HHS Public Access

Author manuscript

Risk Anal. Author manuscript; available in PMC 2021 February 18.

Published in final edited form as:

Risk Anal. 2013 April ; 33(4): 680–702. doi:10.1111/risa.12022.

Oral Poliovirus Vaccine Evolution and Insights Relevant to Modeling the Risks of Circulating Vaccine-Derived Polioviruses (cVDPVs)

Radboud J. Duintjer Tebbens[1], **Mark A. Pallansch**[2], **Jong-Hoon Kim**[1], **Cara C. Burns**[2], **Olen M. Kew**[2], **M Steven Oberste**[2], **Ousmane Diop**[3], **Steven G.F. Wassilak**[4], **Stephen L. Cochi**[4], **Kimberly M. Thompson**[1,5]

[1]Kid Risk, Inc., 10524 Moss Park Rd., Ste. 204-364, Orlando, FL 32832 [2]Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases, Division of Viral Diseases, Atlanta, GA, 30333 [3]World Health Organization, Global Polio Eradication Initiative, Geneva, Switzerland [4]Centers for Disease Control and Prevention, Center for Global Health, Global Immunization Division, Atlanta, GA, 30333 [5]University of Central Florida, College of Medicine, Orlando, FL 32827

Abstract

The live, attenuated oral poliovirus vaccine (OPV) provides a powerful tool for controlling and stopping the transmission of wild polioviruses (WPVs), although the risks of vaccine-associated paralytic polio (VAPP) and circulating vaccine-derived poliovirus (cVDPV) outbreaks exist as long as OPV remains in use. Understanding the dynamics of cVDPV emergence and outbreaks as a function of population immunity and other risk factors may help improve risk management and the development of strategies to respond to possible outbreaks. We performed a comprehensive review of the literature related to the process of OPV evolution and information available from actual experiences with cVDPV outbreaks. Only a relatively small fraction of poliovirus infections cause symptoms, which makes direct observation of the trajectory of OPV evolution within a population impractical and leads to significant uncertainty. Despite a large global surveillance system, the existing genetic sequence data largely provide information about transmitted virulent polioviruses that caused acute flaccid paralysis, and essentially no data track the changes that occur in OPV sequences as the viruses transmit largely asymptomatically through real populations with suboptimal immunity. We updated estimates of cVDPV risks based on actual experiences and identified the many limitations in the existing data on poliovirus transmission and immunity and OPV virus evolution that complicate modeling. Modelers should explore the space of potential model formulations and inputs consistent with the available evidence and future studies should seek to improve our understanding of the OPV virus evolution process to provide better information for policy makers working to manage cVDPV risks.

Correspondence to: Radboud J. Duintjer Tebbens, Kid Risk, Inc., 10524 Moss Park Rd., Ste. 204-364, Orlando, FL 32832, USA, rdt@kidrisk.org.

Keywords

poliovirus; dynamic modeling; outbreak risks

Introduction

Introduced in the 1960s, oral poliovirus vaccines (OPVs) have played a significant role in the dramatic reduction of paralytic poliomyelitis cases globally, and they represent the primary vaccine tool used by the Global Polio Eradication Initiative (GPEI) for the eradication of wild polioviruses (WPVs).[1, p. 741] Polioviruses exist in three stable serotypes (types 1, 2, and 3) and protection from one type offers very little disease protection from the other types.[2, 3] Thus, poliovirus risk management policies must induce protection from all three types and typically require administering multiple doses of vaccine.

As a live, attenuated RNA virus, OPV protects vaccine recipients by causing infections that stimulate immunological responses, and these infections can spread to contacts leading to secondary protection, although the degree of spread varies by serotype.[4-8] Individuals infected with live polioviruses, including OPV, excrete virus until they clear their infections, which may last for varying durations,[8] and this may lead to secondary infections in contacts. Immunological protection from successful vaccination with OPV protects the individual from poliomyelitis, but successfully vaccinated individuals can get asymptomatically re-infected and potentially transmit poliovirus to others, although with a lower probability of becoming infected and a shorter duration of infectiousness if infected.[9-11] While replicating in the body (primarily in the gut), OPV viruses evolve to become more neurovirulent through a process of reversion of the attenuating mutations. Perhaps by random chance, host genetics, and/or other factors, in some cases infectious polioviruses attack the central nervous system and cause vaccine-associated paralytic polio (VAPP) in the vaccine recipient or a contact.[12-14] Replication and reversion may also make the virus more transmissible between people by increasing the amount of infectious viruses excreted (i.e., more exposure to contacts) and/or by introducing genetic changes that improve viral fitness and/or effectiveness with respect to crossing biological infection barriers (i.e., longer exposures, increased bioavailability). With high levels of population immunity, OPV viruses and closely related viruses excreted by recipients and contacts (i.e., OPV-related viruses) die out relatively quickly in the community because they cannot find sufficient numbers of susceptible individuals to continue transmission[5, 7] and the average duration of excretion is shorter for the well-immunized population.[8] However, in the presence of sufficient numbers of fully susceptible and partially infectible immune individuals in a community, OPV and OPV-related viruses can continue to circulate and evolve toward increased neurovirulence over time, which can lead to outbreaks of circulating vaccine-derived polioviruses (cVDPVs) that behave like wild polioviruses (WPVs).[15, 16]

Several comprehensive reviews provide information about past cVPDV events.[17-20] The first detected cVDPV outbreak occurred in 2000-2001 in Hispaniola,[15] and retrospective studies revealed a 1983-93 cVDPV2 outbreak in Egypt,[21] a cVDPV3 outbreak in Poland in 1968 (associated with the experimental USOL-D-bac vaccine),[22, 23] and possibly a

cVDPV2 outbreak in Belarus between 1963-1966.[24] The Global Polio Laboratory Network (GPLN) now regularly identifies cVDPVs, with numerous outbreaks involving all three serotypes occurring in the last decade.[18, 25, 26] We previously characterized and quantified the risks of cVDPVs associated with the use of tOPV for vaccination assuming aggressive continued use of tOPV for routine immunization and supplemental immunization activities.[25] Recognizing the risks of tOPV use, global health leaders called for coordinated tOPV cessation following successful eradication of WPVs, while emphasizing the need for continued high coverage levels until tOPV cessation.[27-30] Inactivated poliovirus vaccine (IPV) currently represents the only option for continued polio vaccination after OPV cessation. IPV effectively prevents poliomyelitis and does not lead to any serious adverse events, but it remains much more expensive than OPV. In addition, the probability of fecal excretion, as well as the amount and duration of fecal excretion, remain much higher for individuals infected with poliovirus after successful vaccination with only IPV than for tOPV, which leads to questions about the ability of IPV alone to stop transmission in populations with conditions that favor efficient fecal-oral poliovirus transmission.[9-11, 31]

Re-licensure of monovalent OPV (mOPV) type 1 (mOPV1) and type 3 (mOPV3) in 2005, and bivalent OPV types 1 and 3 (bOPV) in 2009 led some countries to stop their exclusive use of tOPV for supplemental immunization activities (SIAs), which led to reduced population immunity to type 2 poliovirus and increased the risk of cVDPV2 emergence and circulation.[32-34]) With continued delays in achieving WPV eradication, policy discussions for managing poliovirus risks pre- and post-eradication increasingly focus on the trade-offs associated with use of IPV vs. OPV (i.e., mOPVs, bOPV, and tOPVs)[18, 35, 36] in various settings and potential coordinated cessation of OPV2 by switching all routine tOPV use to bOPV.

