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Risks of Paralytic Disease Due to Wild or Vaccine-Derived Poliovirus After Eradication

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After the global eradication of wild polioviruses, the risk of paralytic poliomyelitis from polioviruses will still exist and require active management. Possible reintroductions of poliovirus that can spread rapidly in unprotected populations present challenges to policymakers. For example, at least one outbreak will likely occur due to circulation of a neurovirulent vaccine-derived poliovirus after discontinuation of oral poliovirus vaccine and also could possibly result from the escape of poliovirus from a laboratory or vaccine production facility or from an intentional act. In addition, continued vaccination with oral poliovirus vaccines would result in the continued occurrence of vaccine-associated paralytic poliomyelitis. The likelihood and impacts of reintroductions in the form of poliomyelitis outbreaks depend on the policy decisions and on the size and characteristics of the vulnerable population, which change over time. A plan for managing these risks must begin with an attempt to characterize and quantify them as a function of time. This article attempts to comprehensively characterize the risks, synthesize the existing data available for modeling them, and present quantitative risk estimates that can provide a starting point for informing policy decisions.

KEY WORDS: Bioterrorism; decision analysis; disease outbreak; laboratory containment; polio eradication; risk analysis; vaccine-associated paralytic poliomyelitis; vaccine-derived poliovirus

1. INTRODUCTION

Historically, three serotypes of wild poliovirus caused frequent infections in young children and reinfections in adults.[1] While the majority of infections lead to mild disease or no symptoms at all, on average approximately one in 200 infections in susceptible individuals causes paralytic poliomyelitis. Currently, use of inactivated poliovirus vaccines (IPV) in high-income countries and the trivalent oral poliovirus vaccine (OPV) in developing countries provide high population immunity against paralytic poliomyelitis in most of the world. The expanded use of these vaccines reduced the annual global burden of paralytic cases significantly from an estimated 350,000 at the launch of the global Polio Eradication Initiative in 1988 to around 1,000 cases in recent years.[2] With the

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global eradication of wild polioviruses approaching,[3] policymakers must identify and evaluate available policies for management of the risk of poliomyelitis after interruption of wild poliovirus transmission.[4] Following discussion about the immunization policy after eradication,[5–10] coordinated cessation of OPV use for routine or supplemental immunization emerges as a necessary policy choice to accomplish the goal of eliminating paralysis due to all wild or vaccine-derived polioviruses.[11,12] Consequently, countries must decide among and implement options for surveillance, stockpiles, outbreak response, containment of poliovirus stocks in laboratories and IPV manufacturing sites, and management of immunodeficient poliovirus excretors, and whether to provide routine IPV immunization or cease routine polio immunization altogether.[4,13,14] Any combination of these decisions carries future costs and risks; quantitative information can assist decisionmakers by informing them about the tradeoffs among strategies. Several studies exist on the economic benefits and costs of wild poliovirus eradication,[15,16] but none to date thoroughly explore quantitatively the risks, costs, and benefits of the future poliomyelitis risk management options. In developing a decision analytic model for poliomyelitis risk management after eradication, analysts must identify the policy options,[4] estimate their costs,[17] and associated risks, and characterize outbreak consequences using a dynamic transmission model.[18] By integrating all of these components into a quantitative model, analysts can more comprehensively explore the tradeoffs among various options in health and economic terms.

Aylward and Cochi presented a framework for characterizing the risks of poliomyelitis after eradication using two categories for "risks related to the continued use of OPV and risks associated with the unsafe handling of wild polioviruses" (Reference 13, p. 42). The first category included sporadic cases of vaccine-associated paralytic poliomyelitis (VAPP) and the likely occurrence of outbreaks due to vaccine-derived polioviruses (VDPVs).[19] OPV viruses replicating for a period of time can revert to neurovirulent and transmissible VDPVs through accumulated mutations in the genome. This can occur as a result of continued person-to-person transmission that can ultimately lead to an outbreak of paralytic cases (cVDPVs). In addition, VDPVs could emerge as a result of prolonged intestinal replication of viruses initially obtained through an OPV infection among individuals with severe immunodeficiencies (iVDPVs). The second risk category includes unintentional release of wild poliovirus from an IPV-manufacturing facility (production of IPV requires growing large amounts of wild poliovirus) or a laboratory, and intentional release of wild polioviruses (i.e., bioterrorism). Unsafe handling of OPV viruses or VDPVs could also potentially lead to outbreaks in the future.

While Aylward and Cochi identify most of these risks and summarize the current frequency and burden of disease associated with each, they recognize that these risks depend strongly on the policies implemented after eradication.[13] We aim to quantitatively assess the probability of VAPP cases and of poliomyelitis outbreaks as a function of population size, time, future poliomyelitis risk management policies, and income level. For high-income countries, the immunization policies include only continuation of the *status quo* of routine IPV immunization, while for low- and middle-income countries they also include continued routine OPV use or cessation of polio vaccinations altogether.[4] We do not address the consequences or burden of disease related to outbreaks, which requires the use of a dynamic disease model,[18] but we discuss the expected burden of VAPP cases in different populations. We also do not assess the probability of undetected continued wild poliovirus circulation given our focus on the time period that starts after assurance of successful interruption of wild poliovirus transmission.

The next section explains the metrics and data we used to assess each risk. We then present the evidence and provide our best quantitative estimates for each risk. We move from the relatively more certain risks (e.g., VAPP from routine OPV use) to the less certain risks (e.g., bioterrorism). Finally, we discuss the limitations in our risk estimates and the potential use of these results in efforts to inform policymakers. The Appendix provides details about the available data and risk calculations.

2. METHODS

2.1. Scope

Following discussions about the risks of cVDPVs, policymakers recognized that minimizing the burden of paralytic polio requires coordinated global cessation of OPV vaccination as soon as possible after assurance of the interruption of wild poliovirus transmission but not longer than necessary, to avoid the risks associated with OPV use.[12] While the exact year still remains uncertain, we define T_0 as the time when the world will implement its poliomyelitis risk management policies for the posteradication era, and consider an analytical time horizon stretching 20 years beyond. This time horizon enables consideration of

the uncertain but important long-term trends, without exceeding the limits of reasonable extrapolations over time.

We do not address the impact of the development of a potential new polio vaccine on the risks (e.g., one that offers the benefits of OPV without causing VAPP or cVDPVs). At this point, any reduction in risk associated with a new vaccine of unknown properties and the cost needed for development for a disease that is almost eradicated remain difficult to project.

We base our quantitative risk estimates on available data from the peer-reviewed literature, conference presentations, or institutional data, and extrapolate when possible and as needed. For OPV cessation scenarios, however, we face significant challenges in extrapolating from historical data because of the unprecedented susceptibility that will exist in the population after eradication due to the absence of exposure to live polioviruses. With uncertainty unavoidable, we use any available qualitative information about the risks, expected trends, and influences over time to develop quantitative estimates. We characterize the uncertainty using ranges assuming a triangular distribution that peaks at the base case for most estimates, or a log-normal distribution for skewed inputs with very long tails, as indicated.

2.2. Stratification by Income Level and Future Policies

We develop risk functions representing the probabilities of outbreaks and VAPP cases for each country for each of the 20 years of the time horizon. To accomplish this, we stratify the world into four types of countries according to the 2002 World Bank income levels (i.e., low (LOW), lower middle (LMI), upper middle (UMI), or high (HIGH)).[20] While imperfect, stratification by income level provides a means to characterize factors that influence the risks (e.g., different levels of routine immunization coverage, vaccine immunogenicity, and sanitation) that correlate with wealth. For convenience, we assume that this stratification does not change over time. For example, in 2001, 2.5, 2.1, 0.5, and 0.9 billion people lived in countries that we classify as low, lower-middle, upper-middle, and high-income, respectively.[20,21]

We use the term *scenario* to refer to a given set of relevant policies for a country in a specified income level (e.g., an upper-middle-income population that uses IPV for routine immunization, does not carry out supplemental immunization activities (SIAs), and maintains a strict policy for enforcing laboratory and IPV-manufacturing site containment).[4] Such characterizations represent typical scenarios of classes of countries that may experience significantly different risks.

2.3. Risk Metrics

We evaluate the risks using two distinct risk metrics. Given that VAPP incidences represent isolated events, we focus on estimating the inputs required to estimate the number of VAPP cases in a given setting. In contrast, the remainder of the risk estimates focus on estimating the probability of outbreaks and not the number of paralytic cases resulting from them, which would require modeling the dynamics of the outbreaks.[18]

We define an outbreak as the occurrence of at least one confirmed case of paralytic poliomyelitis due to wild or circulating vaccine-derived poliovirus. Thus, in estimating outbreak probabilities we do not consider virus reintroductions that "die out" as outbreaks (i.e., unsustained chains of transmission that result in only asymptomatic infections but no paralytic cases). However, our definition includes isolated paralytic cases (with no observed epidemiological link to other virus isolates or paralytic cases).

We assume that the number of outbreaks follows a Poisson distribution and focus on estimating its parameter, λ, which represents the rate of occurrence per year.[22] For a relatively small λ (e.g., less than 0.2), the Poisson distribution approximates the probability of one event in a year (since the probability of one event is $\text{Poisson}(1) = \lambda e^{-\lambda} \approx \lambda$ for small λ). We characterize outbreak rates per 100 million people, recognizing their additivity (i.e., assuming that we can divide the population into a number of equally sized subpopulations and that the initiating events leading to outbreaks follow independent and identical Poisson distributions). This does not preclude the possibility that the outbreak spreads to different subpopulations. Thus, if three outbreaks occurred in low-income countries (with a total population of 25×100 million) over the last six years, this would translate into an average estimated rate of occurrence in low-income settings of $3/(6 \times 25) = 0.02$ per year for each population of 100 million people, or similarly 0.002 outbreaks per year for each population of 10 million people, etc.

3. THE RISK OF VACCINE-ASSOCIATED PARALYTIC POLIOMYELITIS

OPV contains live, attenuated poliovirus strains (i.e., *Sabin* strains) selected for their low

neurovirulence.[1] However, soon after the introduction of OPV it became apparent that in rare instances infection with an OPV virus can lead to VAPP, a form of poliomyelitis clinically indistinguishable from that caused by wild poliovirus. With massive use of OPV for routine or supplementary immunization, ample opportunity exists for infection with the OPV virus due to both administration of the vaccine (i.e., primary infection) and exposure of contacts of vaccine recipients (i.e., secondary infection with a *Sabin*-like virus). We refer to VAPP cases that occur in vaccinees as *recipient VAPP* and to those cases associated with secondary infections as *contact VAPP* (see the Appendix, Section 1.1).

We express the risk of VAPP in terms of the rates of paralytic poliomyelitis per primary OPV infection and per secondary OPV infection, so that the expected number of VAPP cases (V) as a function of time and the scenario equals:

$$V = r_1 \times I_1 + r_2 \times I_2,$$

where r_1 = the rate of paralytic poliomyelitis per primary OPV infection in fully susceptibles,
r_2 = the rate of paralytic poliomyelitis per secondary OPV infection in fully susceptibles,
I_1 = the number of primary OPV infections in fully susceptibles in a year or during an immunization response as a function of time and the scenario, and
I_2 = the number of secondary OPV infections in fully susceptibles in a year or during an immunization response as a function of time and the scenario.

The disadvantage of this approach is the difficulty in estimating the number of susceptibles that typically get infected with OPV. The advantage derives from the direct relationship between OPV infections and the total number of VAPP cases, and the utility of this method for both routine immunization and outbreak response situations. We use U.S. data to estimate rates of 1.9 recipient VAPP cases per million primary OPV infections and 3.7 contact VAPP cases per million secondary OPV infections (see the Appendix, Section 1.2).[23–35] Varying assumptions about the denominators yield ranges of 1.6 to 2.2 recipient VAPP cases per million primary OPV infections and 2.3 to 10.3 contact VAPP cases per million secondary OPV infections. Due to limitations in data available to estimate the risk of VAPP due to monovalent OPV (mOPV) vaccines, we assume equal rates for mOPV and OPV, although greater uncertainty and serotype variability exists for mOPV.[36,37]

Table I shows inputs and rates for the VAPP risk as a function of several scenarios. The overall base case VAPP rate per million OPV infections in susceptibles due to routine immunization shows little variation across the scenarios. In terms of the risk per million in a birth cohort, these base case estimates range from 1.9 to 2.6 VAPP cases (Table I).

4. THE RISK OF OUTBREAKS DUE TO VACCINE-DERIVED POLIOVIRUSES

Infection with the live OPV virus (or with wild polioviruses) leads to excretion of a slightly modified virus. If the OPV virus can accumulate sufficient mutations through continued replication, then it can revert back to a virulent and transmissible form that may cause outbreaks similar to wild poliovirus.[19] The virologic definition of VDPVs includes those strains with between 1 and 15% divergence from the original vaccine strain in the viral protein 1 (VP1) region (by convention, *Sabin*-like viruses diverge less than 1% while wild-type polioviruses consistently diverge more than 15% from the vaccine strain).[19] Several types of VDPVs exist and they warrant different treatment with respect to quantifying the risk of VDPV outbreaks after OPV cessation. In this article we define three mutually exclusive types of VDPV events:

- Circulating VDPV (cVDPV) event: isolation of VDPVs from at least two cases (epidemiologically linked) of paralytic poliomyelitis or acute flaccid paralysis (AFP),
- Immunodeficient VDPV (iVDPV) event: isolation of a VDPV from an immunodeficient person excreting at least six months after infection with the vaccine virus, and
- Ambiguous VDPV (aVDPV) event: isolation of VDPVs from a single immunocompetent AFP or paralytic poliomyelitis patient with or without additional isolates from contacts, or from healthy individuals or the environment in absence of paralytic cases. (We emphasize that by definition we consider the occurrence of at least one confirmed paralytic case as an outbreak, although we note that not all analysts might use this same definition.)

We discuss the first two risks in separate subsections, recognizing that the occurrence of iVDPV events depends on distinctly different factors than the occurrence of cVDPV events, and we assigned each aVDPV event to one of these two categories

Table I. Inputs and Estimates for Prospective Calculation of VAPP Risk

Symbol [and Formula if Derived]	Input	Income Level and OPV Immunization Policy						
		LOW		LMI		UMI		US 1980–1997
		no SIAs	SIAs	no SIAs	SIAs	no SIAs	SIAs	no SIAs
C	Coverage with at least 3 OPV doses	0.68	0.80	0.90	0.95	0.92	0.95	0.75
e	Primary take rate for 3 OPV doses (% seroconverting)	0.71	0.71	0.85	0.85	0.85	0.85	0.95
E	Effective take rate for birth cohorts	0.75	0.99	0.90	0.99	0.92	0.99	0.95
r[r=r1∗C∗e + r2∗(E-C∗ e))/E]	Rate of (recipient + contact) VAPP cases per million (primary + secondary) OPV infections	2.53	2.66	2.15	2.21	2.15	2.21	2.33
rbc [rbc = r∗E]	Rate of VAPP cases per million birth cohort	1.90	2.63	1.93	2.19	1.98	2.19	2.21
	Inputs relating to VAPP due to outbreak response	LOW	LMI	UMI	HIGH			
e1	Primary take rate for 1 OPV dose (trivalent)	0.45	0.65	0.65	0.78			
em1	Primary take rate for 1 monovalent OPV dose (averaging over serotypes)	0.76	0.91	0.91	0.91			
Psec	Proportion of susceptibles secondarily infected per mass immunization round	0.60	0.37	0.30	0.20			

r1 = rate of 1.9 recipient VAPP cases per 100 million primary OPV infections (see the Appendix, Section 1.2); r2 = rate of 3.7 contact VAPP cases per 100 million secondary OPV infections (see the Appendix, Section 1.2)
HIGH = high-income country; LMI = lower-middle-income country; LOW = low-income country; OPV = (trivalent) oral poliovirus vaccine; SIAs = supplemental immunization activities; UMI = upper-middle-income country; VAPP = vaccine-associated paralytic poliomyelitis.

depending on the nature of the event and the strength of the evidence.

