are important, because free riding may occur due to population or herd immunity effects.[24,25] We anticipate that national perceptions about intentional events (ie, bioterrorism) may play a large role in discussions about the preferences of individual nations for making the switch to IPV, and that the financial costs will also be a significant concern. Although some have suggested continued use of OPV until the world can switch universally to what may seem like the "perfect" option of high coverage with IPV,[36] we emphasize that this could represent the worst possible option in terms of costs and cases,[15,16] and thus could truly represent the enemy of the "good" or "better" option of OPV cessation. Although some may suggest that the best way to achieve OPV cessation would be to first switch to high coverage with IPV, on the basis of current technologies and costs, we anticipate logistical challenges associated with this option in the form of insufficient quantities of IPV, inability to achieve high coverage with IPV either through strengthened routine or mass campaigns, and significant financial costs at a time when the Global Polio Eradication Initiative itself faces large financial challenges. We find it difficult to imagine that global health leaders will be able to raise sufficient financial resources to switch the world to IPV unless IPV costs drop dramatically and/or major donors decide that the switch to IPV is something that they would prefer to support instead of directing resources toward other diseases or causes. As we discussed above, switching to IPV will not eliminate the need for a stockpile of vaccine to respond to cVDPVs, but it reduces, to some degree, the expected size of the stockpile needed.

Clearly, if eradication of wild polioviruses represents an unachievable goal due to limits on political, operational, and/or logistical abilities, then global leaders will need to consider their optimal actions in a world with continuing circulation of live polioviruses. We believe that the economic case exists for working to overcome these limits,[7] and we emphasize that prior to deciding to abandon eradication as a goal, national and global health leaders should carefully consider the risks, costs, and benefits of their options and determine who will pay the costs.

Finally, global efforts succeeded in eradication of wild poliovirus type 2 by the original goal year of 2000, regardless of the reality that some regions did not even begin coordinated polio vaccination campaigns until as late as 2001.[37] In this regard, if policy makers decide to seriously consider abandoning the overall goal of polio eradication (ie, eradication of all 3 types of wild polioviruses), then they should consider the option of cessation of type 2 OPV and the possibility of only continuing to vaccinate against types 1 and 3 (ie, as long as type 2 wild polioviruses clearly are no longer circulating). We believe that such an approach would effectively imply a different T_0 for type 2 than for types 1 and 3 with respect to the game theoretical analysis that we presented in Table 4 , but it adds complexity. Although we defined poliovirus type-specific issues as outside the scope of this article beyond this limited discussion, policy makers may want to further consider this limitation. Discussion of the option of cessation of OPV type 2 could also lead to additional consideration of pre-eradication opportunities (eg, switching to a bivalent vaccine containing types 1 and 3) and to different analyses of stockpile needs than addressed in this article. As shown in this article, the need to coordinate actions should represent a priority for national and global health leaders.

Table 1. Point Estimates of the Probability of at Least 1 Outbreak (Defined as 1 or More Cases of Paralytic Polio) During the First 6 or 20 Years After the Time When the World Is Certified as Free of Circulating Wild Polioviruses (T_0) in a Country With a Population of 100 Million People by Income Level, Routine Immunization Policy, SIAs Policy, Containment Policy, Initial Population Immunity Assumption, and VDPV Risk Assumption[11]*