The complexity of the dynamics of poliovirus evolution and transmission complicates efforts to use models to understand cVDPV risks and management options. Although models can provide useful insights for understanding and managing polio risks, relatively little research to date focuses on modeling the evolution and transmission of OPV viruses to quantify the risks of cVDPV emergence and spread. One analysis of post-eradication risks characterized the future probabilities of cVDPVs based on extrapolation of the real cVDPV outbreaks that occurred before 2005 when OPV-using countries only used tOPV for their routine immunization and SIAs (i.e., the frequency of observations, without consideration of the underlying process),[25] which requires updating given the recent changes that included the use of mOPV and bOPV. A different theoretical analysis that recognized cVDPV risks as significant ignored the complex immunity states of the population[37] despite the demonstration by prior models of their importance in poliovirus transmission models.[38] The history of WPV infection and/or vaccination with different types of vaccine and the time since the last infection or vaccination impact individual immunity, including susceptibility to infection, infectiousness to others, duration of infectiousness, and the probability of becoming paralyzed. Although we can model a cVDPV outbreak following the “introduction” of a cVDPV into a population,[38] we face significant challenges with respect to modeling the evolution of OPV viruses to create the “introduction” of the cVDPV, which also depends on population immunity. The challenge arises due to several critical

uncertainties about OPV virus evolution in terms of changing neurovirulence and transmissibility given our inability to observe the evolution process as it occurs.

We define VDPVs on the basis of the amount of genetic change from the parental vaccine strain in the VP1 region of the capsid coding region of the viral genome. The GPEI adopted this definition based on empirical data of associations with outbreaks in 2002 and modified the criteria for VDPV2 from > 1%[39] to > 0.6%[33] VP1 divergence in 2010 based on accumulated characterization of viruses isolated from VDPV outbreaks.[40] The Global Polio Laboratory Network (GPLN) classifies all VDPVs as: cVDPV, iVDPV (isolated from an individual with an immune deficiency), or aVDPV (not readily classified as one of the previous two classes). Our analysis applies the new classification system proposed by the GPLN in June 2012, which defines cVDPVs as VDPVs with evidence of person-to-person transmission and which includes any events with two or more genetically linked poliovirus isolates from acute flaccid paralysis (AFP) and/or non-AFP individuals without evidence of close contact (i.e., not within the same household).[41] This proposed change leads to an increase in the number of cVDPVs, because the prior definition of cVDPVs[26] required isolates from at least two linked paralytic cases (i.e., the new definition counts viruses associated with a single paralytic case for which evidence exists to suggest transmission within the community, including isolates from asymptomatic contacts).

The next section describes the methods we use to update observations of cVDPV and aVDPV events and revisit the prior risk characterization,[25] and the framing of our review of the literature related to the process of OPV virus evolution. We then present the results of our analysis and insights from our review of the evidence of the relationships between the risks of cVDPV outbreaks and population immunity. Finally, we discuss the complexity required to realistically model the dynamics of OPV virus evolution both within an infected individual and along the chains of transmission in a population.

Methods

We begin by reviewing the past cVDPV and aVDPV events to update the information presented previously.[25] We then use the updated data to provide revised assessments of the frequency of cVDPVs.[25] Recognizing the importance of the OPV virus evolution process in estimating risks going forward, we review the literature related to OPV virus evolution and the creation of cVDPVs. We searched PubMed using the keywords, oral poliovirus vaccine, OPV, reversion, vaccine-associated paralytic polio, VAPP, vaccine-derived poliovirus, and cVDPV for papers published in English prior to November 1, 2011. We also searched reference lists of publications that emerged as relevant, which led us to review 232 abstracts and 165 papers. We focused on the evidence related to neurovirulence and transmissibility and how quickly OPV regains the neurovirulent phenotype of a WPV within vaccine recipients and along chains of transmissions in the population. Neurovirulence reflects the capacity of the virus to replicate efficiently and destroy motor neurons, which affects the probability of developing paralysis given infection in fully susceptible individuals (i.e., individuals without immunity acquired from vaccination, infection, or maternal antibodies). Uncertainty remains about the mechanism that leads polioviruses to aggressively attack motor neurons in some individuals while only leading to asymptomatic

infections in others. Neurovirulence may depend on genetic susceptibility, the amount of viral exposure and/or other factors. Transmissibility reflects the ability of the virus excreted from an infected individual to infect another person, which may also depend on the concentration or amount of virus present in excreta, routes of transmission, and the ability of the virus to replicate in humans and survive in the environment.

Results

Review and analysis of cVDPV and aVDPV events

The GPEI routinely tracks the occurrence of VDPVs detected by the GPLN surveillance efforts and reported by other sources. These include viruses isolated from AFP cases and detected through environmental surveillance activities, systematic investigations of immunodeficient patients, and incidental investigations of otherwise healthy individuals. This review of VDPV events does not consider iVDPVs or environmental isolates consistent with shedding from unknown immunodeficient individuals, although the risks posed by these potential sources represent an important consideration.[25]

Table 1 lists of all recognized cVDPV events described globally for the period 2000-2012. The GPEI maintains a cumulative count of the number of cases with cVDPV isolates by country and year updated monthly on its website.[26] Table 1 provides much more detail by separately listing each independent emergence of a cVDPV, including those instances in which more than one concurrent lineage circulates simultaneously within a country and capturing the continued circulation of a cVDPV lineage for a period of greater than one year.

Table 2 lists aVDPV detections for the period 2000-2012. The table includes the VDPV viruses that do not currently meet the criteria for classification as cVDPVs or iVDPVs, either due to the absence of genetic, clinical, or epidemiologic evidence of virus circulation, or isolation indirectly from samples that cannot establish unambiguous evidence of circulation (e.g., environmental surveillance). The GPLN detected most of these viruses from children with AFP and in most situations they are clinically compatible with poliomyelitis. However, the GPLN distinguishes the aVPDVs as different from VAPP on the basis of the extent of genetic change of the virus from the parental vaccine strain (i.e., VAPP cases differ genetically from VDPVs).

Both Tables 1 and 2 reflect the proposed update to the cVDPV definition, and consequently they differ slightly from GPEI summary tables that use an earlier definition.[26] Specifically, Tables 1 and 2 include virus detections from non-AFP individuals found during investigations that provided evidence of community virus circulation. However, we note that we did not include one detected VDPV in an undervaccinated community in Minnesota in 2005 despite evidence of circulation, because the source of this virus remains unknown (given that the U.S. stopped using OPV 5 years earlier) and we do not know with certainty if the virus had already exceeded the VP1 divergence threshold before it reached the immunodeficient index patient and community.[42]

Applying the same approach used earlier to extrapolate historical experience with cVDPVs to the future,[25] Table 3 provides updated estimates of cVDPV risks. The number of events

between 2000-2005 differs from our prior analysis,[25] because (1) some events previously characterized as aVDPVs now classify as cVDPVs according to the current definitions (i.e., Romania 2002, Kazakhstan 2003, Laos 2004, Madagascar 2005), (2) one event previously characterized as an "excluded aVDPV" became a cVDPV after further paralytic cases occurred (i.e., Cambodia 2005-6), and (3) reporting of some events occurred after the time of the previous analysis (e.g., DR Congo cVDPVs 2005 (two events), Nigeria cVDPV 2005, China aVDPVs 2000, 2001, and 2002, Somalia aVDPV 2004 and 2005, Latvia aVDPV 2003).

We emphasize that we conducted our prior analysis before mOPV became a widely used vaccine for SIAs and that our earlier projection of the risk assumed that countries would continue their routine and supplemental immunization with tOPV only. Based on the frequency of cVDPV and aVDPV events before 2005 in countries that conducted no frequent SIAs compared to countries that did, we projected the highest risk of cVDPV outbreaks in countries that use OPV for routine immunization with sub-optimal coverage but that did not conduct SIAs.[25] Beginning in 2006 the GPEI strategy for SIAs to eradicate WPV1 then WPV3 shifted to increased reliance on mOPV1, mOPV3, and shifted again in 2010 to use bOPV. Consequently, many countries significantly reduced the frequency of SIAs with tOPV (i.e., the only currently available OPV vaccine that provides population immunity against type 2) or relied exclusively on routine tOPV immunization for their type 2 population immunity for extended periods of time. Not surprisingly, Table 3 shows a clear increase in the overall frequency of cVDPV and aVDPV events between 2000-2005 and 2006-2011 and provides an updated analysis of cVDPV risks. Notably, Figure 1 shows that the type 2 events that resulted from the drop in population immunity for type 2 associated with the use of mOPVs and bOPV in SIAs accounted for the increase. Improved VDPV surveillance and the change in definition of a type 2 VDPV may partly account for the increase; however, all but one 2011 Yemen cVDPV event would qualify as a cVDPV2 even with the prior virological definition (i.e., of >1% VP1 divergence) and no apparent increase in events occurred for types 1 and 3. Thus, we believe that Figure 1 highlights the importance of explicitly accounting for population immunity in estimating the risk of cVDPV outbreaks, which requires modeling poliovirus transmission[7] and evolution of OPV-related viruses. Although our prior analysis crudely accounted for population immunity by stratifying the risk estimates by presence or absence of regular SIAs with tOPV, that approach no longer suffices due to the variability in OPV serotypes used for SIAs. In addition, experience shows that cVDPV2 outbreaks can occur frequently even in the context of tOPV use if the SIAs are of relatively poor quality (e.g., Nigeria, DR Congo). Models that project cVDPV risks must account for all factors that influence population immunity, including the full history of wild poliovirus transmission, routine immunization coverage, SIAs conducted with each vaccine, and SIA coverage, as well as the conditions with respect to poliovirus transmissibility (e.g., R_0). [7] Moreover, they must integrate the process by which OPV viruses evolve to gain neurovirulence and transmissibility and eventually acquire the same properties as typical homotypical WPVs. Understanding the evidence-base for this process represents a critical first step.