4.1. The Probability of cVDPV Outbreaks

4.1.1. Inventory of Confirmed and Suspected cVDPV Events

Table II separately lists documented episodes of confirmed cVDPVs and suspected cVDPVs that remain classified as aVDPVs given the presence of only a single paralytic case.[38–46] We further categorize the data into events before and after 1999, recognizing that the choice of the time period substantially impacts estimates of outbreak frequencies (derived by dividing the number of outbreaks by the time period). The observation that the last wild-type isolate of the detected VDPV serotype occurred at least three years prior to the event (except for the outbreaks in Peru and possibly in Romania in 1980) suggests that the eradication of a serotype may substantially increase the risk of cVDPVs of that serotype. Consequently, we believe that estimates of prospective risks of cVDPVs should focus on events that occurred between 1999 and 2005, which represents a seven-year period characterized by historically high global OPV use, complete elimination of all type 2 wild polioviruses, and elimination of type 3 and type 1 wild polioviruses in most parts of the world.

Investigators analyzed viruses obtained from six recent cVDPV outbreaks with at least two paralytic cases (Hispaniola, Philippines, Madagascar (twice), China, Indonesia) and six recent aVDPVs isolated from AFP cases (Pakistan, Nigeria, Romania, Kazakhstan, Madagascar (twice)). Reflecting the uncertainty about the appropriate interpretation of the aVDPVs, we consider two risk cases (see Table II): (1) the six confirmed cVDPV outbreaks only and (2) all 12 cVDPV and aVDPV events after 1999. Note that we consider the Dominican Republic outbreak as a part of the Haitian outbreak (i.e., as a single Hispaniola outbreak) since it began with an imported virus from the Haitian outbreak.[42] We classified events as occurring on a background of SIAs if any SIAs

Table II. Characterization of cVDPV and aVDPV Events

Time Period	Country	Serotype	Number of Isolates (% Divergence)[a]	Paralytic Cases	Last Wild Case or Isolate (Excluding Importations)	Last SIAs Before Event	Scenario	Source
Documented cVDPV outbreaks (1999–2005)								
2005	Indonesia	1	≥45 (1.1–3.0)	45	1995	2002	LOW, OPV, no SIAs	(38)
2005	Madagascar	2	4 (1.1–1.8)	3	1997	2002	LOW, OPV, no SIAs	(38)
2004	China (Guizhou)	1	4 (1.0–1.2)	2	< 1985 (WPV2)	SNIDs ongoing	LMI, OPV, SIAs	(39)
2002	Madagascar	2	6 (2.5–3.0)	4	1997	Between 1997 and 1999	LOW, OPV, no SIAs	(40)
2001	Philippines	1	4 (3.1–3.5)	3	1993	1997[b]	LMI, OPV, no SIAs	(41)
2000–2001	Haiti	1	10 (~2.6)	8	1989	<1996	LOW, OPV, no SIAs	(42)
2000–2001	Dominican Republic[c]	1	21 (~1.9)	13	1985	1996	LMI, OPV, no SIAs	(42)
Documented cVDPV outbreaks prior to 1999 (i.e., not included in further analysis)								
1988–1993	Egypt	2	30 (4.0–7.0)	30	1979 (WPV2)	Probably none	LMI, OPV, no SIAs	(43)
Documented aVDPVs with possible circulation (1999–2005)								
2005	Madagascar	2	4 (2.3–2.7)	1	1997	2002	LOW, OPV, no SIAs	(38)
2005	Madagascar	3	8 (1.0–1.8)	1	1997	2002	LOW, OPV, no SIAs	(38)
2002–2003	Kazakhstan	2	2 (2.3)	1	<1985 (WPV2)	1999	LMI, OPV, no SIAs	(39)
2002	Romania	1	8 (1.1–1.3)	1	<1996	SNIDs ongoing	LMI, OPV, SIAs	(44)
2002	Nigeria	2	1 (2.4)	1	1998 (WPV2)	Ongoing	LOW, OPV, SIAs	(44)
2000	Pakistan	2	1 (2.3)	1	1997 (WPV2)	Ongoing	LOW, OPV, SIAs	(45)
Documented aVDPVs with possible circulation prior to 1999 (i.e., not included in further analysis)								
1983	Peru	2	1 (5.8)	1	WPV2 circulation ongoing	Probably none	LMI, OPV, no SIAs	(45)
1980	Romania	1	1 (1.2)	1	Limited WPV1 transmission ongoing	Ongoing	LMI, OPV, SIAs	(46)

Total number of events[d]	**cVDPV outbreaks**	**cVDPV outbreaks and aVDPV events**
Total	7	15
Total 1999–2005 (all on OPV background)	6	12
On *OPV with SIAs* background	1	4
On *OPV without SIAs* background	5	8

[a] Percent divergence refers to the number of nucleotide changes in the VP1 region compared to the parent OPV strain.
[b] However, several provinces not involved in the outbreak conducted SNIDs in 1998 and 1999.
[c] Outbreak involved a strain imported from the Haitian outbreak.
[d] Excluding the cVDPV event in the Dominican Republic since this outbreak involved a strain imported from the Haitian outbreak.
aVDPV = ambiguous vaccine-derived poliovirus; cVDPV = circulating vaccine-derived poliovirus; LMI = lower-middle-income country; LOW = low-income country; OPV = (trivalent) oral poliovirus vaccine; SIAs = supplemental immunization activities; SNIDs = subnational immunization days; VP1 = viral protein 1; WPV1, WPV2 = wild poliovirus type 1, 2, respectively.

occurred in the two years preceding the outbreak. In addition to these cVDPV and aVDPV events, the Appendix (Section 2, Table A3) lists aVDPVs that we did not include in Table II or our risk estimates.[38,40,44,47–58] Thus, our risk estimates rely on the evidence of six confirmed cVDPVs or, alternatively, 12 combined cVDPVs and aVDPVs in seven years with a background of routine OPV immunization, including one confirmed cVDPV or, alternatively, four combined cVDPVs and aVDPVs in seven years in countries carrying out some form of SIAs, as shown at the bottom of Table II.

4.1.2. Dependence on Time and Scenarios

With continued use of OPV, decreased population immunity increasingly appears to represent a key risk factor for the emergence and spread of cVDPVs.[19,59] Therefore, we anticipate that in the context of routine OPV vaccination, regular SIAs

decrease the risk while cessation of SIAs increases the rate of occurrence compared to the risk in OPV-using countries that conduct SIAs. Furthermore, for either SIA policy, population immunity probably correlates with income because of decreased OPV effectiveness[1] and generally lower routine immunization coverage in low-income settings.[21] In addition, poor hygiene, tropical climate, and crowding all correlate with low income, and favor the spread of polioviruses and the emergence of cVDPVs. If OPV use continues but coverage decreases, this would lead to an increase in cVDPV risk over time.

If the world stops OPV use completely, population immunity levels will decrease with the addition of unvaccinated and unexposed birth cohorts. However, the cessation of OPV use in those scenarios ends the routine introduction of large amounts of potential VDPVs through vaccination. Few experiences exist with cessation of OPV to estimate the ability of OPV viruses to persist in such a situation. Since 1962 in Cuba and until the early 1990s in several Eastern European countries, vaccination occurred exclusively during mass OPV campaigns, with no vaccine available between campaigns and virtual absence of wild polioviruses during most of these time periods.[60,61] Studies of the persistence of polioviruses in between campaigns in Cuba found no evidence of OPV virus persisting for longer than a few months,[62–64] and no detected cVDPV events occurred in the months between the OPV campaigns. However, researchers isolated an aVDPV in Romania in 1980, which then also relied exclusively on campaigns (Table II). Furthermore, an aVDPV in Belarus (see the Appendix, Table A3) followed cessation of OPV during 1963–1966 in a local population of about 160,000[56] and suggests some possibility that VDPVs can emerge after stopping OPV use when neighboring populations continue using OPV.

IPV vaccination provides less efficiency in preventing poliovirus excretion than OPV and offers no benefits from secondary immunizations.[65–67] Consequently, the population protection against infections decreases with time after implementation of a policy of switching to IPV. As with the cessation of polio vaccinations altogether, this increases the likelihood that OPV viruses can circulate and become cVDPVs, but at the same time OPV cessation drastically limits the prevalence of OPV viruses. Recent experience of countries transitioning from OPV to IPV provides some insights. New Zealand made a rapid switch from routine OPV to IPV immunization in 2002. A study searching for OPV viruses in several surveillance systems (pediatric, enterovirus, and environmental) found no VDPVs and a rapid decline in prevalence of *Sabin*-like viruses in the months following the switch to IPV (with a few isolates up to 11 months after the switch probably representing OPV virus importations rather than continued circulation).[68] A type 3 outbreak involving viruses derived from an experimental OPV strain (i.e., USOL-D-bac, not used anymore) occurred in Poland in 1968 on a background of low, type 3 (nonenhanced potency vaccine) IPV-immunity.[55,59] The very weak evidence in the Polish experience, which occurred with much lower quality vaccines than currently used, suggests that even in a temperate climate and upper-middle-income setting, VDPVs could emerge, circulate, and cause paralytic poliomyelitis in the context of imperfect (nonenhanced potency) IPV-induced protection[59] and that a switch to IPV (with low coverage) does not exclude the possibility of cVDPVs. Uncertainty still exists concerning the ability of modern IPV vaccines to reduce transmission of polioviruses in developing countries due to the lack of experience with IPV in those settings. Most importantly, the experiences in Belarus, Poland, and New Zealand underscore the risk of failing to coordinate the cessation of OPV globally.

For any policy, the population immunity level at T_0 impacts the probability of cVDPV outbreaks in subsequent years. Based on the experience in countries that already eradicated polio, it appears realistic to assume that countries may stop conducting SIAs and/or maintaining high population immunity at least three years prior to T_0. We refer to this as the realistic population immunity (RPI) scenario. Alternatively, if countries continue SIAs until T_0 or carry out a coordinated pulse to bring coverage in all areas up to more than 90%, this would provide maximum population immunity at T_0, and we refer to this as the maximum population immunity (MPI) scenario.

4.1.3. Quantification of Probability of Outbreaks Due to cVDPVs

For the calculation of the cVDPV outbreak rates, we assume that if routine OPV use continues the rates remain equal to the currently observed rates, and that if routine OPV use ceases in a coordinated fashion then the rates will decay exponentially according to a half-life that depends on the scenario (see the Appendix, Section 2 and Table A4). The initial rate depends on whether regular SIAs continued until T_0. In the event that SIAs continue until T_0 and the policy going forward consists of only routine OPV

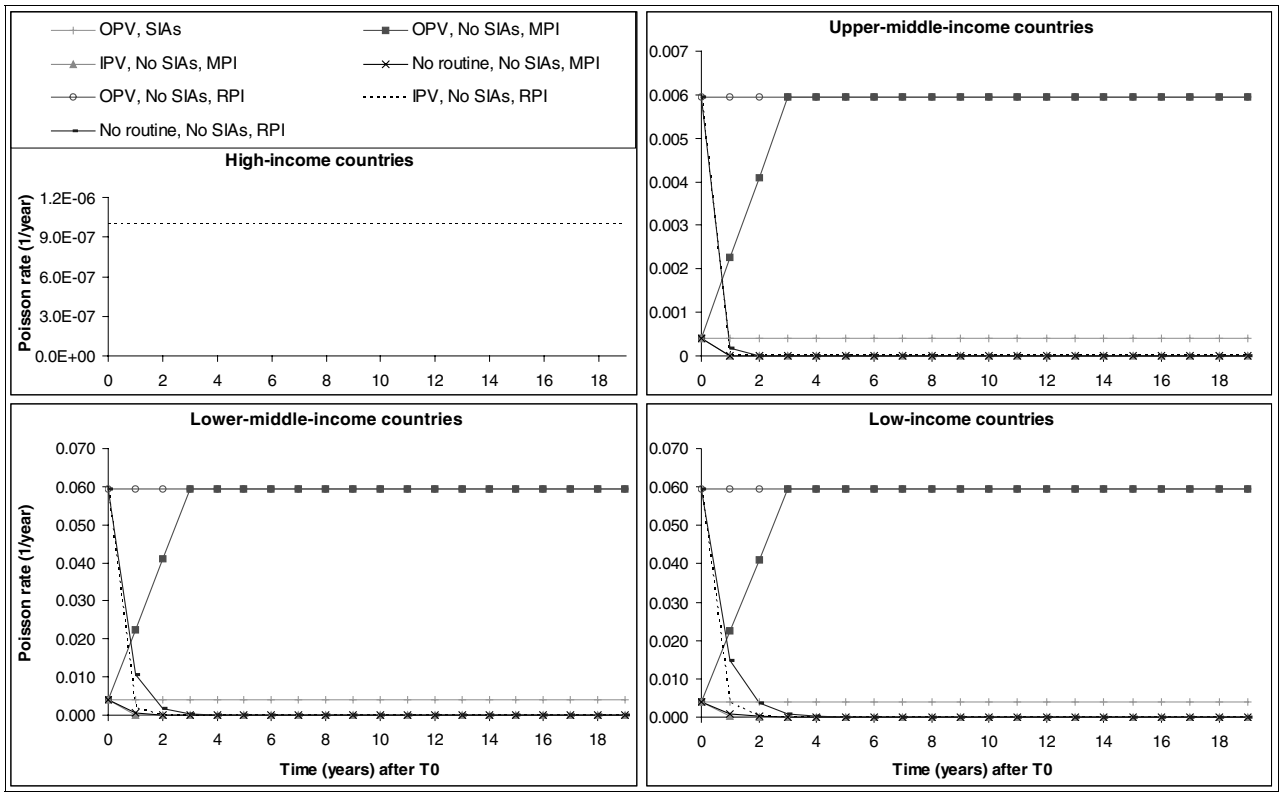

Fig. 1. Yearly (Poisson) rate of occurrence of cVDPV outbreaks per 100 million people, by income level based on only the 6 cVDPV outbreaks from Table II. The scales on the *y*-axis are not all equal. (cVDPV = circulating vaccine-derived poliovirus; IPV = inactivated poliovirus vaccine; MPI = maximum population immunity at T_0; OPV = (trivalent) oral poliovirus vaccine; RPI = realistic population immunity at T_0; SIAs = supplemental immunization activities.)

immunization, the rates increase linearly from the current rate for OPV with SIAs to the rate without SIAs.

We assume that half-lives of the cVDPV risk in IPV-using countries equal half of those in countries that stopped polio vaccinations altogether (i.e., the risk disappears twice as fast in IPV-using countries). We assume that high-income countries switched to IPV on average in 1998 and consequently they face negligible constant risk of cVDPVs (i.e., Poisson rate of one per million per year), with only cVDPV importations from any OPV-using countries or escape of OPV-derived viruses from laboratories possibly leading to cVDPV outbreaks.