Routine	SIAs	VDPV Risk Case	Population Immunity	Containment	Probability of at Least 1 Outbreak (1 or More Cases of Paralytic Polio) in the First 6 or 20 Years After T_0 in a Country With 100 Million People (by Income Level)							
					First 6 Years				First 20 Years			
					LOW	LMI	UMI	HIGH	LOW	LMI	UMI	HIGH
OPV	Yes	cVDPVs	Either	Either	0.02	0.02	0.004		0.08	0.08	0.01	
OPV	Yes	cVDPVs and aVDPVs	Either	Either	0.09	0.09	0.01		0.3	0.3	0.04	
OPV	No	cVDPVs	Realistic	Either	0.3	0.3	0.04		0.7	0.7	0.1	
OPV	No	cVDPVs	Maximum	Either	0.2	0.2	0.03		0.7	0.7	0.1	
OPV	No	cVDPVs and aVDPVs	Realistic	Either	0.4	0.4	0.06		0.9	0.9	0.2	
OPV	No	cVDPVs and aVDPVs	Maximum	Either	0.3	0.3	0.04		0.8	0.8	0.2	
IPV	No	cVDPVs	Realistic	Maintained	0.06	0.06	0.008	0.0007	0.06	0.06	0.02	0.002
IPV	No	cVDPVs	Realistic	Not maintained	0.06	0.06	0.01	0.002	0.08	0.07	0.05	0.006
IPV	No	cVDPVs	Maximum	Maintained	0.005	0.005	0.002	0.0007	0.008	0.006	0.01	0.002
IPV	No	cVDPVs	Maximum	Not maintained	0.007	0.006	0.007	0.002	0.02	0.01	0.04	0.006
IPV	No	cVDPVs and aVDPVs	Realistic	Maintained	0.1	0.09	0.01	0.0007	0.1	0.1	0.02	0.002
IPV	No	cVDPVs and aVDPVs	Realistic	Not maintained	0.1	0.1	0.02	0.002	0.1	0.1	0.05	0.006
IPV	No	cVDPVs and aVDPVs	Maximum	Maintained	0.02	0.02	0.004	0.0007	0.02	0.02	0.01	0.002
IPV	No	cVDPVs and aVDPVs	Maximum	Not maintained	0.02	0.02	0.009	0.002	0.03	0.03	0.04	0.006
No	No	cVDPVs	Realistic	Maintained	0.08	0.07	0.008		0.08	0.07	0.01	
No	No	cVDPVs	Realistic	Not maintained	0.08	0.07	0.008		0.08	0.07	0.02	
No	No	cVDPVs	Maximum	Maintained	0.006	0.005	0.002		0.01	0.009	0.007	
No	No	cVDPVs	Maximum	Not maintained	0.006	0.006	0.002		0.01	0.01	0.01	
No	No	cVDPVs and aVDPVs	Realistic	Maintained	0.1	0.1	0.01		0.1	0.1	0.02	
No	No	cVDPVs and aVDPVs	Realistic	Not maintained	0.1	0.1	0.01		0.1	0.1	0.02	
No	No	cVDPVs and aVDPVs	Maximum	Maintained	0.02	0.02	0.003		0.03	0.02	0.008	
No	No	cVDPVs and aVDPVs	Maximum	Not maintained	0.02	0.02	0.004		0.03	0.02	0.01	

**These estimates are intended to provide context about the relative probabilities under different conditions, not as the actual estimates for any individual country.*
aVDPV = ambiguous vaccine-derived poliovirus; cVDPV = circulating vaccine-derived poliovirus; LMI = lower middle-income country; LOW = low-income country; HIGH = high-income country; OPV = (trivalent) oral poliovirus vaccine; SIAs = supplemental immunization activities; UMI = upper middle-income country

Table 2. Net Present Value of Expected (Fifth Percentile to 95th Percentile) Costs (in Billions of Year 2002 Dollars, 3% Discount Rate) and Expected Number of Outbreaks for Different Decision Options by Income Group (ie, Sums Over All Countries in the Group) for a 20-Year Time Horizon[10,11]

	Low	Lower Middle	Upper Middle	High
Total income group costs ($ billions)				
OPV with SIAs	4.5 (2.8-6.5)	4.4 (2.6-6.9)	3.3 (1.9-5.2)	NA
OPV without SIAs	2.0 (1.1-3.0)	1.2 (0.62-1.8)	0.75 (0.35-1.2)	NA
IPV	5.5 (2.4-7.9)	4.0 (2.5-5.8)	2.2 (1.5-3.1)	9.7 (5.6-15.1)
Number of outbreaks				
OPV with SIAs	7.1 (1-16)	5.3 (0-13)	0.30 (0-1)	NA
OPV without SIAs	51 (23-93)	38 (17-69)	2.0 (0-6)	NA
IPV	2.6 (0-6)	2.0 (0-5)	0.21 (0-1)*	0.025 (0-0)†
No routine	3.4 (0-8)	2.6 (0-6)	0.17 (0-1)	NA

**The expected number of outbreaks with IPV in the upper middle-income group increases to 0.61 (0-3), if we assume that containment is not fully maintained due to the higher chance of release of wild polioviruses from IPV production facilities in countries in this income group.*

†The expected number of outbreaks with IPV in the high-income group increases to 0.077 (0-1), if we assume that containment is not fully maintained due to the higher chance of release of wild polioviruses from IPV production facilities in countries in this income group.