Evidence-base for modeling OPV virus evolution

As small RNA viruses, polioviruses evolve rapidly, and consequently WPVs represent a spectrum of genetic sequences that differ in their neurovirulence,[43] which can be indirectly measured experimentally. Polioviruses may also differ in transmissibility, which we cannot observe and consequently we must infer differences from very limited epidemiological data. Given the continued circulation of WPVs for centuries, we assume that the three WPV serotypes retain sufficient inherent transmissibility to continue to propagate indefinitely in the human population absent other external factors. Based on the observed experience with cVPDV outbreaks, we assume that OPV viruses can become cVDPVs with similar neurovirulence and transmissibility as WPVs and cause outbreaks.[16, 25, 32] However, the properties of OPV-related viruses as they evolve towards cVDPVs remain poorly understood, particularly the properties related to the ability of viruses to transmit.

The process by which polioviruses were attenuated to make OPV influences the relative neurovirulence of each of OPV virus serotype. The OPV serotypes differ from one another with respect to the number of nucleotide differences from their progenitors, of which some represent attenuating mutations (i.e., genetic changes responsible for the attenuated phenotype of OPV viruses). The development of OPV involved successive passages of WPVs in nonhuman cells (e.g., monkey kidney cells).[1] For types 1 and 3, the progenitor strains represent highly neurovirulent strains (i.e., Mahoney for WPV1 and Leon for WPV3), while for type 2, Sabin used a low virulence progenitor wild strain (i.e., P712). Given the lower virulence of P712, researchers and laboratories often use other WPV2 strains (e.g.,MEF-1) or strains isolated from type 2 VAPP cases (e.g., P2/117)[44] or cVDPV2s as neurovirulent reference strains.[45-51]

Studies suggest that susceptible vaccine recipients normally excrete OPV viruses for several weeks after immunization.[9-11, 31] During this period, OPV viruses acquire greater neurovirulence and transmissibility in the gut of the vaccine recipients by selecting against the attenuating mutations through reversion (either by direct back-mutation or by selection for second-site suppressor mutations).[12] Selection against the attenuating mutations may occur by direct selection during replication, facilitated by mutations due to error-prone RNA-dependent RNA polymerase[12, 52] and/or by reversion through recombination, which commonly occurs between OPV virus serotypes,[53] and between OPV and WPV[54] and/or other enteroviruses.[15, 16, 21, 54-57] In addition genetic bottlenecking, in which only a subset of the virus population infects new cells, tissues, or organisms[58, 59] may contribute to random genetic drift and may narrow the quasispecies diversity.[60, 61]

Our review revealed several critical limitations in the existing literature. Animal experiments do not fully represent human disease experiences and they typically rely on the use of a small number of animals and limited number of test doses, which necessitates the use of pathological findings as signals of neurovirulence and significant assumptions about real effects. For example, monkey studies typically report a “mean lesion score” as a measure of neurovirulence, which provides a subjective, semi-quantitative assessment of the severity of lesions developed in neural tissues in monkeys after direct injection of the viruses into the tissues.[62] Studies in PVR-Tg21 transgenic mice expressing the human poliovirus receptor typically report the median paralytic dose (PD50; amount of virus, expressed in $\log_{10}$ cell-

or tissue-culture infectious doses, that apparently paralyzed or killed half (50%) of the animal subjects in the study),[63] with the assessments of paralysis also varying across studies. More importantly, animal experiments require interspecies extrapolation, and the appropriate correlation between outcomes in humans and experimental animals remains unknown. In addition, animal experiments typically use intracerebral or intraspinal inoculation of the virus, whereas infection in humans most likely occurs via oropharyngeal ingestion.

In addition to challenges with interpreting the results of animal studies for humans, polioviruses exist in quasispecies within the host characterized by genetic diversity.[64] With respect to categorization of poliovirus strains as we review the literature, we define “OPV viruses” as those viruses contained in the vaccine product, “OPV-related viruses” as polioviruses genetically closely-related to OPV strains, and “WPVs” as any other polioviruses that are genetically distinct from OPV strains. With the exception of OPV, viruses within these categories may exhibit a spectrum of neurovirulence and presumably also different transmissibility, although the spectrum may differ between categories. The reality that different WPVs of the same serotype may differ significantly in their transmissibility and neurovirulence makes any comparison to WPVs problematic and uncertain. We further recognize that in the process of analysis, laboratories only identify a small number of strains in a sample (e.g., usually the dominant strains present with the largest number of copies), and not the entire set of strains in the mixture that exists in any sample. In addition, sample collection occurs only at a single point in time and may not adequately represent the natural history of the infection in the individual. Given the relatively high rate of change and limitations in sample collection, we cannot know if a sample from excreta collected at any given time faithfully represents the actual individual viruses or even the population of viruses responsible for any observed symptoms, including paralysis, or whether the laboratory-isolated dominant strain from a sample represents the quasispecies diversity in the individual. In particular, significant uncertainty exists about whether the polioviruses isolated from fecal samples of human paralytic cases represent the same viruses that invaded the central nervous system (CNS) and caused paralysis, and the mechanism for CNS invasion in humans remains only partially characterized.

Time delays between the onset of paralysis and sample collection vary, and typically investigators collect only limited numbers of samples. We do not know why approximately one in one million people develops VAPP from receiving OPV or becoming infected by contact with a vaccine recipient.[1] The programmatic distinction between a contact VAPP case and a VDPV case remains largely epidemiological (i.e., traceability to a relatively recent OPV recipient for contact VAPP cases) in the absence of a positive isolate. Viruses from the uncommon community-acquired VAPP cases have not been fully characterized, which suggests that as we learn more about OPV evolution and reanalyze old samples, we might find that some cases previously characterized epidemiologically as community VAPP would be better characterized as VDPVs. We also do not know whether paralytic cases represent purely random events and/or whether they depend on some degree of virus replication (i.e., a threshold) and/or if some individuals (hosts) or polioviruses harbor specific attributes conducive to replication and/or the manifestation of symptoms.

Most poliovirus infections are asymptomatic, which means that we cannot clinically observe who becomes infected. Unlike smallpox, which caused visible symptoms in all infected people, polioviruses appear to cause characteristic paralytic symptoms in only a very small percentage of infections (i.e., < 1% of unimmunized individuals), although the true percent remains uncertain and may vary by serotype and the genetics of the virus strain.[65, 66] The inability to observe infection also implies that significant uncertainty exists about the paralysis-to-infection ratio in humans for all polioviruses.

The existing human data on OPV virus evolution over time rely on information from very small numbers of excreted viruses obtained mainly from previously unvaccinated children and a limited number of VAPP, immunodeficient VDPV (iVDPV), and cVDPV cases. Thus, we learn little from the literature about how OPV and OPV-related viruses behave in re-infected (i.e., prior live poliovirus-infected) and/or IPV-vaccinated individuals.