Figs. 1 and 2 show the cVDPV outbreak rates over time for each policy and income level based on only the confirmed cVDPVs and on the combined cVDPVs and aVDPVs during 1999–2005 as listed in Table II, respectively. The inclusion of the aVDPVs as potential signals of cVDPV risk leads to an increase in the initial rates, but the shapes of the functions remain equal for both cases (note the different scales used in the figures). If OPV were to continue, the rate of occurrence remains constant over time and equal for both income levels, with a much higher risk expected in the absence of SIAs than with continued SIAs. If OPV immunization ceases, the rate starts at the average yearly number of outbreaks per 100 million people on an OPV background with or without SIAs, depending on the population immunity at T_0 (RPI or MPI) and then declines quickly to less than 0.0001 outbreaks per year per 100 million people within five years at all income levels. The decline occurs most rapidly with a switch to IPV in upper-middle-income countries (corresponding to the shortest half-life) and most slowly with cessation of all polio vaccinations in low-income countries (longest half-life). We assume a 10-fold lower initial risk for upper-middle-income countries compared to low- and lower-middle-income countries (assumed to experience similar initial rates based on the observed occurrence of events in Table II). Overall, combining the risk estimates for the RPI scenario with the global population forecasts[20,69]

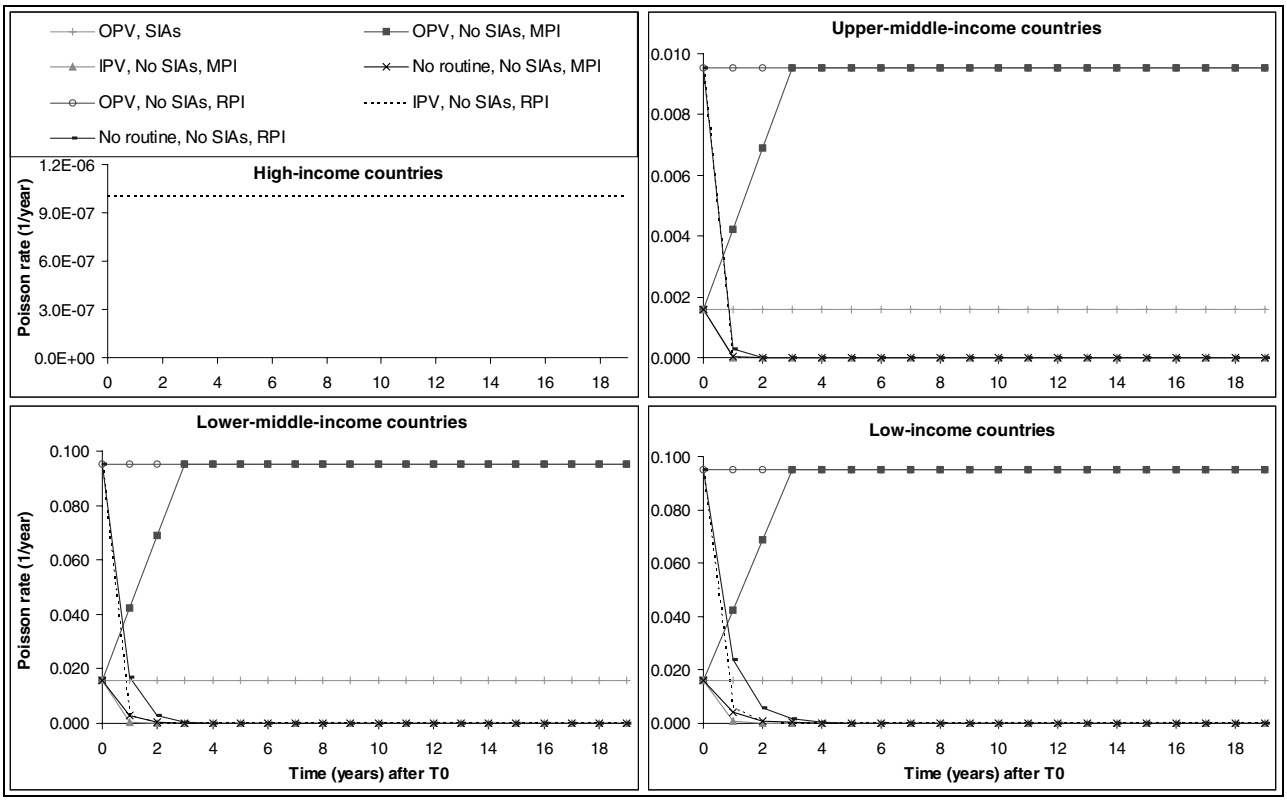

Fig. 2. Yearly (Poisson) rate of occurrence of cVDPV outbreaks per 100 million people, by income level based on the 12 cVDPV and aVDPV events from Table II. The scales on the *y*-axis are not all equal. (aVDPV = ambiguous vaccine-derived poliovirus; cVDPV = circulating vaccine-derived poliovirus; IPV = inactivated poliovirus vaccine; MPI = maximum population immunity at T_0; OPV = (trivalent) oral poliovirus vaccine; RPI = realistic population immunity at T_0; SIAs = supplemental immunization activities.)

suggests a greater than 95% chance of at least one cVDPV outbreak during the first year after cessation of routine immunization, with that risk declining to less than 6% at the end of the third year. If we instead assume the MPI scenario, then the probability equals less than 60% in the first year, declining to less than 1% at the end of the third year.

4.2. The Probability of iVDPV-Related Outbreaks

4.2.1. Inventory of Confirmed and Suspected iVDPVs

Long-term excretion of iVDPV viruses represents a very rare condition found only among persons with primary immunodeficiencies (PIDs) (see the Appendix, Section 3.1).[70–72] Table III lists iVDPVs detected to date.[1,38,39,45,48,71,73–89] Our definition of an outbreak as at least one paralytic case suggests that we should count as an outbreak any iVDPV viruses that spread to the community and cause at least one paralytic case. In this context, iVDPV excretors who developed paralytic poliomyelitis themselves do not represent outbreaks, given their original infection with *Sabin*-like viruses (i.e., not with a VDPV virus). To date, investigators detected or investigated no substantial spread beyond the immunodeficient patients in Table III,[90] and consequently, while the evidence provides some information about the prevalence of iVDPV excretors, it offers little information about the likelihood of outbreaks associated with iVDPVs. However, recent events in an Amish community in Minnesota demonstrated the possibility of circulation of an iVDPV virus in a low-coverage subpopulation in a high-income country.[48]

While most excretors stopped excreting or died within four years of the associated OPV infection, a limited number of iVDPV excretors (all but one diagnosed with common variable immunodeficiency disorder) continued to shed virus for well over five years. Based on the distinction of extended excretion potential, rather than an immunological argument, we

Table III. Documented iVDPV Excretors and Isolations of aVDPVs Suggesting Prolonged Excretion (as of 1/1/06)

Year of Onset of Paralysis or First Sample Collection[a]	Country	Income Level	Immune Deficiency	Paralysis (Yes/No)	Serotype	Age (Years) at Onset of Paralysis or First Sample Collection	Interval Between Associated OPV Dose and Last Positive Sample (Years)[b]	Maximum VP1 Divergence (%)[c]	Estimated Duration of iVDPV Excretion (Years)[d]	Excreting in 2005? (Yes/No)	Outcome	Sources
Chronic iVDPV excretors (excreting more than five years after the associated OPV infection/dose)												
2002	UK	HIGH	CVID	No	2	15	Unknown	6.3	5.8	Yes	Alive	Unpublished
2000	Germany	HIGH	Ab def.	Yes	1	24	Unknown	8.0	8.5[e,f]	Yes	Alive	(1)
1995	UK	HIGH	CVID	No	2	25	23	15.7	22.5[f]	Unknown[g]	Alive	(73)
1990	Germany	HIGH	CVID	Yes	1	7	Unknown	8.3	7.8	No	Alive	(74)
1986	US	HIGH	CVID	No	1 and 2[h]	11	9.6	11.8	9.1[f]	Unknown	Alive	(1, 45)
1981	US	HIGH	CVID	Yes	1	17	7.6	10.0	7.1	No	Died	(75)
Suspected iVDPVs detected through environmental sampling												
2003	Slovakia	UMI	NA	NA	2	NA	NA	15.0	15.8[e,f]	Yes	NA	(76)
2002	Estonia	UMI[i]	NA	NA	3	NA	NA	13.3	12.8	No[j]	NA	(77)
1998	Israel	HIGH	NA	NA	2	NA	NA	13.8	14.3[e,f]	Yes[k]	NA	(39, 78)
Prolonged iVDPV excretors (excreting between six months and five years after the associated OPV infection/dose)												
2005	China	LMI	Unknown	Yes	2 and 3[l]	2	Unknown	2.7	2.2[m]	Yes	Alive	(79)
2005	S. Arabia	UMI	Unknown	Yes	2	0.9	Unknown	1.9	1.4	Yes	Died	(38)
2005	Iran	LMI	CVID	Yes	2 and 1[n]	0.6	0.7	1.1	0.2[m]	Yes	Alive	(38)
2003	Peru	LMI	Agamma	Yes	2	0.8	0.8	1.2	0.3	No	Alive	(39)
2003	Thailand	LMI	A/hypogamma	Yes	2	1.5	1.3	2.2	0.8	No	Unknown	(80)
2002	Kuwait	HIGH	MHC II def.	No	2	2	0.9	2.0	0.4	No	Died	Unpublished
2002	UK	HIGH	ICF syndrome	No	2	1.5	Unknown	2.5	2.0	No	Alive	Unpublished
2001	Taiwan	HIGH	CVID	Yes	1	8	2.7	3.5	2.2	No	Alive	(81)
1998	Argentina	UMI	XLA	Yes	1	3	Unvaccinated	2.8	2.3	No	Alive	(82)
1995	US	HIGH	SCID	Yes	2	0.3	3.7	2.1	3.2	No	Died	(71)
1995	Iran	LMI	Ab def.	Yes	2	1.5	Unvaccinated	2.2	1.0[o]	No	Died	(1)
1990	US	HIGH	SCID	Yes	2	1.3	0.8	1.9	0.3	No	Died	(71)
1987	UK	HIGH	CVID	No	2	34	Unknown	4.1	3.6	No	Alive	(83)
1980	US	HIGH	Agamma	Yes	2	1.7	1[p]	Unknown	0.5	No	Died	(71)
1977	Japan	HIGH	XLA	Yes	2	3	3.4	Unknown	2.9	No	Died	(84,85)
1962	UK	HIGH	Hypogamma	No	3	20	1.8	2.3	1.3	No	Died	(86,87)
1962	UK	HIGH	Hypogamma	No	1	3	2.7	Unknown	2.2	No	Died	(88,89)

(*Continued*)

Table III. (*Continued*)

Year of Onset of Paralysis or First Sample Collection[a]	Country	Income Level	Immune Deficiency	Paralysis (Yes/No)	Serotype	Age (Years) at Onset of Paralysis or First Sample Collection	Interval Between Associated OPV Dose and Last Positive Sample (Years)[b]	Maximum VP1 Divergence (%)[c]	Estimated Duration of iVDPV Excretion (Years)[d]	Excreting in 2005? (Yes/No)	Outcome	Sources
Immunodeficient persons excreting diverged viruses, but no longer than six months after the associated OPV infection (excluded from further analysis)												
2005	US	HIGH	SCID	No	1	0.6	Unvaccinated	≥2.3	NA	Yes	Alive	(48)
2005	Spain	HIGH	SCID	Yes	2	0.7	Unknown	≥2.5	NA	Yes	Alive	(38)
1991	US	HIGH	CVID	Yes	2	0.7	0.4	1.4	NA	No	Alive	(71)
1989	US	HIGH	Agamma	Yes	1	0.6	0.3	1.1	NA	Unknown	Unknown	(71)
1986	US	HIGH	XLA	Yes	2	0.9	0.4	2.0	NA	No	Alive	(71)

[a] Indicates year of onset of paralysis for paralytic cases or year of first sample collection for iVDPV excretors without paralysis.
[b] "Unknown" in this column indicates insufficient information exists to determine associated OPV dose, or evidence exists that associated infection was secondary.
[c] Percent divergence refers to the number of nucleotide changes in the VP1 region compared to the parent OPV strain.
[d] If (statistically) consistent with recorded mutation rate of virus, duration estimate equals interval between the associated OPV dose and last positive sample minus the first six months (during which we assume excretion of *Sabin*-like viruses similar to viruses that immunocompetent individuals excrete after OPV infection). Otherwise, we estimate this assuming a molecular clock with a rate of 1% nucleotide divergence per year.
[e] The maximum VP1 divergence refers to a virus isolated at least 16 months ago (as of 1/1/06), therefore we added 16 months to the duration estimate, assuming continued excretion during 2005.
[f] Duration may increase in future as excretion continues.
[g] Virus isolated in 2004 but no specimens taken in 2005.
[h] Investigators isolated a type 1 iVDPV with 5.4% VP1 divergence in 1986 and two subpopulations of type 2 iVDPVs with 10.9% and 11.8% VP1 divergence in 1992, respectively. No recent virus detection occurred, but no evidence exists of absence of excretion.
[i] Although the virus detection occurred in an upper-middle-income country, no further detections occurred. We assume the excretor represents an otherwise unidentified chronic excretor who visited from a high-income country. In further analysis, we classify the excretor as a high-income excretor.
[j] Environmental surveillance failed to detect the virus after 2002.
[k] Last positive sample from 2004 with only negative samples during 2005 does not negate excretion in 2005.
[l] Investigators isolated type 2 iVDPVs with up to 2.3% VP1 divergence and a type 3 iVDPVs with 2.7% VP1 divergence.
[m] May become a chronic excretor in the future if excretion continues.
[n] Virus is *Sabin* 2 - *Sabin* 1 recombinant, VP1 divergence refers to *Sabin* 2.
[o] Duration estimated as the age at onset of paralysis minus six months.
[p] Not including a neural isolate obtained at autopsy approximately 4.3 year after last OPV dose.
Ab def. = antibody deficiency; Agamma = agammaglobulinemia; aVDPV = ambiguous vaccine-derived poliovirus; CVID = common variable immunodeficiency disorder; IPV = inactivated polio vaccine; HIGH = high-income country; hypogamma = hypogammaglobulinemia; ICF = Immunodeficiency-centromeric instability-facial anomalies; iVDPV = immunodeficient vaccine-derived poliovirus; LMI = lower-middle-income country; MHC II def. = major histocompatibilty complex class II molecule deficiency; NA = not applicable; OPV = oral poliovirus vaccine (any formulation); SCID = severe combined immunodeficiency disorder; SIAs = supplemental immunization activities; UMI = upper-middle-income country; VPI = viral protein 1; XLA = X-linked agammaglobulinemia.

define for our analysis the following two types of iVDPV excretors:

- Prolonged excretors: individuals excreting VDPVs at least six months but no longer than five years after the associated OPV infection.
- Chronic excretors: individuals excreting VDPVs at least five years after the associated OPV infection.

In the context of OPV cessation, chronic excretors carry the greatest risk of reseeding VDPVs in a population with much reduced population immunity. However, this type of excretor appears to survive only in high- and possibly upper-middle-income countries. During 44 years of widespread OPV use (1962–2005), investigators detected six chronic excretors, 15 prolonged excretors (including three with uncharacterized viruses), and two prolonged excretors with the potential to become chronic excretors (Table III). We also include in our analysis three virus isolates from the environment that strongly suggest the presence of a chronic excretor. In addition, we list five aVDPVs with more than 1% VP1 divergence from the original OPV strain associated with immunodeficient patients who excreted for less than six months, but we exclude these from further analysis given their short durations of excretion. In estimating the duration of iVDPV excretion, we exclude the first six months of excretion because we consider viruses excreted during that period to be within the period observed with OPV viruses that immunocompetent persons excrete after immunization or contact exposure. Thus, for vaccinated iVDPV excretors, we assume that the total duration of excretion equals the time from the associated OPV infection until the last positive sample minus six months, unless evidence suggests a different duration of excretion. In those cases (e.g., unvaccinated iVDPV excretors and environmental iVDPV isolates), we estimate the duration of excretion from the divergence of the virus to the original OPV strain and assume a rate of 1% (range 0.9–1.3) nucleotide divergence in the VP1 region per year.[91] This amounts to an average duration of excretion of approximately 11.5 years for chronic excretors and 1.6 years for prolonged excretors, and a total of 131 person-years of iVDPV excretion without occurrence of an outbreak.