IPV = inactivated poliovirus vaccine; NA = not applicable, refers to a policy permutation that we did not model; OPV = oral poliovirus vaccine; SIAs = supplemental immunization activities

Table 3. Key Assumptions of the Models That Generated mOPV Demand for the Stockpile

Modeling Aspect	Assumptions	References
Analytic time horizon	Outbreak and response model limited to 2-year time horizon after virus introduction, such that viruses that do not lead to detected cases within 2 years do not necessitate a response. For Figure 1, the "no routine" ("universal IPV") results reflect approximately 86% (78%) of outbreaks for which virus detection and all 3 response rounds occurred within 2 years of the virus introduction, approximately 12.5% (19%) of outbreaks that did not lead to detection within 2 years, and approximately 1.5% (3%) of outbreaks for which detection occurred within 2 years, but some or all of the response rounds occurred more than 2 years after the virus introduction with the doses for all response rounds included in the totals.	15,16
Interpopulation spread	The model does not account for outbreaks due to outbreak virus exportations or exportations of OPV viruses used for the outbreak response.	15,16
Population immunity	Preoutbreak immunity profile depends on the time elapsed and policies followed after OPV cessation.	9,11, 13-16
Population size	Outbreak population sizes randomly drawn on the basis of the projected distribution of population size.	15,16,28
Response	Response strategy of 3 mOPV rounds covering 90% of each cohort born since cessation, rounded to the next multiple of 5. For example, with "no routine" a response 7 years after cessation would target all children younger than 10 years, whereas with continued IPV the response would target only children younger than 5 years. The model assumes that the response rounds would control the outbreaks.	13-16
Surveillance	Outbreak detection occurs at the onset of the fifth paralytic case, and the first response round starts 70 days after detection.	13-16

mOPV = monovalent oral poliovirus vaccine; IPV = inactivated poliovirus vaccine

Table 4. Consequences Matrix for Options Related to the Simple OPV Cessation Game

Action Taken by Self	Action Taken by Others							
	Stop OPV Prior to T_0		Stop OPV at T_0		Stop OPV After to T_0		Use OPV Indefinitely	
	Costs for Self	Costs for Others	Costs for Self	Costs for Others	Costs for Self	Costs for Others	Costs for Self	Costs for Others
Stop OPV prior to T_0	C_{pre}	C_{pre}	C_{pre}	C_{min}	$C_{pre} + C_{exp}$	C_{post}	$C_{pre} + C_{inf}$	C_{max}
Stop OPV at T_0	C_{min}	C_{pre}	C_{min}	C_{min}	$C_{min} + C_{exp}$	C_{post}	$C_{min} + C_{inf}$	C_{max}
Stop OPV after T_0	C_{post}	$C_{pre} + C_{exp}$	C_{post}	$C_{min} + C_{exp}$	$C_{post} + C_{exp}$	$C_{post} + C_{exp}$	$C_{post} + C_{inf}$	C_{max}
Use OPV indefinitely	C_{max}	$C_{pre} + C_{inf}$	C_{max}	$C_{min} + C_{inf}$	C_{max}	$C_{post} + C_{inf}$	C_{max}	C_{max}

cVDPV = circulating vaccine-derived poliovirus; OPV = oral poliovirus vaccine
C_{exp} = expected costs of increased risk of circulating vaccine-derived polioviruses (cVDPVs) exported to other countries due to delayed OPV cessation and paid for by other countries
C_{inf} = expected costs of increased risk of cVDPVs exported to other countries indefinitely and paid for by other countries ($C_{inf} > C_{exp}$)
C_{imp} = expected costs of increased risk of cVDPVs imported from neighbors ($C_{imp} > C_{vac1}$)
C_{min} = cost of vaccinating with OPV until time of coordinated OPV cessation (T_0), including costs of vaccination until T_0, vaccine-associated paralytic polio (VAPP) treatment costs, and response and treatment costs associated with potential cVDPV outbreaks within the country's own borders, with the minimum risk of cVDPVs due to coordinated cessation
C_{max} = cost of vaccinating with OPV indefinitely, including vaccination costs before and after T_0, VAPP treatment costs, and increasing expected risks and costs of creating cVDPV outbreaks within the country's own borders[15,16]
C_{own} = expected costs of increased risk of cVDPV outbreaks within a country's own borders due to use of OPV after T_0
$C_{pre} = C_{min} + C_{imp} - C_{vac1}$ = expected costs of stopping OPV before T_0 ($C_{pre} > C_{min}$)
$C_{post} = C_{min} + C_{own} + C_{vac2}$ = expected costs of stopping OPV after T_0 ($C_{post} > C_{min}$)
C_{vac1} = expected costs of vaccination avoided by stopping OPV prior to T_0
C_{vac2} = expected costs of vaccination paid extra by stopping OPV after T_0

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