Attenuation and reversion

The ability of polioviruses to cause paralysis varies significantly. Estimates suggest paralysis-to-infection ratios for all WPV serotypes combined ranging from <0.001 to 0.045, with the highest values for type 1 based on U.S. data from 1952.[65-67] In contrast, U.S. data on paralysis in OPV recipients yielded estimates of approximately 1 VAPP case per million first OPV doses, with VAPP most frequently associated with OPV3, followed by OPV2, and only very rarely OPV1.[68-70] The frequency of VAPP following a first dose of tOPV appears similar between studies, although different serotype distributions have been observed with tOPV[71] and more uncertainty exists about VAPP rates associated with mOPV use.[72-74] The evidence shows relatively higher frequencies per infection in susceptibles for contact VAPP than for recipient VAPP,[25] which may indicate somewhat greater neurovirulence of OPV-related viruses than OPV, although characterization of exposure to contacts remains highly limited. Specifically, the denominator remains unknown, and although we might reasonably guess the number of household contacts and assume complete mixing within households, the number of contacts outside the home remains poorly characterized. The high frequency of type 2 VAPP (especially among immunodeficient patients) compared to type 1 VAPP observed in the U.S. remains consistent with the high frequency of type 2 cVDPV events in Tables 1 and 2. However, the infrequency of type 3 cVDPVs despite the high frequency of type 3 VAPP in immunocompetent recipients and contacts in the US remains not understood.

While the evidence clearly demonstrates lower neurovirulence from attenuated strains, significant uncertainty exists about the relative importance of the various attenuating mutations. Collectively, the literature suggests that in OPV-related viruses at least some of the attenuating mutations are selected against relatively quickly (i.e., within days), although differences probably exist with respect to the numbers of attenuating mutations lost and speed of loss by serotype. The cVDPV outbreaks that occurred reveal that after some period of transmission in a population with susceptible people, OPV-related viruses may regain neurovirulence comparable to WPVs with highly uncertain initial evolution rates that most likely vary by serotype. However, the literature provides insufficient quantitative information

about the time period required or the nature of the OPV reversion process and it reveals that all polioviruses may exhibit neurovirulence along a spectrum.

Numerous studies show potential attenuating mutations for each serotype of OPV virus based on: (1) sequence comparisons between OPV virus strains and parental WPVs[75, 76] (2) sequence comparisons and/or neurovirulence testing in monkeys or mice of recombinant virus strains (i.e., swapping genetic segments between attenuated and neurovirulent strains) and/or site-directed mutants,[47, 50, 77-84] (3) OPV-related virus mutant strains after exposure to high temperature,[85] (4) OPV-related virus strains excreted by immunocompetent vaccine recipients without VAPP,[48, 86-89] (5) OPV-related virus strains isolated from VAPP cases, [44-46, 48, 90-99] (6) strains isolated during cVDPV outbreaks,[15, 57, 100, 101] (7) strains excreted by immunodeficient VDPV excretors,[102-106] (8) strains obtained during sequential passages after OPV administration in humans,[107] (9) strains obtained during sequential passages of OPV-related viruses in monkey tissues,[108] and (10) strains obtained from passages in cell culture.[109] Collectively, the evidence does not provide conclusive information about the relative importance of the specific attenuating mutations, although it consistently reveals the presence of more attenuating mutations for type 1 than for types 2 or 3. With relatively fewer attenuating mutations leading to relatively faster complete loss of attenuating mutations, not surprisingly OPV types 2 and 3 produce the majority of VAPP cases in vaccine recipients.[69, 70, 110] However, the dynamics underlying the reversion of the attenuating mutations and the resulting increase in neurovirulence and transmissibility remain highly uncertain.

OPV1—Several studies identified and explored the importance of different attenuating mutations in OPV1 viruses, including analyses of recombinants of OPV1 and its progenitor (Mahoney, a lab-adapted highly-neurovirulent WPV1 reference strain), studies of site-directed mutants of both strains in monkeys or transgenic mice expressing human poliovirus receptor, and cell culture experiments. These studies characterized mutations conferring attenuation of neurovirulence and/or increased temperature sensitivity, which correlates with attenuation, throughout the genome (e.g., nt 21 (5’-UTR), 189 (5’-UTR), 480 (5’-UTR), 935 (VP4-65), 2438 (VP3-225), 2795 (VP1-106), 2879 (VP1-134), 6203 (3D-73), 7441 (3’-UTR)) and identified the mutation at nt position 480 as one of the most critical, although the degree to which each potential attenuating mutation influences neurovirulence remains unclear.[77, 81, 82, 97, 111] Several studies show that some of the attenuating mutations of OPV1 revert in primary vaccine recipients over the period of excretion, although reversion at nt position 480, which can occur by direct reversion or by a compensating substitution at nt position 525, varies with respect to the proportion of primary vaccine recipients and time in different studies.[18, 79, 112] The virus strains isolated from type 1 VAPP cases also show the reversion of several attenuating mutations, most notably at nt position 480. [48, 51, 86, 88, 89, 91, 93-97] One study in transgenic mice with uncertain extrapolation to humans showed that the PD_{50} values range from 4.5 to 5.8 for VAPP viruses, which suggests greater neurovirulence than OPV1 (PD_{50} around 8.0) and lower neurovirulence than the lab-adapted WPV1 Mahoney strain (PD_{50} around < 2.3).[91] Another study suggests relatively lower neurovirulence of OPV-related viruses from type 1 VAPP cases (PD_{50} ranging from 5.7 to 7.5), and gives bounding values for OPV1 (≥7.7) and Mahoney (2.4).[97] The viruses

isolated from a immunodeficient patients with a type 1 VDPV (iVDPV1) showed reversion at nt position 480 along with other reversions,[97, 113] with neurovirulence in transgenic mice comparable to that of Mahoney virus at 49 days post-vaccination.[113] Cell culture experiments showed that OPV1 viruses lose a few attenuating mutations after exposure to high temperature yielding viruses with comparable neurovirulence to Mahoney virus based on testing in monkeys.[85]

A few limited studies show the reversion of OPV1 following transmission in multiple people. One study monitored the change of neurovirulence of virus through five successive passages at approximately one-week intervals in healthy infants aged 8 to 12 months fed mOPV1.[114] Direct injection into the brains of monkeys of the virus collected during passage 4 caused paralysis in 1 out of 2 and during passage 5 caused paralysis in 6 out of 18 monkeys.[114] By comparison Mahoney virus caused paralysis in all 9 monkeys.[114] Another study that assessed lesion scores in monkeys for viruses isolated during five successive passages from the same clinical trial in healthy human infants fed mOPV1 over 3 months suggested that neurovirulence of the viruses increased gradually with observed lesion scores of 1.76 (passage 1), not reported (passage 2), 2.31 (passage 3), 2.27 (passage 4) and 2.72 (passage 5), compared to with lesion scores for OPV1 (1.2) and Mahoney (3.2).[107] Viruses isolated during cVDPV outbreaks in the Philippines and Hispaniola exhibited neurovirulence similar to Mahoney virus in transgenic mice.[15, 57] Phylogenetic analyses suggest relatively long circulation of these viruses (e.g., > 1 year) before they caused recognized outbreaks.[15, 57]

Collectively, the literature suggests that at least some of the critical attenuating mutations in OPV1 are selected against in a significant fraction of immunocompetent vaccine recipients over the period of excretion, which leads to an increase in the neurovirulence as the virus evolves. However, the neurovirulence of the virus appears unlikely to reach the extreme level of Mahoney virus during the normal excretion period of an immunocompetent vaccine recipient. Over a longer period of transmission in a population with susceptible people and/or with prolonged infection in an immunodeficient patient, OPV1 may regain neurovirulence comparable to WPVs.