4.2.2. Dependence on Time and Scenarios

While the individual risk of becoming an iVDPV excretor is extremely low, even in the presence of massive, global OPV use, the population risk of iVDPV-related outbreaks may change after T_0 for several reasons. Among the available immunization policies, OPV routine immunization leads to the highest prevalence of iVDPV excretors, but high population immunity reduces the impact and likelihood of iVDPV-related outbreaks. With cessation of OPV use, we anticipate that the prevalence of iVDPVs will approach 0 within several years in developing countries, depending on the duration of excretion and the survival of iVDPV excretors, which appears lowest in low-income settings.[92] However, OPV cessation will limit the ability of the surrounding community to stop transmission of viruses excreted by an iVDPV excretor. Therefore, the risk of iVDPV-related outbreaks in those instances may initially increase over time. We emphasize that all of the known chronic excretors occurred in developed countries (i.e., six in high-income countries, with an additional three possible iVDPV excretors detected through environmental surveillance in upper-middle or high-income countries), and it remains unclear whether the increased risk due to a higher transmissibility of polioviruses in low-hygiene settings outweighs the decreased risk due to a shorter survival of immunodeficient people in those settings.

Risk management strategies, such as identification and education of immunodeficient excretors and/or immunization of their contacts, may further reduce the risk of iVDPV-related outbreaks by reducing the number of secondary infections from an iVDPV excretor and increasing the immunity barrier provided by the immediate surroundings. Although attempts to use existing antivirals for one known chronic excretor failed,[73] new technology involving treatment of iVDPVs with an antiviral may become available at some point, which could reduce the viral output of iVDPV excretors and thus the risk of iVDPV excretors causing an outbreak. However, this would require substantial investment in the development of such an antiviral, and given that antivirals can reduce excretion only for identified excretors, we remain uncertain about its overall effectiveness and whether society will make this investment.

4.2.3. Quantification of Probability of Outbreaks Due to iVDPVs

We model the probability of outbreaks due to iVDPVs in any given year as the product of the prevalence of long-term iVDPVs excretors and the conditional probability of an outbreak given the

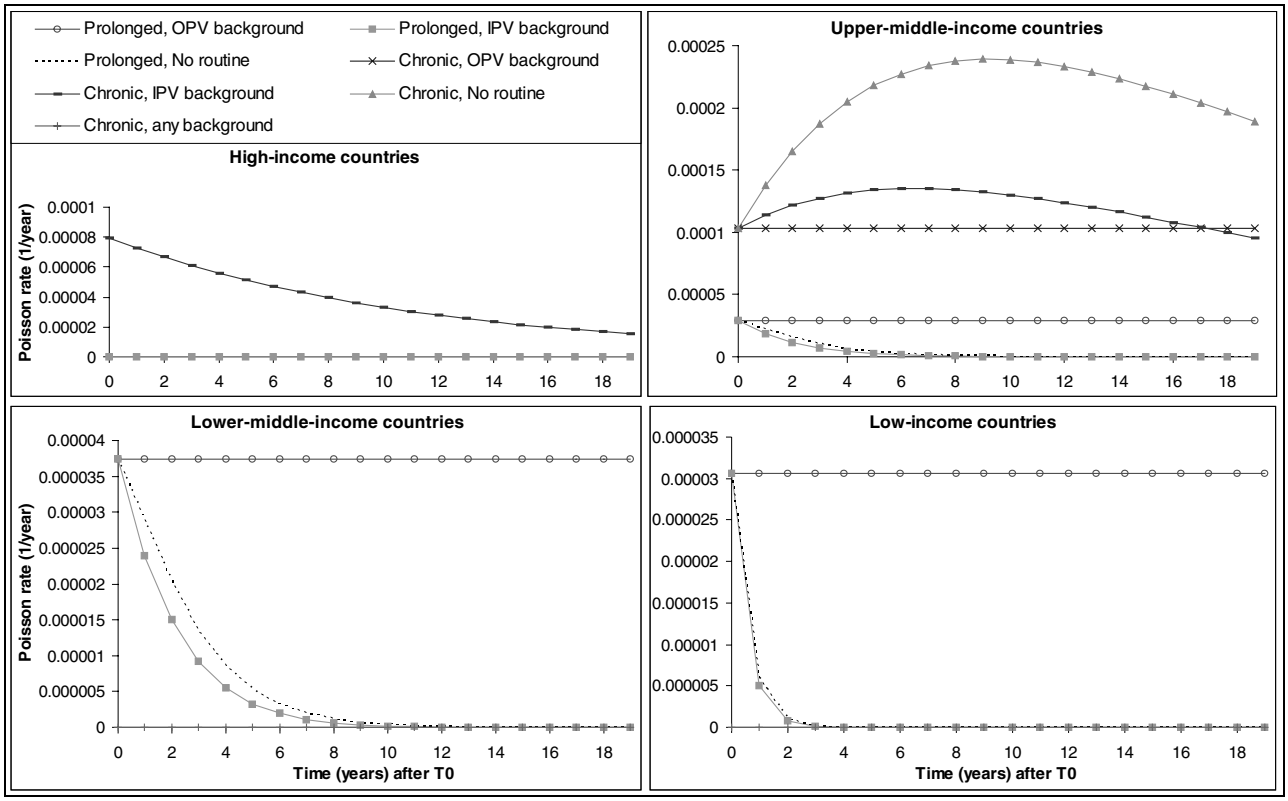

Fig. 3. Yearly (Poisson) rate of occurrence of outbreak due to iVDPVs per 100 million people. For the OPV scenario we assume equal rates with or without supplemental immunization activities. The scales on the *y*-axis are not all equal (IPV = inactivated poliovirus vaccine; iVDPV = immunodeficient vaccine-derived poliovirus; OPV = (trivalent) oral poliovirus vaccine).

presence of at least one iVDPV excretor. While we assume that both the prevalence and the conditional probability remain constant if OPV use continues, we modeled an exponential decay of the prevalence (the mean duration of excretion determines the rate) but a linear increase in the conditional probability in the case of OPV cessation. We calculate the outbreak rates for chronic and prolonged excretors separately (see the Appendix, Section 3.2 and Table A5).

Fig. 3 shows the breakdown of the outbreak rates by prolonged or chronic excretors by income level. Due to the lack of chronic excretors in low- and lower-middle-income countries, we expect very low Poisson rates despite the increasing conditional probability of an outbreak given an iVDPV as time since OPV cessation elapses. However, the existence of chronic excretors in upper-middle-income countries suggests that these countries face the highest risk of iVDPV-related outbreaks in the medium-long term, although if they switch to IPV this risk would decrease more rapidly. High-income countries experience the lowest conditional probability of an outbreak given an excretor due to good sanitation (i.e., low virus transmissibility) and population immunity and also experience lower prevalence of iVDPV excretors than upper-middle-income countries due to the cessation of OPV use dating back to 1998 on average (which reduced the introduction of new iVDPV excretors into the population). We based the outbreak rates in Fig. 3 on the observed prevalence of prolonged and chronic iVDPV excretors to date, which probably underestimates the true number of excretors (see the Appendix, Section 3.3). Aggregated globally, the very small annual risk estimates imply a probability of approximately 4% of at least one outbreak due to iVDPVs during the 20-year timeframe (assuming IPV continuation in high-income countries, but complete cessation elsewhere), with an approximately 3% probability of at least one outbreak in upper-middle- and high-income countries.

5. THE RISK OF OUTBREAKS DUE TO WILD POLIOVIRUSES

The risk of outbreaks due to wild polioviruses represents the most uncertain risk category. However, we know wild polioviruses could reemerge through several pathways and that this risk may dominate as the risks associated with OPV use disappear. While we provide our current best estimates for these risks, we rely on very limited data and judgment as we consider two types of events that could lead to wild poliovirus outbreaks after T_0:

- An unintentional breach in containment of wild poliovirus stocks in a laboratory or in an IPV manufacturing facility, and
- An intentional release of wild poliovirus through an act of bioterrorism.

5.1. Unintentional Breach in Containment of Poliovirus Stocks

5.1.1. Containment Breaches in the Past

Limited reports suggest that reintroduction of wild poliovirus from an unintentional breach in containment poses the risk of greatest concern for reemerging wild poliovirus after eradication.[6,93–95] While direct transmission from a laboratory to the environment remains theoretically possible (e.g., through sewage), high levels of population immunity probably concealed any such historical laboratory escapes, which make it difficult to assess the historic frequency of these events.[95] Escapes via infection of laboratory workers provide some evidence about a breach in containment for this pathway. The WHO reports 12 known cases of poliomyelitis between 1941 and 1976 associated with virus use in laboratories infecting laboratory workers, which occurred predominantly in the prevaccine era and included two deaths.[95] In addition, researchers isolated a wild poliovirus in two separate events in the Netherlands; one strain from the son of a worker in an IPV manufacturing facility accidentally exposed to a prototype virus strain, and one from a child exposed to another reference strain from an unknown origin.[96] These events demonstrate the potential for unintentional virus release into a population through asymptomatic infection of laboratory workers.[6] More recently, investigators isolated viruses closely related to a laboratory reference strain of type 2 wild poliovirus (i.e., MEF-1) in India,[97] including from three AFP cases in 2000, five in 2002, and two in 2003 (years that followed the global elimination of the naturally occurring type 2 wild polioviruses). Finally, the fact that the last case of smallpox occurred after a laboratory release of virus in the United Kingdom underscores the importance of managing this risk after eradication of a disease.[95]

5.1.2. Dependence on the Scenario and Time

The probability of an outbreak due to a wild poliovirus containment breach depends on the amount of virus stocks (i.e., the number of IPV production sites or laboratories that continue to keep wild polioviruses after T_0), the probability of virus release from such places, and the likelihood that a release actually leads to an outbreak. WHO published a global action plan for laboratory containment aimed at reducing the first two risks.[95,98]

Although implementation of containment guidelines substantially reduces the risks of unintentional release of poliovirus, countries that do not maintain high-quality containment after T_0 will experience a relatively higher risk of an outbreak. Thus, a country's decision to maintain/enforce long-term laboratory containment substantially reduces the risk of an unintentional wild poliovirus release.

We expect that developed countries will continue to maintain the highest numbers of laboratories containing (potentially) wild poliovirus infectious materials but also the most rigorous containment. While these countries currently also produce the entire global IPV supply,[99] low- or middle-income countries may elect to produce their own IPV for economic reasons if they switch to IPV. The greater likelihood of outbreaks in these countries, given the generally higher transmissibility of polioviruses and uncertainty about the protection from IPV against infections, suggests an increased risk. This risk motivates some discussion on the feasibility of making IPV from *Sabin* strains rather than wild virus strains.[8]

The likelihood that a release of wild virus leads to an outbreak correlates inversely with virus transmissibility and the population immunity where the release occurs. As discussed, population immunity depends on the vaccination policy, with increasing time since stopping OPV use and lower income both implying lower population immunity.

5.2. Intentional Release

With the anthrax attacks in the United States in the fall of 2001 demonstrating the reality of bioterrorism and leading to significant concerns about the potential use of smallpox as a bioweapon, clearly any

discussion of future risks must consider the possibility of intentional releases of poliovirus. Some proponents of aggressive biodefense lean toward the assumption that society should act as if intentional reintroduction of an eradicated disease will occur with certainty (i.e., with probability 1, although with no time period specified), while others argue that the risks remain so remote that they approach 0. In reality, the best estimate of the risk lies somewhere in between, and the uncertainty around the best estimate also represents a narrower range. The trend of this risk over time remains very uncertain, driven by important cultural and political factors. Similar to the other risks involving a release of virus, the conditional probability of an outbreak given a release increases as population immunity decreases (i.e., with increased time since the end of vaccination). Given uncertainty and lack of data about this risk, we rely on judgment and focus on presenting bounding estimates of the risks and on characterizing their potential dependence on the vaccination policy, such that they increase as population immunity decreases in countries that stop vaccination.

5.3. Quantification of Wild Poliovirus Outbreak Risks

As with the risk of iVDPV-related outbreaks, we estimate the Poisson rates for wild poliovirus outbreaks as the product of the probability of a virus release and the probability of an outbreak given a single release. Although we recognized many dependencies of the frequency of wild poliovirus outbreaks, we focused on the most significant influences on our already very uncertain base case estimates. Table IV displays the inputs we use to estimate the risk function for wild poliovirus outbreaks. The risk function follows from adding the three possible types of releases (laboratory, IPV production site, or intentional) and multiplying by the appropriate income level dependent conditional probability of an outbreak given a release. We assume that the conditional probability functions remain linear over time, similar to those we used for iVDPV-related outbreaks.

We estimate the frequency of virus releases from a laboratory at one per 1,000 years per 100 million people in high- and upper-middle-income countries. However, we assume a five-fold increase in risk for countries that do not maintain containment guidelines. Given the likelihood of a much lower prevalence of laboratories containing polioviruses in low- and lower-middle-income countries, we estimate a 10-fold lower frequency of releases of one per 10,000 years per 100 million people in those countries. In aggregate (using average world population 2010–2029 by income level), this amounts to approximately an expected 0.4 releases globally over 20 years (given enforced containment), with approximately three-fold higher frequency at the two highest income levels.

Given the current use of large amounts of wild polioviruses in IPV production, we assume much higher risks for release from an IPV manufacturing site (i.e., for countries that domestically produce IPV). We assume that high- and upper-middle-income countries will probably produce IPV domestically if their routine immunization policy involves IPV, and we estimate a 10-fold higher risk of virus release from IPV production sites than from laboratories, or one release per 100 years per 100 million people (given maintained containment). In contrast, we assume that low- and lower-middle-income countries probably will not produce their own IPV, and consequently we assume a frequency of only one release per 1,000 years per 100 million people (this assumes that a small, but nonzero chance exists that these countries might produce IPV domestically). For universal IPV use, this translates into approximately four IPV production site releases globally over the entire 20-year period, assuming a linear relationship between the frequency of releases and amount of IPV use. If a country does not use IPV for routine immunization, we assume a very low frequency (i.e., 10^{-6}) of releases, attributed to the remote possibility of maintained IPV production capacity for outbreak response. We suggest future sensitivity analyses explore a range of effectiveness of containment for IPV production sites and for laboratories.

We estimate the frequency of attempts at intentional releases for all countries as equal to virus escapes from laboratories in developed countries with enforced containment if the policy involves OPV cessation. If not, we estimate a 10-fold lower frequency, based on an assumption of less attractiveness of polioviruses as a bioweapon. Given the absence of historical data and the inherent uncertainty in predicting the future geopolitical situation, we emphasize the need to vary this frequency over a wide range (see Table IV).

We multiply the frequency of releases by a conditional probability of an outbreak given a release of 0.05 in low-income countries at T_0 and up to 0.5 at 20 years after OPV cessation, and as a result the Poisson rates reflecting the wild poliovirus outbreak risks all remain small. Fig. 4 shows the outbreak rates over time for each scenario. The aggregated rates lead to a global expected number of wild poliovirus outbreaks from any source during 20 years after T_0 between approximately 0.02 (continued OPV with SIAs) and

Table IV. Inputs Used for the Estimation of the Risk Functions for Wild Poliovirus Outbreaks

Input	Base Case	Min	Max[a]	Notes
Number of releases per year due to breach in laboratory containment per 100 million people, HIGH and UMI	0.001	0	0.01*	Judgment
Number of releases per year due to breach in laboratory containment per 100 million people, LOW and LMI	0.0001	0	0.001*	Judgment
Number of releases per year due to escape from IPV manufacturing facilities per 100 million people if policy involves IPV, HIGH, UMI	0.01	0	0.05*	Judgment; assumes HIGH and UMI countries would produce IPV domestically
Number of releases per year due to escape from IPV manufacturing facility per 100 million people if policy involves IPV, LOW, LMI	0.001	0	0.015*	Lower risk than in HIGH and UMI due to lower likelihood of domestic IPV production in LOW and LMI countries
Number of releases per year due to escape from IPV manufacturing facility if routine immunization policy involves no IPV	0.000001	0	0.000015*	Small risk pertaining from any maintained IPV production capacity for outbreak response
Number of intentional releases per year per 100 million people, cessation, any income level	0.001	0	0.015*	Upper bound approaches 1 release per 300 million people during the 20 years
Number of intentional releases per year per 100 million people, IPV or OPV routine, any income level	0.0001	0	0.0015*	Reflects a 10-fold lower risk than under a policy of cessation
Relative risk if containment not maintained, any income level	5	1	10	Judgment
P(outbreak|release), LOW in year T_0	0.05	0.001	0.1	Judgment
Relative risk P(outbreak|release), LMI vs. LOW in year T_0	0.625	0.5	1	Judgment
Relative risk P(outbreak|release), UMI vs. LOW in year T_0	0.25	0.1	1	Judgment
Relative risk P(outbreak|release), OPV with SIAs, year 20 vs. year T_0	1	0.8	1.2	Judgment
Relative risk P(outbreak|release), OPV without SIAs, year 20 vs. year T_0	2	1	3	Judgment
Relative risk P(outbreak|release) year 20 vs. year T_0 with IPV in LOW, LMI and UMI	5	1	10	Judgment
Relative risk P(outbreak|release) 20 years after T_0 with cessation (i.e., of OPV and IPV) in LOW, LMI and UMI	10	1	20	Judgment; base case yields P(outbreak|release) 20 years after T_0 of 0.5, 0.31 and 0.13 in LOW, LMI, and UMI, respectively
Relative risk P(outbreak|release) IPV, HIGH, any year vs. LOW in year T_0	0.1	0	0.25	Judgment

[a]An asterisk behind the estimate in this column indicates that we interpret the "max" end of the range as the 99th percentile and the base case estimate as the mean of a log-normal distribution bounded at the "min" of the range. Absence of an asterisk implies that we interpret the range as minimum and maximum values of a triangular distribution peaking at the base case estimate.
HIGH = high-income country; IPV = inactivated poliovirus vaccine (any formulation); LMI = lower-middle-income country; LOW = low-income country; SIAs = supplemental immunization activities; OPV = (trivalent) oral poliovirus vaccine; UMI = upper-middle income country.