OPV2—The literature on OPV2 viruses reveals similar uncertainties. Studies identified the two mutations at nt positions 481 (5’-UTR), which is a homologous site in PV2 to nt position 480 in PV1, and 2909 (VP1) as major determinants for the attenuated phenotype,[47, 49, 50] while mutations at nt positions 437 (5’-UTR), 868 (VP4), and/or 4076 (2B) lead to weak attenuating effects.[50] Testing in monkeys of OPV2 viruses with reversion of mutations at both nt position 481 and 2909 showed an increase in the mean lesion score from about 0.27 to 1.53, compared to a mean lesion score of 1.84 for type 2 strain P2/117 isolated from a VAPP patient.[50] Analyses of viruses excreted by both asymptomatic vaccine recipients[86, 88, 112, 115] and type 2 VAPP cases [46, 48] reveal reversions of attenuating mutations at nt position 481 in the 5’UTR. Viruses isolated during type 2 cVDPV outbreaks in Egypt from 1988 to 1993 also showed reversion, recombination, and selection against the attenuating mutations at nt positions 481 and 2909, in addition to vaccine/non-vaccine recombination.[21] Isolates of OPV-related viruses[116] from river and sewage water within 3 months of routine OPV immunization in Japan also revealed a

reversion of the attenuating mutation at nt position 481.[117] One study isolated viruses during 4 passages at 7-day intervals in children and reported an increasing proportion of monkeys paralyzed by the viruses (i.e., 0/10, 2/20, 12/33, and 6/19 for passage 0 (OPV strains), 1, 2, and 3 or more, respectively).[118] Neurovirulence of the OPV2-related viruses also increased with time of replication in the human gut with the proportion of paralyzed monkeys increasing from 0/10 (passage 0), 1/9 (passage 1), 0/2 (passage 2), 5/17 (passage 3), 4/12 (passage 4), to 9/21 (passage 5).[118] Overall, OPV2 includes a small number of attenuating mutations relative to virulent type 2 strains from VAPP cases (e.g., P2/117) and consequently OPV2 viruses may regain neurovirulence comparable to WPV2 relatively quickly, possibly within immunocompetent primary vaccine recipients, which may explain the relatively higher frequency of type 2 VAPP cases compared to type 1 VAPP cases.[70, 110] Studies of five type 2 cVDPVs excreted by people paralyzed during the outbreak in Madagascar in 2001-2002 suggest that the viruses circulated for 1-2 years before recognition of the outbreak.[56] However, the literature does not provide direct evidence of the time required for OPV2 viruses to regain neurovirulence comparable to WPV2 strains.

OPV3—Finally, studies of OPV3 viruses suggest the three mutations at nt positions 472 (5'-UTR), which is a homologous site in PV3 to nt position 480 in PV1, 2034 (VP3), and 2493 (VP1) contribute significantly to the attenuated phenotype.[83, 84, 87, 90, 119] In monkey studies, introductions of WPV3-like (i.e., those present in P3/Leon/37) reversions at position 472 only, position 2034 only, and both positions 472 and 2034, respectively, led to mean lesion scores of approximately 1.6, 1.3, and 2.1, respectively, compared to the mean lesion score for OPV3 of approximately 0.41 and for P3/Leon/37 of 2.7.[84] Another study found that reversion of mutation at nt position 2493 in the vaccines distributed in the U.S. caused an increase in the mean lesion score from 0.34 to 1.31,[83] while the effects of all three reversions at nt positions 472, 2034, and 2493 remains unknown. Comparison of the sequences of isolates from vaccine recipients[86, 88, 112, 115, 119] and from neuronal tissues of monkeys[119] inoculated with OPV3 show that the attenuating mutation at nt position 472 in 5'-UTR reverts quickly. A study of viruses excreted from healthy human infants fed mOPV3 through seven successive passages over a 3-month period of virus replication in the human gut reported neurovirulence of OPV3 that increased quickly from a lesion score of 2.2 (at 4 days) to a lesion score of 2.8 (at 18 days) when tested in monkeys.[107] The study reported a maximum lesion score of 3.2 for the virus excreted after passage 7 (after 109 days), which falls at the upper end of the range of lesion scores for WPV3 strains of 2.3 to 3.2.[107] Viruses isolated from type 3 VAPP cases show the reversion of nt position 472 and exhibit high neurovirulence in monkey tests.[120] Type 3 viruses isolated from an immunodeficient patient (i.e., iVDPV3) showed reversion of the attenuating mutation at nt position 472, and tests in monkeys showed mean lesion scores of the excreted viruses of 1.03 and 1.62 at 36 and 391 days after vaccination, respectively, compared to mean lesion scores of 0.44 for OPV3 and 3.13 for Leon.[105] Collectively, these studies suggest that OPV3 may regain neurovirulence comparable to WPV3s relatively quickly (e.g., within two weeks) in vaccine recipients and the neurovirulence may increase further during subsequent transmission.

Transmissibility

The predominance of asymptomatic infections limits the direct study of poliovirus transmission, and we do not fully understand the mechanism(s) or critical factors of transmission. Transmissibility reflects both the ability of the virus to replicate in the intestinal and oropharyngeal tissues and the ability of the virus to survive in fomites long enough to be ingested by contacts at sufficiently high doses to lead to fecal-oral or oropharyngeal transmission. One review[121] describes the complexity of estimating transmissibility of OPV viruses and WPVs and suggests lower transmissibility of OPV viruses relative to WPVs despite many limitations in the data on secondary transmission of OPV and WPV viruses in families, institutions, and communities. Limited data on the epidemiological characteristics of viruses from cVDPV outbreaks suggest that OPV viruses may eventually revert to the level of transmissibility of WPVs.[15, 16] No data exist on the transmissibility of OPV-related viruses that are evolving towards cVDPVs since chains of transmission are not observed and these viruses have not yet demonstrated the ability to cause outbreaks.

Estimates of the rates of total nucleotide substitution into the poliovirus capsid region appear similar on average across serotypes[43] and for WPVs, cVDPVs and iVDPVs.[43, 105, 106] However, the literature provides little evidence about reversion times of OPV viruses with different attenuating mutations within one host versus along chains of transmission.

Although some attenuating mutations may account for the most important increases in transmissibility, the full spectrum of genetic sites that influence transmission remains unknown. The GPLN characterizes viruses according to the degree of divergence in the VP1 region compared to the OPV parent strain. VP1 divergence provides an indicator of the time since the originating OPV infection based on a biased sample of viruses that transmitted (during which both reversion of attenuating mutations and other mutations occur), with approximately 1% VP1 divergence expected to occur per year.[43, 122] The GPLN classifies type 1 and 3 viruses with 9 or fewer substitutions (< 1%) in the VP1 region and type 2 viruses with 5 or fewer substitutions (< 0.6%) in the VP1 region as ‘normal’ vaccine-related viruses (i.e., Sabin-like viruses, equivalent to OPV-related in this paper) that reflect OPV vaccination and some limited evolution in the primary vaccinee and spread to close contacts.[41] The GPLN considers type 1 and 3 viruses with ≥ 10 and type 2 viruses with ≥ 6 substitutions in the VP1 region as VDPVs, because this much divergence correlates with demonstrated circulation in a population, and is empirically derived from cumulative virus characterization data from GPEI surveillance and the GPLN. The increase in transmissibility of OPV-related viruses as VP1 divergence increases from 0% to the operational classification threshold of VDPVs remains unknown.

Implications for modeling OPV virus evolution and cVDPV risks

Our review of the literature reveals relatively little precise data with respect to the characterization of inputs for modeling OPV virus evolution as a function of time and/or loss of attenuating mutations. Uncertainty exists about the number of critical attenuating mutations, which most likely varies by serotype as discussed above. While the literature suggests a clear relationship between loss of attenuation and replication fitness, the

quantitative effect of increasing replication fitness on neurovirulence and transmissibility remains very uncertain, despite a clear correlation.

We identified different possible options for modeling the OPV virus evolution process. One option assumes that a small number of key attenuating mutations fully dictate neurovirulence and transmissibility (independent of order of the changes), with reversion of a given number of key attenuating mutations corresponding to one reversion state (e.g., 6 stages for type 1, 3 for type 2, and 3 or 4 for type 3 based on key attenuations suggested in VDPV reviews discussed above).[12, 18, 35, 52] For example, the first stage after OPV2 corresponds to a virus with one of the two important attenuating mutations reverted and the second with both attenuating mutations reverted, which represents a virus with the same properties as a typical WPV2. Limited data indicate rapid reversion of key attenuating mutations in immunocompetent vaccine recipients with no VAPP,[86, 88, 107, 118] but uncertainty remains about the actual timing of these mutations with with subsequent new infections and the relationship between the number of reverted attenuating mutations and neurovirulence and/or transmissibility. Another option approximates a continuous reversion process by assuming a large number of reversion stages reflecting a larger number of substitutions that could combine in different ways to affect neurovirulence and transmissibility. VP1 divergence provides a means to estimate the duration of replication (or circulation) since the time of the initiating OPV dose, assuming a correlation exists, whereas selected substitutions precede most substitutions accumulating by genetic drift. Thus, this formulation assumes that the percent VP1 divergence correlates with the effect of combinations of all mutations that occur over time on neurovirulence and transmissibility. Other options also exist, restricted primarily by the limited evidence presented above and the requirement that models should make assumptions about reversion times consistent with the current GPLN definitions of VDPVs and assuming approximately 1% VP1 synonymous changes per year.[41] However, uncertainty remains about the kinetics of early reversion steps and one study observed significant VP1 divergence within the limited excretion period of a vaccine recipient.[123] Moreover, it remains possible that VDPVs continue to acquire increased ability to transmit after they reach the VP1 divergence thresholds from the GPLN, which would mean that the time to reach those thresholds provides a lower bound for the duration of the full evolution process from OPV transmissibility to homotypical WPV transmissibility.

Figure 2 provides a conceptual representation of the two options discussed above for modeling the OPV evolution process. To emphasize that the reversion process varies for each individual virus, but that models might capture the average behavior, the figure shows both the random evolution path for 10 viruses that originate as OPV viruses (i.e., vaccine given to an individual) and the “population average” (based on the average of 100 random virus evolution trajectories). In reality viruses will not continue to evolve once they find no more susceptible hosts, but for simplicity Figure 2 assumes that viruses continue to replicate in the OPV recipients and contacts (i.e., it assumes continued access to sufficient numbers of susceptible individuals for sustained transmission). The evolution process in Figure 2a assumes that only 3 attenuating mutations (or alternatively 2 key attenuating mutations with the third representing the cumulative effect of all remaining weakly attenuating mutations) account for all the difference between OPV and a homotypical WPV (i.e., an example for

serotype 2). Consequently, each individual virus reaches the "fully-reverted" stage with assumed WPV-like properties in only 3 reversion steps in the example shown, although as discussed above the number of reversion steps will depend on serotype. Based on limited observation from healthy OPV recipients,[86, 88, 107, 118] these few mutations typically revert at a rapid rate. The evolution process in Figure 2b assumes that each change in the VP1 region highly correlates with progress toward full reversion in a more gradual process (i.e., approximately 10 mutations per year). As noted, the GLPN defines viruses more than 1% VP1 divergence (> 0.6% for type 2) compared to OPV as VDPVs based on the observed ability of these viruses to cause outbreaks and exhibit behavior indistinguishable from WPVs. However, we do not know if further evolution of viruses beyond 1% VP1 divergence results in further increases in transmissibility. While in reality VP1 divergence continues to occur beyond 1%, Figure 2b truncates the process at 10 mutations (i.e., by characterizing them as "more than 1%") to convey the idea that at some point further genetic drift may only randomly affect neurovirulence and transmissibility within a clear increasing direction due to loss of attenuation. Thus, Figure 2b characterizes all viruses with more than 1% VP1 divergence as essentially the same. However, the threshold of 1% VP1 divergence reflects an operational definition and may not reflect the true point beyond which no further attenuation, which remains uncertain. The average time to reach the GPLN thresholds of VP1 divergence in a population remains substantially longer than the time to revert individual attenuating mutations, and therefore the overall reversion process is slower in Figure 2b than in Figure 2a. For both models, we expect a faster process for type 2 than type 1 (i.e., both fewer attenuating mutations and lower VP1 divergence threshold for type 2 than 1), but uncertainty remains about whether type 3 reverts at a similar speed compared to type 2 (same number of attenuating mutations) or type 1 (same VP1 divergence threshold).

Mapping the reversion process onto concrete properties such as the (relative) paralysis-to-infection ratio (PIR) and basic reproductive number (R_0) compared to typical homotypic WPVs represents a separate challenge for modeling as we do not know quantitatively how much increases in the PIR or R_0 correspond with each attenuating mutation or VP1 nucleotide change. Poliovirus transmission and evolution models to support cVDPV outbreak risk estimation might capture the average PIR and R_0 by reversion stage using a plausible functional form. For example, building on the concept discussed by Chumakov et al,[35] Figure 3 shows a potential relationship between age of virus and average PIR for each serotype, based on an assumed logarithmic increase in the natural logarithm of the PIR with each reversion stage. Given differences by type in both the speed of the reversion process and the PIR for OPV (i.e., based on recipient VAPP rates[70]) and WPV,[65] the curves differ by serotype. However, we emphasize that no data exist to directly determine such a relationship, particularly with respect to R_0 and the rate of reversion for type 3 (which produced VAPP at a relatively high rate but VDPVs at a relatively low rate compared to the other types), and thus that models should test different assumptions to determine relationships that produce results consistent with observed emergences of cVDPVs in some situations and lack of emergence of cVDPVs in other situations.[124]

Discussion

The risks of cVDPVs remain an important threat to the achievement of the ultimate goal of ending all cases of paralytic poliomyelitis. Unfortunately, the existing literature provides relatively little insight into the quantification of inputs for modeling the OPV virus evolution process. The inability to observe evolution as it occurs precludes direct statistical modeling and complicates modeling the dynamics of the process. Modelers should explore the space of potential model formulations and inputs consistent with the available evidence and seek to replicate the actual experiences that occur in different settings and situations. Fitting a wide range of situations (e.g., the emergence of cVDPVs that occurred in various countries and the absence of cVDPVs in developed countries and in many developing countries) should constrain the models to some degree.[124]

We summarized the available and uncertain data on the occurrence of cVDPVs as they relate to independent emergence events to more accurately reflect the outcomes that could be analyzed or modeled in the context of population risk factors. Rather than simply looking at the number of cases, which as for WPV importations more directly reflects the effectiveness of control, this synthesis gives more information related to the risk of emergence. However, characterization of the risks of cVDPVs prospectively based on prior experience provides imperfect and uncertain estimates that depend on the extent to which future choices that impact population immunity match with past and present experience. The recent shift to the use of mOPVs and bOPV represented a deviation from the decades of experience using trivalent vaccines and changed the risks of cVDPVs differentially by serotype.

The narrow focus in the literature on loss of attenuation of the Sabin strains contained in OPV reflects the limited availability and practicality of observational or experimental data to inform an understanding of the links between the properties of neurovirulence, attenuation, replicative fitness, and transmission in the natural host. The available data also do not provide sufficient inference to effectively bound the dynamic elements of the process and highlight specific incongruous observations. For example, the data consistently show that key reversions occur rapidly, even in the vaccine recipient, and increase neurovirulence in animals, while epidemiologic data show relatively few VAPP or cVDPV cases. Our review of the data indicates that modeling efforts must take into account the distinct differences between the three serotypes, which differ both in the virulence of the WPV strains and in the relative degree of attenuation of each virus used to generate OPV strains. Thus, the serotypes differ with respect to their absolute levels of virulence and stability of associated OPV (Figure 3). Quantitative characterization of the reversion process remains a challenge, and the previous qualitative characterizations may still represent the best representation possible,[35] with the caveat that those estimates reflect the use of tOPV for vaccination against all serotypes and differences exist between serotypes such that we anticipate relationships for the serotypes like those depicted in Figure 3. Despite the conceptual linkage between the use of a vaccine containing an inherently unstable RNA virus subject to direct selection against the attenuating alleles, the observational data on recipient VAPP and the process of cVDPV emergence may not reflect linked pathways. Instead, we observe an apparent paradox for OPV types 1 and 3. Specifically, despite its relatively greater attenuation, type 1 OPV causes much less recipient VAPP than type 3, but type 1 cVDPV events occur more frequently than

type 3 outbreaks. Part of the mystery probably relates to differences in the relative transmissibility of the OPV viruses compared to homotypical WPVs and possibly absolute transmissibility of WPV1 vs. WPV3, but these remain hypotheses that defy practical testing due to our inability to observe transmission.