1.1 (switch to IPV without enforcing containment). Although small compared to the initial VDPV risks, in the event of OPV cessation, wild poliovirus outbreaks may represent the most important risk in the longer term. The risk of an intentional release remains the most difficult to estimate given the lack of data.

6. DISCUSSION

This analysis provides the first comprehensive quantitative synthesis of the existing data related to the risks of poliomyelitis after wild poliovirus eradication. These estimates provide a starting point for analyses of the tradeoffs between the risks, costs, and

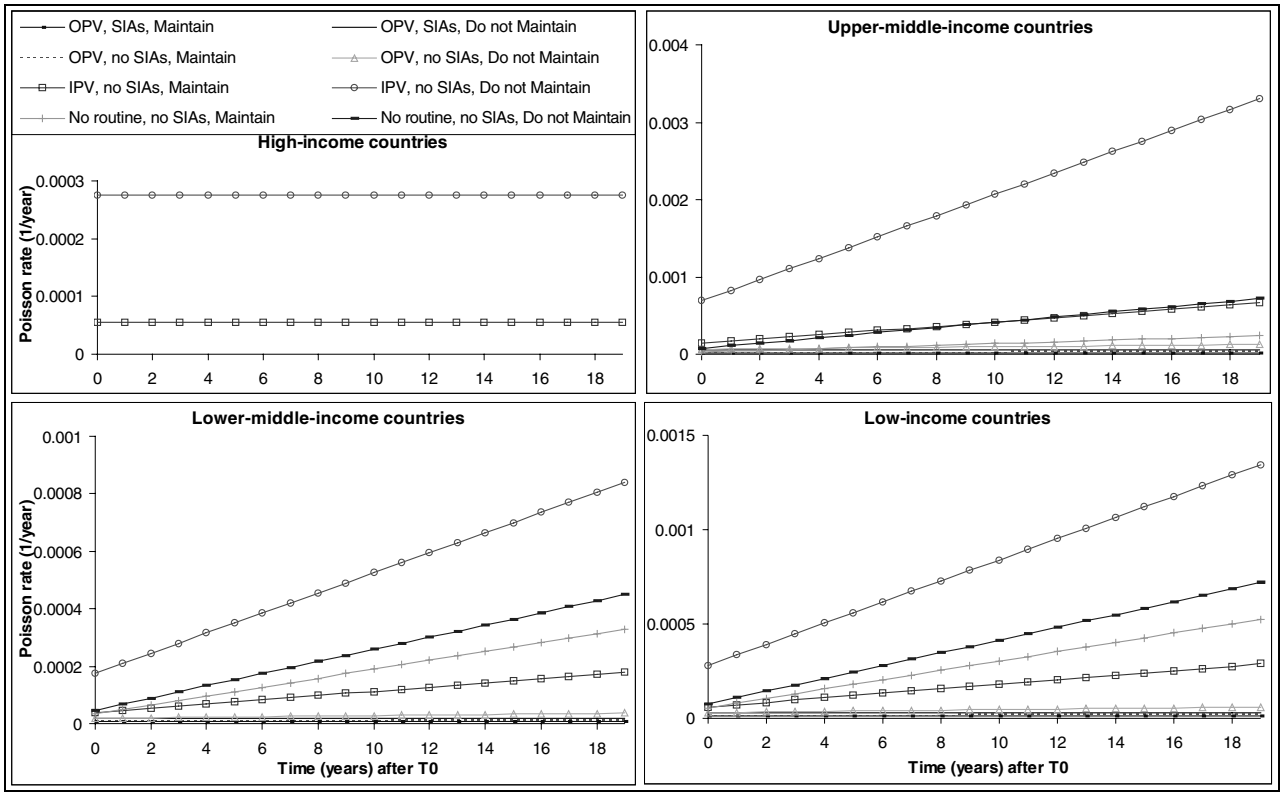

Fig. 4. Yearly (Poisson) rate of occurrence of wild polio outbreaks per 100 million people as a function of time and scenario. Maintain refers to the policy decision to maintain containment standards. Scales on the *y*-axis are not all equal. (IPV = inactivated poliovirus vaccine; OPV = trivalent oral poliovirus vaccine; SIAs = supplemental immunization activities.)

benefits of different policy choices. We anticipate that this effort will stimulate discussions and iterations of the estimates, and we hope that future studies will further develop these initial estimates and update them as conditions change and knowledge evolves. We emphasize that our approach relies on using simple functions to represent complicated concepts that in reality depend on many factors, and that these assumptions may suffice for some analyses even if they prove insufficient for others.

We highlight several limitations of our analysis by emphasizing that some of our key assumptions significantly simplify the complex reality. For example, our characterization of risk per 100 million people represents a simplification of the real world in which viruses spread from one population to another with no recognition of boundaries, as exemplified in recent exportations of poliovirus from Nigeria and India to 21 other countries.[100] However, this represents an issue for the modeling of the outbreak magnitude rather than the frequency of initiating events leading to outbreaks. Our characterization implies that we view outbreak events as independent events, equally likely to originate from any subpopulation within an income level. The rates represent the average frequency in a scenario and neglect heterogeneities within income levels. This represents an important simplification of the true variability among countries. For example, while the validity of our assumption that high-income countries switched to IPV in 1998 appears valid on average, the aVDPV event in Taiwan (see the Appendix, Table A3) demonstrates the possibility that some high-income countries may continue using OPV up to T_0 and thus face a higher risk of iVDPVs than countries that switched to IPV earlier.

Also, our framework that models policies over a 20-year time horizon may not represent the preference of countries and may not cover the possible future options that may emerge (e.g., the use of antivirals to reduce iVDPV risks). We may also fail to adequately cover all of the potential mixed strategies that may truly emerge after T_0 (e.g., use of IPV only

until the risks of VDPV outbreaks decrease to a point where stopping IPV vaccination does not lead to a significant risk). We emphasize that our estimates refer to the time period following successful polio eradication in all six World Health Organization (WHO) regions,[101] implying that no more wild polioviruses persist in any population or the environment, not even undetected viruses. The biology of polioviruses indicates a low probability that the virus will persist in the environment.[93] However, high-quality surveillance remains critical in assuring that no clinical cases occur without detection. In a setting of poor surveillance, wild poliovirus strains can continue to circulate for as long as seven years without detection, as recently experienced in Central Africa.[102]

A further limitation of our estimation of the risks associated with continuation of OPV in most countries lies in the assumption that coverage remains at the current levels. In reality, resource-scarce countries probably cannot maintain their current coverage beyond the point of global eradication, and pre-eradication experience demonstrates that coverage drops in polio-free countries without external financial support. Therefore, the constant outbreak risk estimates for countries continuing OPV may represent a best-case scenario. However, we accounted for this effect by modeling risk with or without SIAs and assuming that the frequency of recent cVDPV outbreaks reflects a world where still 75% of OPV-using countries conduct periodic SIAs.

We anticipate iteration on these risk estimates as events continue to evolve and further research results become available. For example, ongoing and future investigations of possible iVDPVs detected through environmental surveillance or the prevalence of asymptomatic iVDPV excretors could influence related risk estimates and characterization of the uncertainty. An investigation in Slovakia did not succeed in finding the individual associated with the detected virus, but further research concerning these types of events remains very important to fully understanding their implications.[76] Understanding the existing uncertainties helps to identify priority topics for research.

Our estimation of the VAPP rates ignores any variability across different settings of the probability that an OPV infection results in paralysis. Only the typical proportions of primary and secondary OPV infections, which follow from setting-specific coverage levels and primary and effective seroconversion rates, determine the eventual VAPP incidence. Our approach also supposes different rates of VAPP per infection depending on the nature of the infection (i.e., vaccine administration vs. secondary infection). The base case VAPP rates per million birth cohort from Table I (ranging from 1.9 to 2.6 per million birth cohort) yield somewhat lower estimates than recent estimates of the global burden of VAPP, which assumed a range of two to four cases per million in a birth cohort.[1,103] The lower end of this range reflects the U.S. experience, while the upper end reflects the VAPP incidence in India in 2001 divided by the size of the birth cohort. In India in 1999, the cohort risk of VAPP appeared even higher at a rate of seven per million birth cohort.[104]

Our simple model for the cVDPV outbreak rates does not incorporate several important factors that influence the risk of cVDPV outbreaks. First, our assumption about the rapidly declining prevalence of OPV viruses dominates the risk, and it reflects a lower-middle-income country (Cuba) with very good population immunity and sanitation. Extrapolation of these results to settings of lower hygiene and/or population immunity requires caution.[63,105] The observed decline in detection of OPV viruses corresponds to a situation of OPV cessation immediately after a mass immunization campaign to boost population immunity. From a global perspective, a comparable, optimal level of population immunity would occur only if all currently OPV-using countries discontinue routine OPV use after a final globally synchronized immunization day just prior to cessation. No experience exists with countries that stop OPV use in an environment of suboptimal population immunity and poor hygiene, and the decline in virus prevalence in those settings may occur much more slowly than in Cuba.

Second, coordinated cessation represents a crucial factor. If some countries discontinue OPV while other countries continue to use OPV, especially neighbors, the former provide an ideal opportunity for the emergence of cVDPVs. Evidence of frequent OPV virus importation in non-OPV-using countries exists now, with researchers in IPV-using high-income countries regularly isolating OPV viruses through various surveillance systems.[68,106] We assume for purposes of our risk estimates that cessation occurs in a coordinated fashion. In the event of uncoordinated cessation, countries that stop OPV may effectively face an increased risk instead of experiencing a decreased risk.

Third, doubling the speed of decay in cVDPV outbreak rates for IPV versus no routine immunization represents a fairly arbitrary assumption. However, its impact on the aggregate outbreak risk (i.e., the integral under the curves in Figs. 1 and 2) remains

limited given that both outbreak rates assume the same starting point. Furthermore, during the period of the highest cVDPV risk (i.e., soon after OPV cessation) the influence of IPV immunization of infants on the immunity in the general population likely remains small.

Fourth, responding to poliomyelitis outbreaks with mOPV or OPV after cessation of routine OPV vaccination and SIAs represents an important opportunity for emergence of cVDPVs since any area not covered by a response would face a risk of importing vaccine strains used in response to the outbreak. While this risk decreases as a function of the intensity of contact with the outbreak population, reduced population immunity after OPV cessation implies that OPV strains used in the response could, with some probability, reestablish circulation and create cVDPVs. We currently lack evidence to quantify this risk.

Regarding the estimation of the rates of iVDPV-related outbreaks, we emphasize that our base case analysis includes three possible chronic iVDPV excretors detected through environmental surveillance, and no other evidence exists for the possibility of chronic excretors in upper-middle-income countries. The interpretation of these environmental iVDPVs drives the risk in these countries. We also assumed zero prevalence of chronic iVDPV excretors in low- and lower-middle-income countries, although it remains possible that in the future improved sanitation and medical service in those countries will allow longer survival of persons with severe immunodeficiencies. This would imply an increased risk of iVDPV-related outbreaks in those countries, although probably such excretors would only survive in those subpopulations with the best hygienic conditions (and thus the lowest outbreak risk) within these countries.

We encountered a number of difficulties in modeling the functional relationship between population immunity in the different income levels over time and the conditional probability given a transmissible poliovirus introduction (see the Appendix, Section 3.2). The linear relationship we assumed simplifies the reality and ignores many complexities, and thus interpreting the rates of iVDPV or wild poliovirus outbreaks requires caution. Similarly, very limited data exist to support our wild poliovirus release frequencies and consideration of the uncertainty remains crucial for the potential use of these estimates for future analyses. Improved quantification of the uncertainty in each risk might require further iteration and warrant formal expert elicitation.[107] In the context of using the risk estimates presented here in a decision analytic model, analysts should appreciate the uncertainty in each risk estimate.[108] Global, national, and regional policymakers face significant challenges and, most importantly, they must decide how to coordinate the transition to future immunization policies. We believe that discussions should occur soon to allow sufficient opportunity for planning and implementation. Our estimates of the cVDPV outbreak risk soon after OPV cessation dominate in most scenarios, even with our assumption of coordinated cessation. If coordination efforts fail, we expect that the cessation of polio vaccinations would unnecessarily increase the risk. On the other hand, failure to stop OPV vaccinations virtually guarantees increasing numbers of cVDPV outbreaks as SIA activities wane and the global population continues to increase. We further find it imperative that decisionmakers continue to plan and begin implementation of processes to develop a vaccine stockpile and to prepare for the likely possibility of an outbreak after OPV cessation. Clearly, future studies should recognize the existence of potential risks and assess costs related to developing, maintaining, and using a polio vaccine stockpile. We emphasize that responding to an outbreak with either OPV or mOPV also represents a potential for generating vaccine-derived polioviruses, and policymakers must factor this into the discussions and decisions as they evaluate and develop much-needed posteradication response plan(s). Although discussing the magnitude of outbreaks lies beyond the scope of this article, we emphasize that a late response implies an important risk of large numbers of paralytic poliomyelitis cases.[14,18,109,110] The number of expected paralytic cases in the event of an outbreak differs depending on the policies and income level and increases as time since OPV cessation elapses.

Given the reality of the risks discussed in this article, we emphasize that efforts to minimize and manage the risks must not promise zero risk or create an expectation that no outbreaks can occur after eradication. Combining all of the risk estimates with the global population forecasts[20,69] suggests an approximately 50 to 100% chance of at least one outbreak during the first 20 years after T_0 global OPV cessation with the lower bound assuming MPI, cVDPV low-risk case and maintained containment and the higher bound assuming RPI, cVDPV high-risk case and weaker containment. If low- and middle-income countries all switch to IPV, the range of risk estimate decreases to approximately 40% to almost 100%.

With continued OPV use the probability of at least one outbreak is greater than 99% for either cVDPV risk case, with more outbreaks expected per year if countries stop boosting population immunity by conducting SIAs. Thus, the world must prepare for the posteradication transition and commit to sustained eradication and containment, which may require redefining the goal after interruption of wild poliovirus transmission as continued absence of sustained circulation of polioviruses (including VDPVs). In this context, any outbreak that occurs, particularly during the process of OPV cessation, does not undermine or undo the achievement of global eradication, and this analysis suggests that policymakers should assume some nonzero chance of at least one outbreak during the transition period and prepare for it.