This review highlights two major areas in which knowledge gaps exist that prevent more detailed representation of OPV reversion to cVDPVs. First, numerous studies examined excreted virus from primary recipients of vaccine or individual cases, but in general we lack good information about successive infections. Therefore, we cannot directly observe the patterns of successive changes during person-to-person transmission. In addition, because of the low paralysis-to-infection ratio, we cannot directly observe or practically measure human virulence, and no examination of the aggregate data exists that might characterize uncommon but more significant events in a very large population. Second, very few data exist to inform the characterization of increasing transmission associated with reversion. Not surprisingly, the inability to observe transmission of the virus (i.e., detecting the virus primarily only by detecting cases that occur with a relatively low rate per number of infections) makes characterization of transmission challenging. With respect to both of these areas, the absence of adequate animal models for human disease represents a significant limitation. The existing models animal models for polio all use very high paralysis to infection outcomes due to the practical laboratory limitations (i.e., the need to minimize the numbers of animals used), but this makes extrapolation of the experimental animal data to humans difficult. Similarly, no validated proxy measurements exist to determine or measure the transmissibility of a virus. While it makes sense to assume a simple correlation between replicative fitness and transmission, potential dilution and threshold effects, and other factors, increase the uncertainty about these assumptions and raise questions about the appropriate use of the available data in modeling.

Even though this review focuses on the virus, other factors may influence cVDPV emergence, in particular population immunity.[7] Population immunity may emerge as far more important than any particular virologic trait. In a complex dynamic transmission setting, the rate-limiting step in the emergence process may depend on population susceptibility and the ability to support transmission instead of properties of the virus, and this may mean that complex contact patterns that exist between the members of the population represent a much more important concern. Specifically, while data suggest relatively comparable secondary attack rates for OPV and WPV (especially for type 2),[8, 125] the difference may be larger for community spread. This would imply that secondary OPV spread can substantially improve population immunity induced by OPV through infection of close contacts [4, 6, 126] while remaining self-limited such that it does not lead to outbreaks.[5] Similarly, heterogeneity and stochasticity may help explain both the correlations between cVDPV emergence and lower population immunity as well as the observed frequency of emergence events. These considerations allow for several approaches to modeling the risk of cVDPV emergence.

Acknowledgments

The authors thank the World Health Organization (WHO) Polio Research Committee for grant APW200179134 that supported the review and synthesis of the evidence related to OPV evolution. We thank the U.S. Centers for Disease Control and Prevention (CDC) for supporting the updated assessment of cVPDV risks under Cooperative Agreement U66IP000519-01. The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the WHO or CDC. The authors thank Drs. Qi Chen, Jane Iber, Jing Shaw, Roland Sutter, and Gregory Wallace for helpful input and the Global Polio Laboratory Network for information.

References

1. Sutter RW, Kew OM, Cochi SL. Poliovirus vaccine-live In: Plotkin SA, Orenstein WA, Offit PA, editors. Vaccines. Fifth ed: Saunders Elsevier; 2008 p. 631–686.
2. Salk JE. Requirements for persistent immunity to poliomyelitis. American Journal of Medical Science 1956;232(4):369–377
3. Hammon WM, Ludwig EH. Possible protective effect of previous type 2 infection against paralytic poliomyelitis due to type 1 virus. American Journal of Hygiene 1957;66(3):274–280 [PubMed: 13478577]
4. Chen RT, Hausinger S, Dajani AS, Hanfling M, Baughman AL, Pallansch MA, Patriarca PA. Seroprevalence of antibody against poliovirus in inner-city preschool children. Journal of the American Medical Association 1996;275(21): 1639–1645 [PubMed: 8637136]
5. Más Lago P, Bravo JR, Andrus JK, Cornellas MM, Galindo MA, de Quadros CA, Bell E. Lesson from Cuba: Mass campaign administration of trivalent oral poliovirus vaccine and seroprevalence of poliovirus neutralizing antibodies. Bulletin of the World Health Organization 1994;72(2):221–5 [PubMed: 8205641]
6. Benyesh-Melnick M, Melnick JL, Rawls WE, Wimberly I, Barrera Ora J, Ben-Porath E, Rennick V. Studies of the immunogenicity, communicability and genetic stability of oral poliovaccine administered during the winter. American Journal of Epidemiology 1967;86(1): 112–136 [PubMed: 4378110]
7. Thompson KM, Pallansch MA, Duintjer Tebbens RJ, Wassilak SGF, Cochi SL. Modeling population immunity to support efforts to end the transmission of live polioviruses. Risk Analysis:In Press
8. Duintjer Tebbens RJ, Pallansch MA, Chumakov KM, Halsey NA, Hovi T, Minor PD, Modlin JF, Patriarca PA, Sutter RW, Wright PF, Wassilak SGF, Cochi SL, Kim J-H, Thompson KM. Expert review on poliovirus immunity and transmission. Risk Analysis:In press
9. Ghendon YZ, Sanakoyeva II. Comparison of the resistance of the intestinal tract to poliomyelitis virus (Sabin's strains) in persons after naturally and experimentally acquired immunity. Acta Virologica 1961;5:265–73
10. Henry JL, Jaikaran ES, Mason PJ, Barnes JM, Beale AJ. A study of polio vaccination in infancy: Excretion following challenge with live virus by children given killed or living poliovaccine. Journal of Hygiene Cambridge 1966;64:105–120
11. Public Health Laboratory Service. The excretion of type 1 poliovirus after challenge following primary immunization with quadruple, Salk, and Sabin vaccines. Monthly Bulletin of the Ministry of Health and Public Health Laboratory Service 1965;24:365–369
12. Minor PD. The molecular biology of poliovaccines. Journal of General Virology 1992;73(pt. 12):3065–3077
13. Mueller S, Wimmer E, Cello J. Poliovirus and poliomyelitis: A tale of guts, brains, and an accidental event. Virus Research 2005; 111(2): 175–193 [PubMed: 15885840]
14. Jegouic S, Joffret ML, Blanchard C, Riquet FB, Perret C, Pelletier I, Colbere-Garapin F, Rakoto-Andrianarivelo M, Delpeyroux F. Recombination between polioviruses and cocirculating coxsackie a viruses: Role in the emergence of pathogenic vaccine-derived polioviruses. PLoS Pathog 2009;5(5):e1000412 [PubMed: 19412342]
15. Kew O, Morris-Glasgow V, Landaverde M, Burns C, Shaw J, Garib Z, Andre J, Blackman E, Freeman CJ, Jorba J, Sutter R, Tambini G, Venczel L, Pedreira C, Laender F, Shimizu H, Yoneyama T, Miyamura T, van Der Avoort H, Oberste MS, Kilpatrick D, Cochi S, Pallansch M, de

Quadros C. Outbreak of poliomyelitis in Hispaniola associated with circulating type 1 vaccine-derived poliovirus. Science 2002;296(5566):356–359 [PubMed: 11896235]