This article does not deal with other potentially important risks, including the financial risks that may impair the ability to actually implement a preferred policy option, in particular the costly option of vaccinating with IPV indefinitely.[111] Clearly, countries must continue to weigh the risks of VAPP and VDPVs associated with the use of OPV, and the costs associated with any options they choose.

We suggest several important areas for future research: the functional relationship between population immunity in different income levels over time and the conditional probability of outbreak given a virus introduction, the sensitivity of detection for iVDPVs, the implications of the environmental iVDPV isolates, the uncertain potential of IPV to prevent outbreaks in low-hygiene settings, and the design of outbreak response strategies and a vaccine stockpile. Nevertheless, in the context of the risk framework presented by Aylward and Cochi,[13] we believe that this article offers a significant step further down the path of quantification and consequently toward improved and more informed decision making.

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APPENDIX

This appendix provides additional background information, details, and formulas for the calculations, and elaborates on some of the assumptions and input estimates for each risk. We organize the appendix into sections for each risk following the structure of the main article.

1. Additional Information Related to the VAPP Risk

1.1. Factors Affecting the Risk of VAPP

Table A1 summarizes individual risk factors for contracting VAPP, including the lack of prior immunity, genetic presusceptibility (i.e., primary immunodeficiencies),[28] infection with type 3 OPV (as opposed to the other two serotypes),[27,36,112,113] and intramuscular injections.[61,114] The rapid rate of genetic mutation among polioviruses means that the viruses that OPV recipients excrete can evolve and acquire higher neurovirulence than the original vaccine virus. Therefore, secondary OPV infection may present a higher risk than primary OPV infection (i.e., vaccination) in fully susceptible individuals.

At the population level, the risk in terms of expected annual number of VAPP cases due to routine immunization depends primarily on two factors: the amount of OPV used and the density of susceptibles. In a stable population with a low, constant density of susceptibles, the amount of OPV administered yearly to the birth cohort remains the main factor influencing the incidence of VAPP. In the context of routine OPV use with high coverage, industrialized countries reported relatively consistent rates of paralytic poliomyelitis of about 0.3 to 0.7 (recipient plus contact) VAPP cases per million distributed or administered doses.[25–27,29,113,115,116] These studies also reported consistent rates of first-dose recipient VAPP cases ranging from 0.7 to 1.5 cases per million first doses.

However, the literature suggests that the population risk for VAPP does not follow a linear relationship in the number of doses. India administered 733 million OPV doses in 1999 to about 125 million children aged less than five years, representing an average of over five doses per child.[104] Despite a high overall

Table AI. Factors Influencing the Risk of VAPP at an Individual Level and During an Outbreak Response After OPV Cessation

Individual Risk Factors	Effect
Lack of prior immunity from maternal antibodies, previous wild or OPV virus infection, or previous IPV vaccination. Age at first OPV dose and birth order may impact risk (with older siblings benefiting from increased maternal antibody titers due to recent secondary OPV exposure of their mothers from vaccination of the first sibling).	Prior immunity eliminates risk of VAPP
Genetic presusceptibility, such as primary immunodeficiencies involving B-cell system abnormalities (e.g., agammaglobulinemia or hypogammglobulinemia).[28] No evidence exists that HIV presents a risk factor.[6] No other currently identifiable genetic predisposition factors exist.	Persons with primary immunodeficiencies face several 1,000-fold higher risk
Frequent intramuscular injections soon after OPV vaccination (provocation poliomyelitis).[61,114]	Increased risk of VAPP
Type 3 OPV virus infection. Recipient or contact VAPP is most frequently associated with type 3 infections both for (trivalent) OPV and mOPV.[27,37] Contact VAPP with OPV type 1 occurs very rarely in industrialized countries, but more frequently in developing countries.[27,112,113]	Highest risk with type 3, then type 2, then type 1
Primary OPV infection (i.e., vaccination) vs. secondary OPV infection.	Secondary OPV infection may represent somewhat higher risk (although little evidence supports this)
Factors influencing population risk during an outbreak response involving OPV	**Effect**
Lack of prior population immunity.	Potential for large number of VAPP cases in postcessation response
Vaccine used in response.	Same serotype variability as for individual risk
Amount of OPV used, with more use of OPV leading to more OPV infections, but coverage and timing influence the proportion of secondary vs. primary infections and therefore probably the number of VAPP cases.	Functional relationship unclear
Setting-specific seroconversion rates of the vaccine. Higher seroconversion rates imply a higher proportion of primary OPV infections and therefore probably a lower number of contact VAPP cases (seroconversion rates appear generally lower in developing countries).[118]	High seroconversion rates reduce risk of contact VAPP

HIV = human immunodeficiency virus; IPV = inactivated poliovirus vaccine; mOPV = monovalent oral poliovirus vaccine; OPV = (trivalent) oral poliovirus vaccine; VAPP = vaccine-associated paralytic poliomyelitis.

incidence of approximately 0.18 VAPP cases per million people that year, this corresponded to a very low rate of 0.2 cases per million administered doses. For comparison, the United States experienced an overall incidence between 1980 and 1995 of only 0.032 VAPP cases per million people annually (i.e., nearly a factor of 6 lower), but this corresponded to a two-fold higher rate of approximately 0.4 cases per million distributed doses.[25,103,104,117–119]

The lower section of Table A1 lists a number of factors that influence the population risk for VAPP in the event of an outbreak response involving OPV.[36,118]

1.2. Calculation of the VAPP Rates

Assuming VAPP rates independent of the setting, we based our estimates on U.S. data because of the large size of the data set, the completeness and consistency of these data, and our access to them. A total of 89 recipient and 58 contact VAPP cases (including cases in immunodeficient persons) occurred in the United States during 1980–1997,[23,24,27] for an average size of the annual birth cohort of nearly 4 million.[31] Three major U.S. surveys provide coverage estimates among two-year-old children covering most of this time period.[33] We assume that the results of the U.S. Immunization Survey of children born through 1983 underestimated the true coverage by 15%, based on comments in Simpson *et al*.[33] We do not adjust data for the National Health Interview Survey of children born 1989–1991 and the National Immunization Survey of children born after 1991.[30,33] Deriving estimates for missing years from any available retrospective surveys among preschoolers[34,35] and interpolating between remaining years, we obtain an average coverage (weighed by birth cohort sizes) for children born 1980–1997 of approximately 75% (i.e., coverage by age two with three or more OPV doses). We further assume a primary seroconversion rate of 95% for three OPV doses (averaging over serotype-specific rates)[1] and that on

Table A2. OPV VAPP Rates Estimation Using Reported Cases,[23,24,29] Adjusted Vaccination Coverage (See Text),[33–35] Seroconversion Rates,[1] and Population Data[31] from the U.S. Between 1980 and 1997

Symbol [and Formula if Derived]	Input	Value	Notes
T	Take rate for 3 OPV doses	0.95	Approximate average of serotype-specific seroconversion rates
E	Effective take rate, i.e., proportion of each birth cohort eventually seroconverting due to OPV infection	0.95	Judgment
B	Average size of US birth cohort 1980–1997 (in millions)	3.87	
C	Average coverage with 3 or more OPV doses by age 2	0.75	See text
I1 [I1 = T ∗ B ∗ C]	Number of primary OPV infections (i.e., first infections in OPV recipients) in each birth cohort (in millions)	2.76	Count successful trivalent OPV vaccination as 1 infection although in reality it amounts to 3 infections. This cancels out later because we also count VAPP cases due to all 3 serotypes
I2 [I2 = E ∗ B-I1]	Eventual number of secondary OPV infections in each birth cohort (in millions)	0.91	
Y	Number of years between 1980 and 1997	18	
rV	Reported recipient VAPP cases (including recipient iVAPP), US 1980–1997	89	Includes recipient iVAPP cases
cV	Reported contact VAPP cases (including contact iVAPP), US 1980–1997	58	Includes contact iVAPP cases
cr	Completeness of reporting	0.96	Derives from comparing number of reported cases during 1980–1991 (as of 2004[23,24]) with number of cases expected for this period after correcting for underreporting[29]
ArV [ArV = rV/(cr ∗ Y)]	Average yearly number of recipient VAPP cases, US 1980–1997 (including recipient iVAPP)	5.17	
AcV [AcV = cV/(cr ∗ Y)]	Average yearly number of contact VAPP cases, US 1980–1997 (including contact iVAPP)	3.37	
r1 [r1 = ArV/I1]	Recipient VAPP cases per million primary OPV infections in fully susceptibles	1.87	Lower bound 1.56 (if C = 0.90) and upper bound 2.17 (if C = 0.65)
r2 [r2 = AcV/I2]	Contact VAPP cases per million secondary OPV infections in fully susceptibles	3.71	Lower bound 2.28 (if E = 1.0 and C = 0.65) and upper bound 10.3 (if C = 0.75 and E = 0.8)
RR [RR = r2/r1]	Relative risk *contact VAPP* vs. *recipient VAPP*	1.98	
TVI [tVI=(rV+cV)/(cr ∗ Y ∗ E ∗ B)]	Rate of total VAPP cases per million total (primary and secondary) OPV infections	2.33	

iVAPP = immunodeficient VAPP; OPV = (trivalent) oral poliovirus vaccine; VAPP = vaccine-associated paralytic poliomyelitis.

average 95% of each birth cohort eventually seroconverts (with all three serotypes) due to primary or secondary OPV infections (i.e., the effective take rate).

Using these numbers, Table A2 shows the breakdown by primary and secondary infections, and the VAPP rates that follow. This results in rates of 1.9 recipient VAPP cases per million OPV infections and 3.7 contact VAPP cases per million secondary OPV infections.

The effective take rate estimate (of 95%) impacts only the contact VAPP rate. Although the true effective take rate remains uncertain, given generally high seroprevalence in children by age five,[30,32] its range most likely does not exceed 80% to 100% for U.S. cohorts born since 1980. Using these bounds yields a range for the contact VAPP rate of 3.1 to 10.3 per million secondary OPV infections. However, this implies a very limited range of 2.1 to 2.6 total VAPP cases per total number of OPV infections in susceptibles (i.e., aggregating recipient and contact VAPP). The average vaccination coverage drives the ratio of primarily to secondarily infected individuals and therefore the difference in risk estimates for recipient and

contact VAPP per infection. For example, if we vary the average coverage between 65% (i.e., the average without correcting for underestimation) and 90% (i.e., the coverage in the 1990s), we obtain contact VAPP rates of 2.6 and 9.2 cases per million secondary OPV infections, respectively (with other inputs kept at their base case values).

Only 16 of the 58 contact VAPP patients observed between 1980 and 1997 were born during that time period and onset of contact VAPP occurred at an average age of approximately 25 years.[23,24] This approach implicitly assumes that the same number of contact VAPP cases reported between 1980 and 1997 would eventually occur in the cohort born between 1980 and 1997 given the same level of routine OPV vaccination. However, the United States switched to a sequential IPV-OPV schedule in 1997 and to an all-IPV schedule in 2000 (and consequently members of this birth cohort would no longer experience potential cases of contact VAPP), so we cannot verify this assumption. Increased vaccination coverage reported during 1980–1997 correlated inversely with the proportion of contact VAPP cases in that birth cohort.[23,24,27]

For outbreak response after OPV cessation, mOPV is emerging as the preferred vaccine given its more efficient seroconversion compared to trivalent OPV[37,118] and given that trivalent OPV would unnecessarily reintroduce poliovirus serotypes not related to the outbreak.[14] Therefore, we must consider the VAPP risk associated with potential mOPV use for outbreak response. While we can rely on extensive data about VAPP from trivalent OPV use, limited documented experience exists with VAPP cases from widespread mOPV use. Only four large population-based studies in the United States and Hungary provide some limited basis for quantitative estimates for VAPP associated with mOPV.[37] Dömök describes the only data set in the context of widespread mOPV use for largely susceptible birth cohorts,[36] but the type 3 mOPV strain used at the time probably does not reflect the properties of the currently used strains. Given the limitations in the available data, we assume similar risks as we obtained for trivalent OPV, including the wide uncertainty ranges that remain consistent with the variability across serotypes based on the experience in Hungary (Reference 36, Table 2).

Note that both in the calculation of the observed risk of VAPP (Table A2) and in the estimation of the future risk of VAPP (Table I), we neglected the influence of maternal antibodies. The fact that newborns may benefit from some level of antibodies, which decays at a half-life of about 28 days,[120] implies that some proportion of first OPV infections, especially those associated with doses given at early age, do not represent OPV infections in *fully* susceptibles. Consequently, by implicitly counting each first infection as an infection to a fully susceptible, we probably overestimate the number of OPV infections in fully susceptibles, resulting in lower VAPP rates (i.e., r_1 and r_2) because we overestimate the denominator of potentially VAPP-causing infections (recalling that presence of antibodies protects against VAPP). However, if we assume that the extent of overestimation in the calculation of VAPP rates in the past equals that in the prospective estimation of the number of secondary infections (i.e., I_1 and I_2), then the effects of neglecting maternal antibodies cancel out when multiplying the VAPP rates by the numbers of OPV infections. In the event of a massive outbreak response with OPV, this approach might underestimate the number of VAPP cases because only a very small proportion of first OPV infections would then occur in infants still protected through maternal antibodies.

2. Calculation of cVDPV Outbreak Rates

For completeness, Table A3 lists documented aVDPV events that we did not include in our analysis given weak evidence for circulation or their emergence from settings unrepresentative of the current situation (e.g., the event in Poland appears to have involved widespread circulation but did not involve an OPV strain currently in use). Table A4 (top) shows the average annual frequency of cVDPV outbreaks per 100 million people in low- or lower-middle-income settings both with and without SIAs during 1999–2005 based on the outbreaks counted in Table II.

Two competing trends drive this risk after OPV cessation: (1) a rapid decline in the prevalence of vaccine-derived viruses, which implies a decreased outbreak risk, and (2) a decrease in population immunity as newborn children remain unvaccinated, which implies an increased outbreak risk. Conditioning on the prevalence leads to the following expression for the probability of a cVDPV outbreak:

$$
\begin{aligned}
&P(cVDPV\ outbreak)\\
&\quad = P(prevalence \geq 1\ virus)\\
&\qquad \times P(outbreak \mid prevalence \geq 1\ virus)\\
&\qquad + P(prevalence = 0\ viruses)\\
&\qquad \times P(outbreak \mid prevalence = 0\ viruses)\\
&\quad = P(prevalence \geq 1\ virus)\\
&\qquad \times P(outbreak \mid prevalence \geq 1\ virus)
\end{aligned}
$$

Table A3. aVDPV Events Not Included in the Risk Estimates[a]

Year	Country	Income Level	Serotype	Number of Isolates (% Divergence)[b]	Paralytic Cases	Notes	Sources
2005	Cambodia	LOW	3	2 (1.9–2.1)	1	Patient immunocompetent but community spread undetected (as of 1/1/2006)[c]	Unpublished
2005	US	HIGH	1	4 (~ 2–2.5)[d]	0	In religious community with very low IPV coverage; one additional infected immunocompromised child listed in Table III	(48)
2004	Japan	HIGH	2	1 (1.2)	0	Single isolate from a healthy child obtained during a stool survey	(38)
2004	Syria	LMI	2	1 (1.1)	1	In context of high national OPV coverage	Unpublished
2004	Lao PDR	LOW	2	3 (1.1)	1	In context of local gaps in OPV coverage	Unpublished
2003	Mongolia	LOW	1	1 (1.3)	0	In context of high national OPV coverage	(44)
2002	Taiwan	HIGH	1 and 2	2 (1.1–1.3)	1	Type 1 (1.1% divergence) isolated from an AFP case, type 2 (1.3% divergence) from a contact	Unpublished
2002	Zimbabwe/ Ireland	LOW/ HIGH	1	17 (1.1–1.5)	0	All viruses isolated in Ireland over a 4-month period from a healthy child born from an HIV-positive mother and vaccinated in Zimbabwe	(50)
2001	Syria	LMI	2	3 (1.3–1.5)	1–3	In context of high national OPV coverage; total number of cases uncertain	Unpublished
2001	Madagascar	LOW	2	1 (1.0)	1	Unrelated to Madagascar cVDPV outbreak but also in context of very low OPV coverage	(40)
1999	Russia	LMI	1	1 (2.6)	1	Isolate from an orphanage	(51)
1999	Russia	LMI	3	1 (1.8)	0	Isolate from an orphanage	(52)
1994	Japan	HIGH	2	1 (1.4)	0	Isolate from sewage	(53,54)
1968	Poland	UMI	3	8 (NR)	464	Outbreak virus related to USOL-D-Bac strain; background of poor IPV-induced immunity; percent divergence from *Sabin* strain not reported and not applicable because the starting point was a USOL-D-Bac strain	(55)
1965	Belarus	LMI	2	9 (1.1)	0	In context local OPV cessation; only the most divergent among the 9 isolates showed more than 1% VP1 divergence	(56)

[a]Further VDPVs with little over 1% VP1 divergence and weak evidence for significant spread of, or insufficient information about, the virus have been detected through AFP or other surveillance in recent years.(38,39,44,47,49,57,58)

[b]Percent divergence refers to the number of nucleotide changes in the VP1 region compared to the parent OPV strain.

[c]This event was confirmed as a cVDPV outbreak with the detection of a second AFP case in January 2006

[d]Virus presumably originated from a separate, unidentified prolonged excretor.

AFP = acute flaccid paralysis; aVDPV = ambiguous vaccine-derived poliovirus; cVDPV = circulating vaccine-derived poliovirus; HIGH = high-income country; IPV = inactivated poliovirus vaccine; LMI = lower-middle-income country; LOW = low-income country; NR = not reported; OPV = (trivalent) oral poliovirus vaccine; SIAs = supplemental immunization activities; SNIDs = subnational immunization days; UMI = upper-middle-income country; VP1 = viral protein 1.

The first term on the right-hand side of the equation declines over time after OPV cessation. Three data sets from Cuba where OPV cessation occurs twice a year consistently show sharp declines in virus prevalence with different virus detection methods (i.e., serology, stool samples of children, environmental sampling).(62,64) Fig. A1 shows the limited serology data and the best-fit exponential decay curve for unvaccinated infants reflecting secondary exposure to circulating OPV viruses following a National Immunization Day (NID). The stool samples and environmental sampling data also show rapid decay.(62,64)

Table A4. Inputs to the cVDPV Outbreak Risk Estimation, Based on Frequency of Events During 1999–2005 (See Table II), Country-Specific Policies of OPV Vaccination During This Period and 2000–2005 Population Data[69]

	Input	cVDPVs	cVDPVs and aVDPVs	Note
	Calculation of initial risk on OPV background			
Y	Number of years considered	7	7	1
Nsia	Number of outbreaks on OPV with SIAs background 1999–2005, LOW or LMI	1	4	
Nnosia	Number of outbreaks on OPV without SIAs background 1999–2005, LOW or LMI	5	8	
P	Population in OPV-using countries 1999–2005 (in 100 millions), LOW or LMI	48	48	2
F	Fraction of OPV-using population in countries conducting SIAs	0.75	0.75	3
Lsia [Lsia = Nsia/(Y ∗ P ∗ F)]	Average annual frequency of outbreaks on background of OPV with SIAs per 100 million people at risk, LOW or LMI	0.004	0.016	
Lnosia [Lnosia = Nnosia/(Y ∗ P ∗ (1-F))]	Average annual frequency of outbreaks on background of OPV without SIAs per 100 million people at risk, LOW or LMI	0.060	0.095	

	Other inputs (all by assumption/judgment)	Base case	Min	Max	Note
RRumi	Relative risk *UMI* vs. *LOW or LMI*	0.1	0.05	0.5	
Hlowstop	Half-life (LOW, stop) in years	0.5	0.25	1	
Hlmistop	Half-life (LMI, stop) in years	0.4	0.25	1	
Humistop	Half-life (UMI, stop) in years	0.2	0.1	0.5	
RRhipv	Relative half-life with IPV vs. stop	0.5	0.33	1	
Kopv	Decay constant (any income level, any OPV continuation policy)	0	0	0	4
Lhigh	Risk in HIGH	0.000001	0	0.00001	5
Y	Number of years to reach *OPV without SIAs* level after stopping SIAs	3	1	5	6

[1] 1999–2005 by assumption.
[2] Assumes all low- and lower-middle-income countries used OPV during 1999–2005.
[3] Equals sum of population of countries doing SIAs in each year of 1999–2003 divided by world population minus high-income countries times five years. This assumes the ratio remained constant through 2005. We characterize the uncertainty using a triangular distribution over the range 0.5 to 0.9 peaking at 0.75.
[4] This decay implies that the risk is constant over time if OPV use continues.
[5] Reflects a small risk of any cVDPV importations or escapes of OPV-derived viruses from a laboratory. We characterize the uncertainty using a log-normal distribution with mean at the base case estimate and 99th percentile at the "Max" value.
[6] This input determines how fast the rate for OPV-using countries stopping SIAs increases to the *OPV without SIAs* level if population immunity is optimal at T_0 (i.e., assuming SIAs continue until T_0 or a coordinated immunization push is held at T_0). We assume the increase is linear.
aVDPV = ambiguous vaccine-derived poliovirus; cVDPV = circulating vaccine-derived poliovirus; HIGH = high-income country; IPV = inactivated poliovirus vaccine; LMI = lower-middle-income country; LOW = low-income country; SIAs = supplemental immunization activities; OPV = (trivalent) oral poliovirus vaccine; UMI = upper-middle-income country.

Although the prevalence of OPV viruses does not equal the probability that prevalence of virus exceeds 1, we assume that both decline at a similarly rapid rate.

The second term on the right-hand side of the equation depends on many factors, including the transmissibility of polioviruses and immunity to infections in the population. While random virus mutations and person-to-person spread ultimately determine whether a virus leads to an outbreak, population immunity thresholds (dependent on the transmissibility of the virus) probably play an important role in the potential for outbreaks given the prevalence of a virus.[121] If we knew exactly the population immunity profile and transmissibility of the virus, we could more confidently predict that either the probability of an outbreak given the prevalence of at least one virus approaches 1 (population immunity below threshold) or that the probability approaches 0 (population immunity above threshold). However, we remain uncertain

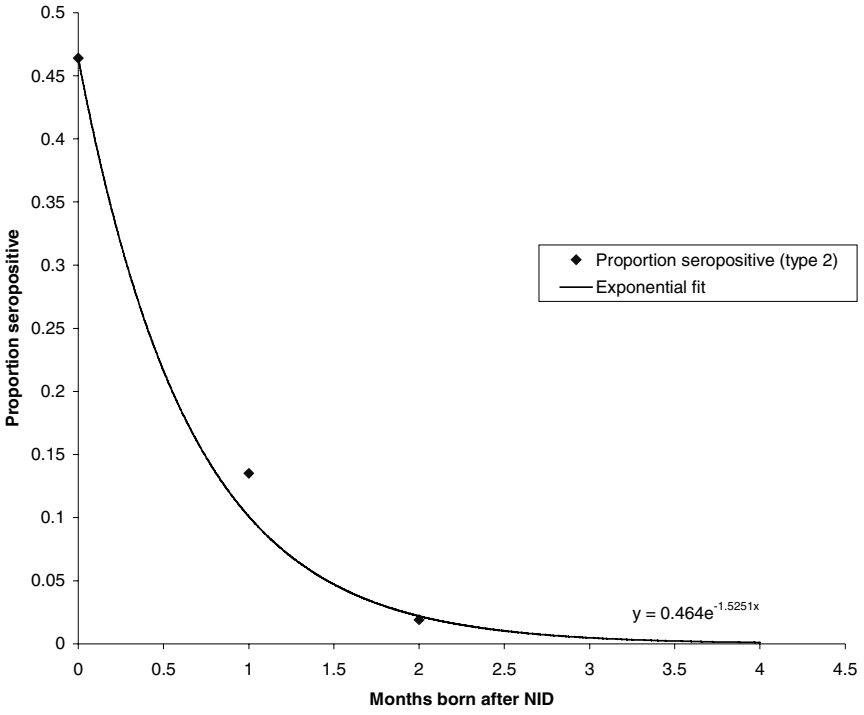

Fig. A1. Reduction in seroprevalence of unvaccinated infants born between national immunization days (NIDs) in Cuba (Reference 64, Table 3). Given the lack of maternal antibodies at age of sample collection (i.e., prior to next NID) and absence of routine immunization between NID rounds, seropositivity indicates prior (secondary) exposure to circulating oral polio vaccine viruses. The fit corresponds to an exponential decay with a half-life of approximately 0.45 months. The same data set showed a faster decay for the other two serotypes (Reference 64, Table 3).

about the true transmissibility of OPV viruses as they evolve toward VDPVs and the effective immunity that polio vaccines provide against infections. In addition, important variability exists both in the immunity and the transmissibility even within income strata (e.g., contact patterns in populations, serotypes, hygiene, climate, and seasons). Consequently, although clearly the conditional probability of an outbreak given the prevalence of at least one virus will increase with time after OPV cessation, the time at which immunity decreases to below the threshold in a given population remains challenging to predict.

We make the simplifying assumption that this conditional probability increases at a much slower rate than the exponential decay of the virus prevalence, which implies that the first term on the right-hand side dominates. Given this assumption, we approximate the resulting decline in the overall risk by an exponential decay, distinct from the virus prevalence decay, with a decay parameter k, where k represents the aggregate effect of the two competing trends. Consequently, the following generic formula represents our characterization of the Poisson rate of occurrence of cVDPV outbreaks in low- and middle-income countries, with the inputs shown in the lower section of Table A4:

$$\lambda_{\text{cVDPV}} = \{\lambda_{\text{without SIAs}} + (\lambda_{\text{with SIAs}} - \lambda_{\text{without SIAs}}) \times 1_{\text{MPI}}\} \times rr_{\text{income}} \times \text{Exp}[-k \times (1 - 1_{\text{OPV}}) \times y],$$

where

$\lambda_{\text{with SIAs}}$ = the initial average annual frequency of cVDPV outbreaks per 100 million people on a background of OPV with SIAs in low- and lower-middle-income countries,

$\lambda_{\text{without SIAs}}$ = the initial average annual frequency of cVDPV outbreaks per 100 million people on a background of OPV without SIAs in low- and lower-middle-income countries,

rr_{income} = the relative initial frequency of cVDPV outbreaks compared to low- and lower-middle-income countries,

k = the constant of the exponential decay of the rate of occurrence (equals Ln(0.5)/*half-life* and depends on the scenarios),

1_{MPI} = 1 with maximum population immunity at T_0 or 0 with realistic population immunity,

1_{OPV} = 1 for policies involving OPV and 0 otherwise, and
y = the year after T_0.

To capture the impact of the population immunity at T_0, we assume for the RPI scenario that the initial Poisson rate equals the average frequency of cVDPV outbreaks on a background of OPV without SIAs, while for the MPI scenario we assume that it equals the average frequency of cVDPV outbreaks on a background of OPV with SIAs. For a policy of continued OPV without SIAs, but with maximum population immunity at T_0, we linearly increase the Poisson rate to the $\lambda_{\text{without SIAs}}$ level over N years, where $N = 3$ at the base case:

$$\lambda_{\text{cVDPV}} = \begin{cases} [\lambda_{\text{with SIAs}} + (\lambda_{\text{without SIAs}} - \lambda_{\text{with SIAs}}) \times y/N] \times rr_{\text{income}}, & \text{if } y \le N \\ \lambda_{\text{without SIAs}} \times rr_{\text{income}}, & \text{if } y > N \end{cases}$$

where N = number of years to reach $\lambda_{\text{without SIAs}}$ level after stopping SIAs.

3. Additional Information Related to the Risk of Outbreak Caused by iVDPVs

3.1. Studies Addressing the Incidence of Long-Term Excretion Among Individuals with PIDs

Two recent investigations of the likelihood of long-term excretion in individuals with PIDs found no long-term excretors among 384 persons with PIDs in Italy,[72] the United States, Brazil, Mexico, and the United Kingdom.[70] Both studies concluded that long-term excretion appears rare, and Halsey *et al.* reported a 95% confidence interval upper bound of 1.0% for the probability of observing 0 iVDPV excretors among 306 persons with immunoglobulin G deficiencies.[70] With the prevalence of individuals with PIDs who could potentially excrete long term roughly estimated at 1:100,000 in high- and upper-middle-income countries,[70] this translates into an upper bound for the prevalence of iVDPV excretors in those countries of 140 (i.e., 1.4 billion people × 1/100,000 × 0.01). Estimating the number of PIDs in developing countries remains a challenge,[70,92] but we expect much smaller numbers (despite larger and younger populations in developing countries) because of the shorter survival of individuals with PIDs. Although HIV currently represents the most prevalent form of immunodeficiency, particularly in developing countries, no known iVDPV excretors exist among HIV-infected persons and the risk of prolonged excretion appears low.[28,71,122]

3.2. Calculation of the Rates of iVDPV-Related Outbreaks

The small Poisson rate for the iVDPV risk approximates the probability of an outbreak due to an iVDPV in a year per 100 million people and equals the probability of the presence of (at least) one iVDPV excretor times the conditional probability of an outbreak in one year given the presence of an iVDPV excretor.

We assume that the prevalence equals the probability of at least one iVDPV excretor (mathematically justified given the very low prevalence of iVDPV excretors per 100 million people). We base our estimates of the prevalence of prolonged and chronic excretors on the data in Table III. We estimate the prevalence as the product of the incidence of first OPV infections, which we define as the annual number of successful vaccinations and secondary immunizations of fully susceptible persons, the rates of iVDPV excretors per first infection and the mean duration of excretion beyond the first six months after the last OPV infection. With steady-state routine OPV immunization, the prevalence per 100 million people as a function of income level equals:

$$Prev_{\text{iVDPV}} = b \times (d_{\text{prolonged}} \times r_{\text{prolonged}} + d_{\text{chronic}} \times r_{\text{chronic}}),$$

where

b = the income-level-dependent average birth rate,
$r_{\text{prolonged}}$ = the rate of prolonged iVDPVs excretors as a function of income level,
$d_{\text{prolonged}}$ = the mean duration of excretion of prolonged excretors beyond the first six months after the associated OPV infection, in years and as a function of income level,
r_{chronic} = the rate of chronic iVDPVs excretors as a function of income level, and
d_{chronic} = the mean duration of excretion of chronic excretors beyond the first six months after the associated OPV infection, in years and as a function of income level.

These formulas assume that in the presence of routine OPV immunization and absence of wild poliovirus transmission the entire birth cohort

Table A5. Inputs for Estimation of iVDPV-Related Outbreak Risks Based on Documented iVDPVs (Table III) and Population Data[21,69]

Input	Base Case	Min	Max[a]	Notes
Documented chronic iVDPV excretors,* HIGH	8	8	8	These numbers in fact represent underestimates of the true number of iVDPV excretors due to imperfect surveillance sensitivity for iVDPV detection; refer to Appendix for a discussion
Documented chronic iVDPV excretors, UMI	1	1	1	
Documented chronic iVDPV excretors, LOW and LMI	0	0	0	
Documented prolonged iVDPV excretors,** HIGH	10	10	10	
Documented prolonged iVDPV excretors, UMI	2	2	2	
Documented prolonged iVDPV excretors, LOW and LMI	5	5	5	
Number of first OPV infections, 1962–2005 (×100 M), HIGH	4.5	4.5	4.5	Assume this equals half of current population
Number of first OPV infections, 1962–2005 (×100M), UMI	2.5	2.5	2.5	Assume this equals half of current population
Number of first OPV infections, 1962–2005 (×100 M), LOW and LMI	15	15	15	Assume this equals half of current population younger than 15 years
Incidence of chronic iVDPV excretors per 100 million first OPV infections, HIGH	1.8	1.8	1.8	
Incidence of chronic iVDPV excretors per 100 million first OPV infections, UMI	0.4	0.4	0.4	
Incidence of chronic iVDPV excretors per 100 million first OPV infections, LOW and LMI	0.0	0.0	0.0	
Incidence of prolonged iVDPVs excretors per 100 million first OPV infections, HIGH	2.2	2.2	2.2	
Incidence of prolonged iVDPVs excretors per 100 million first OPV infections, UMI	0.8	0.8	0.8	
Incidence of prolonged iVDPVs excretors per 100 million first OPV infections, LOW and LMI	0.3	0.3	0.3	
Mean duration of excretion for chronic excretors (after the first six months), all countries	11.5	10.0	21.0*	Average of all chronic iVDPV excretors; upper end assumes duration of 25 years for currently excreting chronic excretors
Mean duration of excretion for prolonged excretors (after the first six months), HIGH, UMI, and LMI (years)	1.6	1.0	2.0	Average of all prolonged excretors
Mean duration of excretion for prolonged excretors (after the first six months), LOW (years)	0.5	0.1	1.5	Judgment
Average birth rate, HIGH	0.011	0.011	0.011	Average over projected birth rates for 2010–2029
Average birth rate, UMI	0.015	0.015	0.015	Average over projected birth rates for 2010–2029
Average birth rate, LMI	0.014	0.014	0.014	Average over projected birth rates for 2010–2029
Average birth rate, LOW	0.023	0.023	0.023	Average over projected birth rates for 2010–2029
P(outbreak|excretor) per year, *status quo* average	0.001	0	0.015*	Judgment
Relative risk P(outbreak|excretor) on OPV background, *HIGH* vs. *status quo average*	1.0	1.0	1.0	Judgment
Relative risk P(outbreak|excretor) on OPV background, *UMI* vs. *status quo average*	1.5	1.0	3.0	Judgment
Relative risk P(outbreak|excretor) on OPV background, *LMI* vs. *status quo average*	5.0	3.0	7.0	Judgment
Relative risk P(outbreak|excretor) on OPV background, *LOW* vs. *status quo average*	8.0	5.0	10.0	Judgment
Relative risk P(outbreak|excretor) on OPV background, year 20 vs. year T_0	1.0	0.95	1.5*	Judgment
Relative risk P(outbreak|excretor) on IPV background, year 20 vs. year T_0, LOW, LMI, UMI	5.0	1.0	10.0	Judgment; for HIGH we assume the conditional probability remains constant
Relative risk P(outbreak|excretor) 20 years after cessation (i.e., of OPV and IPV), LOW, LMI, and UMI (not applicable for HIGH given continued IPV use)	10.0	7.5	12.5	Judgment; base case yields P(outbreak|excretor) 20 years after T_0 of 0.08, 0.05 and 0.015 in LOW, LMI, and UMI, respectively
Ratio reported/true number of iVDPV excretors without paralysis	1.0	0.08	1.92	See text for discussion of this uncertainty range

[a]An asterisk behind the estimate in this column indicates that we interpret the "Max" end of the range as the 99th percentile and the base case estimate as the mean of a log-normal distribution bounded at the "Min" of the range. Absence of an asterisk implies that we interpret the range as minimum and maximum values of a triangular distribution peaking at the base case estimate.

*We define chronic excretors as those individuals excreting iVDPVs more than five years after associated OPV infection.

**We define prolonged excretors as those individuals excreting iVDPVs no more than five years but no less than six months after associated OPV infection.

IPV = inactivated poliovirus vaccine; HIGH = high-income country; iVDPV = immunodeficient vaccine-derived poliovirus; LMI = lower-middle-income country; LOW = low-income country; OPV = oral poliovirus vaccine (any formulation); UMI = upper-middle-income country.

eventually acquires an OPV infection due to vaccination or secondary OPV spread, regardless of income level or immunization coverage. In reality, less than 100% may seroconvert, especially in low-income countries that stop SIAs. Thus, if SIAs continue, then the prevalence of iVDPV excretors may in reality increase. However, we assume that this increased risk cancels out against the better population immunity with SIAs and we do not model the difference in risk for a scenario of OPV with or without SIAs.

Table A5 displays our best estimates of the inputs in the above formula. We obtain the value of the rates of iVDPV excretors ($r_{\text{prolonged}}$ and r_{chronic}) by dividing the number of documented iVDPV excretors by the total number of OPV recipients or people immunized secondarily prior to receiving IPV or contracting a wild poliovirus infection during approximately 40 years of widespread OPV use. For high- and upper-middle-income countries we roughly estimate this at 450 and 250 million people, respectively, representing half of the current population in those countries.[20,21] For low- and lower-middle-income countries, we estimate this at 1.5 billion people, corresponding to the current number of people aged less than 15 years, given that widespread OPV use started approximately 15 years ago in these countries. Thus, using the numbers of iVDPVs from Table IV, we estimate $r_{\text{prolonged}} = 10/4.5 \sim 2.2$ and $r_{\text{chronic}} = 8/4.5 \sim 1.8$ excretors per 100 million first OPV infections in high-income countries, $r_{\text{prolonged}} = 2/2.5 \sim 0.8$ and $r_{\text{chronic}} = 1/2.5 \sim 0.4$ in upper-middle-income countries, and $r_{\text{prolonged}} = 5/15 \sim 0.3$ and $r_{\text{chronic}} = 0$ in low- and lower-middle-income countries. In the absence of documented prolonged excretors in low-income countries, we artificially set their average duration of excretion at 0.5 year to reflect the shorter survival of persons with PIDs in those countries. For the other income levels, we assume $d_{\text{prolongeed}} = 1.6$ years and $d_{\text{chronic}} = 11.5$ years based on the durations in Table III.

The prevalence formula results in estimates for $Prev_{\text{iVDPV}}$ of 0.005, 0.009, 0.116, and 0.272 per 100 million people for low-, lower-middle-, upper-middle-, and high-income countries, respectively, using average birth rates in 2001 (which inversely correlate with income).[20,21] Multiplying by the total populations (year 2001) in each income level in multiples of 100 million, this translates into aggregate *status quo* prevalence of iVDPV excretors of 0.12, 0.20, 0.58, and 2.51 for low-, lower-middle-, upper-middle-, and high-income countries, respectively.

In a scenario involving OPV cessation, we assume the prevalence follows an exponential decay at a rate of 1 over the average duration of excretion per year (i.e., *initial rate* $\times$ $\text{Exp}(-y/d)$, where $y =$ the year after cessation and $d =$ the average duration of excretion).

Estimation of the conditional probability of an outbreak given the presence of an iVDPV excretor as a function of time and scenario remains problematic. A theoretical, deterministic condition prescribes that the initial *net reproductive number* (R_{n}, defined as the average number of secondary infections that an infectious person causes) must exceed 1 for a single virus introduction to cause an outbreak (i.e., if each new infection leads to only <1 new infections on average the outbreak will die out, but if each leads to >1 new infections on average the outbreak can take off). Given the proportion of susceptibles (s) in a population and the *basic reproductive number* (R_0, defined as the average number of secondary infections that an initial infection causes in a entirely susceptible population), the net reproductive number satisfies the equation $R_{\text{n}} = R_0/s$.[121] If we assume that R_0 behaves as a random variable, then we can estimate the theoretical probability of an outbreak per secondary iVDPV infection as a function of s as follows:

$$P(\textit{outbreak in income level } i \mid 1 \textit{ virus introduction}) = 1 - P_i(R_0 \leq 1/s),$$

where $P_i =$ the income-level-specific probability distribution for R_0. Unfortunately, this probability depends heavily on the choice of the probability distribution. For example, if the median value of R_0 falls far from the threshold of $1/s$ (e.g., a median R_0 of 9 or less in a population where $s = 10\%$), the spread in the probability distribution of R_0 dominates the resulting conditional outbreak probability. Estimating risk ratios with different values of s based on this theoretical threshold remains challenging given substantial variability and uncertainty in R_0.

With a median $R_0 > 10$ and $s > 10\%$, values not uncommon for wild polioviruses in low-income settings,[123,124] the outbreak probability exceeds 0.5 regardless of the variance of R_0. The lack of observed iVDPV-related outbreaks despite the theoretically high probability in those settings may reflect the absence of iVDPV excretors due to the low survival rate of people with PIDs in developing countries. In addition, we remain uncertain about the R_0 for iVDPVs. Consequently, it remains difficult to find a functional relationship between population immunity and the conditional probability of iVDPV-related outbreaks given the presence of an iVDPV excretor.

The only data basis for estimating the probability of outbreaks given the presence of an iVDPV excretor remains the fact that none of the iVDPV excretors to date led to any outbreak of additional paralytic cases (although two very recent events in Minnesota and Spain demonstrated the capacity of iVDPV viruses to circulate).[38,48] The sum of all duration estimates in Table III suggests 131 person-years of iVDPVs excretion (i.e., not including the first six months of virus excretion). This translates into a 95% confidence interval upper bound for the probability of an iVDPV outbreak in any year where an iVDPV excretor exists of 0.023 (based on the assumption that this probability follows a Bernoulli distribution).[22,125] Thus, a reasonable estimate of the average probability of an iVDPV outbreak during a year in the presence of an iVDPV excretor in the context of an OPV background and a developed country should not exceed the upper bound.

We estimate the annual probability of iVDPV outbreaks given the presence of an iVDPV excretor during the *status quo* of 0.001 (characterizing the uncertainty with a log-normal distribution with mean at 0.001 and 99th percentile at 0.015) in the context of limited information, although multiplication by the relative risk for the income level implies a maximum risk with continued OPV of 0.008 in low-income countries. We assume that iVDPV excretors effectively immunize their close contacts prior to excreting highly diverged viruses, and this reduces the risk that iVDPV excretors initiate outbreaks. Furthermore, we assume that iVDPV excretors typically lack pharyngeal excretion and survive only in relatively good hygiene settings with limited fecal-oral spread, and consequently the conditional probability of outbreaks given iVDPV excretion remains lower than this probability for wild virus introductions. Table A5 also provides estimates for the relative risk 20 years after T_0 compared to T_0, and we use simple linear interpolation to express this probability as a function of time although we recognize the limited evidence and significant uncertainties. In the event of OPV cessation, we assume a relative risk after 20 years compared to T_0 such that the probability of an outbreak given iVDPV excretion equals 0.08 after 20 years in low-income countries stopping polio vaccinations altogether (Table A5).

To obtain the time-dependent Poisson rates we multiply the prevalence of iVDPV excretors by the annual probability of an outbreak given a single iVDPV excretor such that the annual rate of occurrence of iVDPV-related outbreaks per 100 million people in low-, lower-middle-, and upper-middle-income countries equals:

$$\begin{aligned}\lambda_{\text{iVDPV}} = [(rr_{20} - 1) \times \text{y}/20 + 1] \times P_{outbreak|\text{iVDPV}} \\ \times rr_{\text{p|income}} \times b \times \{r_{\text{prolonged}} \times d_{\text{prolonged}} \\ \times \text{Exp}[-y \times (1 - 1_{\text{OPV}})/d_{\text{prolonged}}] + r_{\text{chronic}} \\ \times d_{\text{chronic}} \times \text{Exp}[-y \times (1 - 1_{\text{OPV}})/d_{\text{chronic}}]\},\end{aligned}$$

where

1_{OPV} = 1 for policies involving routine OPV use and 0 otherwise,
$P_{\text{outbreak|iVDPV}}$ = the baseline yearly probability of an outbreak given the presence of a single excretor,
$rr_{\text{p|income}}$ = the relative risk of $P_{\text{outbreak|iVDPV}}$ for a given income level compared to the baseline probability,
rr_{20} = the relative risk 20 years after T_0 as a function of the routine immunization policy (i.e., OPV, IPV, or stop) and income level, and
y = the year after T_0.

Consistent with our assumption that high-income countries switched to IPV in 1998 (on average) and assuming $rr_{\text{income}} = rr_{\text{p|income}} = 1$, the formula for the rate of occurrence of iVDPV outbreaks in high-income countries equals:

$$\begin{aligned}\lambda_{\text{iVDPV}} = P_{\text{outbreak|iVDPV}} \times rr_{\text{p|income}} \\ \times b \times \{r_{\text{prolonged}} \times d_{\text{prolonged}} \\ \times \text{Exp}[(y + T_0 - 1998)/d_{\text{prolonged}}] \\ + r_{\text{chronic}} \times d_{\text{chronic}} \\ \times \text{Exp}[-(\text{y} + T_0 - 1998)/d_{\text{chronic}}]\}.\end{aligned}$$

3.3. Uncertainty about the True Number of iVDPVs

While our base case analysis accounts only for those iVDPV excretors detected to date, important uncertainty exists regarding the true number of iVDPV excretors. In this subsection, we address the uncertainty about the number of iVDPV excretors (without distinguishing chronic and prolonged excretors) and present an estimate for the true number of iVDPVs based on very limited prior knowledge using Bayes' theorem.[126] As future research regarding iVDPVs becomes available, this approach allows updating the estimates to reflect the reduced uncertainty. Table III reveals that individuals with PIDs both with and without paralysis can become iVDPV excretors. Systematic clinical surveillance (i.e., AFP or

passive poliomyelitis surveillance) can detect iVDPV excretors who developed paralysis through analysis of viruses and follow-up of paralytic patients with PIDs. Although clinical surveillance probably does not detect paralytic iVDPV excretors with 100% sensitivity, the primary uncertainty remains the true number of iVDPV excretors without paralysis. Limited screening of persons with PIDs exists to detect any iVDPV excretors without paralysis, and consequently we do not know how many people with PIDs commonly get investigated for long-term poliovirus excretion.

We use Bayesian updating[126] to combine our uncertainty about the investigated number of persons with PIDs and the results of prior studies that provided a denominator (i.e., 384 persons with immunoglobulin G deficiencies)[70,72] to obtain a distribution for the true number of iVDPV excretors. We focus on upper-middle and high-income countries because of the greater survival of PIDs in those countries. We define θ as the probability that a person with a PID currently excretes an iVDPV. We rely on estimates of $M = 4$ iVDPV excretors without paralysis that we know currently excrete (Table III; includes environmental isolates) and estimates of the prevalence of individuals with PIDs (excluding immunoglobulin A deficiencies) of roughly 1 per 100,000 in developed countries,[70] or 14,000 in upper-middle and high-income countries, to get the prior distribution for θ. Thus, we know that the number of investigated persons with PIDs must lie between 4 and 14,000, and lacking further knowledge we assume equal likelihood for values within that range (i.e., prior distribution for $\theta \sim \text{Uniform}(k_1,k_2)$, with $k_1 = M/14{,}000$ and $k_2 = 1$, or an expected value of approximately 0.5). We use a binomial(n, θ) distribution to represent the number of iVDPVs (y) in a sample of size n given θ. Using Bayes theorem, we derive the following posterior distribution for θ given the observation of $y = 0$ iVDPVs among n persons with PIDs:

$$P(\theta|\mathrm{y} = 0, n) = (1-\theta)^{\mathrm{n}} \times (n+1)/[(1-k_1)^{\mathrm{n}+1} - (1-k_2)^{\mathrm{n}+1}].$$

Using the observation of 0 iVDPV excretors among 384 persons with PIDs, we estimate a mean of this distribution of 0.0029. This translates into an estimate for the prevalence of 40 chronic excretors without paralysis with a 95th percentile of 112 (compared to four chronic excretors where we only include identified excretors (i.e., at the base case)), or ratios of 0.1 and 0.04 reported to actual excretors without paralysis, respectively. Assuming that about half of the iVDPV excretors get paralysis, although our characterization includes iVDPV excretors that one may not consider cases of strong evidence (e.g., environmental isolates or patients without characterized viruses), we model a range of the ratios of reported iVDPV excretor to actuals of 0.08 to 1.92, with the best estimate remaining 1.

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