16. Estivariz CF, Watkins M, Handoko D, Rusipah R, Deshpande J, Rana BJ, Irawan E, Widhiastuti D, Pallansch MA, Thapa A, Imari S. A large vaccine-derived poliovirus outbreak on Madura island--Indonesia, 2005. Journal of Infectious Diseases 2008;197(3):347–54
17. Kew O, Wright P, Agol V, Delpeyroux F, Shimizu H, Nathanson N, Pallansch M. Circulating vaccine-derived polioviruses: Current state of knowledge. Bulletin of the World Health Organization 2004;82:16–23 [PubMed: 15106296]
18. Kew OM, Sutter RW, de Gourville EM, Dowdle WR, Pallansch MA. Vaccine-derived polioviruses and the endgame strategy for global polio eradication. Annual Review of Microbiology 2005;59:587–635
19. Wringe A, Fine PE, Sutter RW, Kew OM. Estimating the extent of vaccine-derived poliovirus infection. PLoS One 2008;3(10):e3433 [PubMed: 18958288]
20. Minor P Vaccine-derived poliovirus (VDPV): Impact on poliomyelitis eradication. Vaccine 2009;27(20):2649–52 [PubMed: 19428874]
21. Yang C, Naguib T, Yang S, Nasr E, Jorba J, Ahmed N, Campagnoli R, van der Avoort HGAM, Shimizu H, Yoneyama T, Miyamura T, Pallansch MA, Kew OM. Circulation of endemic type 2 vaccine-derived poliovirus in Egypt from 1983 to 1993. Journal of Virology 2003;77(15):8366–77 [PubMed: 12857906]
22. Martin J, Ferguson GL, Wood DJ, Minor PD. The vaccine origin of the 1968 epidemic of type 3 poliomyelitis in Poland. Virology 2000;278(1):42–9 [PubMed: 11112479]
23. Kostrewski J, Kulesza A, Abgarowicz A. The epidemic of type 3 poliomyelitis in Poland in 1968. Epidemiologic Reviews (Warsaw) 1970;24:89–103
24. Korotkova EA, Park R, Cherkasova EA, Lipskaya GY, Chumakov KM, Feldman EV, Kew OM, Agol VI. Retrospective analysis of a local cessation of vaccination against poliomyelitis: A possible scenario for the future. Journal of Virology 2003;77(23): 12460–12465 [PubMed: 14610170]
25. Duintjer Tebbens RJ, Pallansch MA, Kew OM, Cáceres VM, Jafari H, Cochi SL, Aylward RB, Thompson KM. Risks of paralytic disease due to wild or vaccine-derived poliovirus after eradication. Risk Analysis 2006;26(6): 1471–1505 [PubMed: 17184393]
26. World Health Organization. Circulating vaccine-derived poliovirus, 2000–2011. 2011: http://www.polioeradication.org/Dataandmonitoring/Poliothisweek/Circulatingvaccinederivedpoliovirus.aspx, accessed December 16 2011
27. World Health Organization. Global Polio Eradication Initiative - Strategic Plan 2010-2012. Geneva; 2010. Report No.: WHO/Polio/10.01.
28. World Health Organization. Conclusions and recommendations of the Ad Hoc Advisory Committee on Poliomyelitis Eradication, Geneva, 21–22 September 2004. Weekly Epidmiological Record 2004;79(45):401–408
29. World Health Assembly. Poliomyelitis: Mechanism for management of potential risks to eradication (resolution 61.1). Geneva: World Health Organization; 2008 http://apps.who.int/gb/ebwha/pdf_files/WHA61-REC1/A61_Rec1-part2-en.pdf
30. Thompson KM, Duintjer Tebbens RJ. The case for cooperation in managing and maintaining the end of poliomyelitis: Stockpile needs and coordinated OPV cessation. The Medscape Journal of Medicine 2008; 10(8): 190 [PubMed: 18924642]
31. Onorato IM, Modlin JF, McBean MA, Thoms ML, Losonsky GA, Bernier RH. Mucosal immunity induced by enhanced-potency inactivated and oral polio vaccines. Journal of Infectious Diseases 1991;163:1–6
32. Wassilak SGF, Pate MA, Wannemuehler K, Jenks J, Burns C, Chenoweth P, Abanida EA, Adu F, Baba M, Gasasira A, Iber J, Mkanda P, Williams AJ, Shaw J, Pallansch MA, Kew OM. Outbreak of type 2 vaccine-derived poliovirus in Nigeria: Emergence and widespread circulation in an underimmunized population. Journal of Infectious Diseases 2011;203(7):898–909
33. Centers for Disease Control and Prevention. Update on vaccine-derived polioviruses--worldwide, July 2009-March 2011. MMWR Morb Mortal Wkly Rep 2011;60(25):846–850 [PubMed: 21716199]

34. Kew OM. Reaching the last one per cent: Progress and challenges in global polio eradication. Current Opinion in Virology 2012;2:188–198 [PubMed: 22482715]
35. Chumakov K, Ehrenfeld E, Wimmer E, Agol VI. Vaccination against polio should not be stopped. Nat Rev Microbiol 2007;5(12):952–8 [PubMed: 17965726]
36. Thompson KM, Duintjer Tebbens RJ, Pallansch MA, Kew OM, Sutter RW, Aylward RB, Watkins M, Gary HE Jr., Alexander JP Jr., Jafari H, Cochi SL. The risks, costs, and benefits of possible future global policies for managing polioviruses. American Journal of Public Health 2008;98(7): 1322–1330 [PubMed: 18511720]
37. Wagner BG, Earn DJ. Circulating vaccine derived polio viruses and their impact on global polio eradication. Bulletin of Mathematical Biology 2008;70(1):253–280 [PubMed: 17934778]
38. Duintjer Tebbens RJ, Pallansch MA, Kew OM, Cáceres VM, Sutter RW, Thompson KM. A dynamic model of poliomyelitis outbreaks: Learning from the past to help inform the future. American Journal of Epidemiology 2005;162(4):358–372 [PubMed: 16014773]
39. Centers for Disease Control and Prevention. Update on vaccine-derived polioviruses--worldwide, January 2008-June 2009. Morbidity and Mortality Weekly Report 2009;58(36): 1002–1006 [PubMed: 19763076]
40. World Health Organization. Summary of discussions and recommendations, 16th informal consultation of the global polio laboratory network, 22-23 September 2010, WHO/HQ. Geneva: World Health Organization; 2010.
41. Centers for Disease Control and Prevention. Update on vaccine-derived polioviruses--worldwide, April 2011 - June 2012. Morbidity and Mortality Weekly Report 2012;61(37):741–746 [PubMed: 22992572]
42. Alexander JP Jr., Ehresmann K, Seward J, Wax G, Harriman K, Fuller S, Cebelinkski EA, Chen Q, Jorba J, Kew OM, Pallansch MA, Oberste MS, Schleiss M, Davis JP, Warshawsky B, Squires S, Hull HF. Transmission of imported vaccine-derived poliovirus in an undervaccinated community in Minnesota. Journal of Infectious Diseases 2009; 199(3):391–397
43. Jorba J, Campagnoli R, De L, Kew O. Calibration of multiple poliovirus molecular clocks covering an extended evolutionary range. Journal of Virology 2008;82(9):4429–4440 [PubMed: 18287242]
44. Kew OM, Nottay BK, Hatch MH, Nakano JH, Obijeski JF. Multiple genetic changes can occur in the oral poliovaccines upon replication in humans. Journal of General Virology 1981;56(Pt 2):337–347
45. Pollard SR, Dunn G, Cammack N, Minor PD, Almond JW. Nucleotide sequence of a neurovirulent variant of the type 2 oral poliovirus vaccine. Journal of Virology 1989;63(11):4949–4951 [PubMed: 2552175]
46. Equestre M, Genovese D, Cavalieri F, Fiore L, Santoro R, Perez Bercoff R. Identification of a consistent pattern of mutations in neurovirulent variants derived from the sabin vaccine strain of poliovirus type 2. Journal of Virology 1991;65(5):2707–2710 [PubMed: 1850043]
47. Macadam AJ, Pollard SR, Ferguson G, Dunn G, Skuce R, Almond JW, Minor PD. The 5' noncoding region of the type 2 poliovirus vaccine strain contains determinants of attenuation and temperature sensitivity. Virology 1991; 181(2):451–458 [PubMed: 1707566]
48. Muzychenko AR, Lipskaya G, Maslova SV, Svitkin YV, Pilipenko EV, Nottay BK, Kew OM, Agol VI. Coupled mutations in the 5'-untranslated region of the Sabin poliovirus strains during in vivo passages: Structural and functional implications. Virus Research 1991;21(2): 111–122 [PubMed: 1661980]
49. Ren RB, Moss EG, Racaniello VR. Identification of two determinants that attenuate vaccine-related type 2 poliovirus. Journal of Virology 1991;65(3): 1377–1382 [PubMed: 1847458]
50. Macadam AJ, Pollard SR, Ferguson G, Skuce R, Wood D, Almond JW, Minor PD. Genetic basis of attenuation of the Sabin type 2 vaccine strain of poliovirus in primates. Virology 1993;192(1):18–26 [PubMed: 8390752]
51. Guillot S, Otelea D, Delpeyroux F, Crainic R. Point mutations involved in the attenuation/neurovirulence alternation in type 1 and 2 oral polio vaccine strains detected by site-specific polymerase chain reaction. Vaccine 1994;12(6):503–507 [PubMed: 8036823]
52. Agol VI. Vaccine-derived polioviruses. Biologicals 2006;34(2): 103–108 [PubMed: 16650771]

53. Cuervo NS, Guillot S, Romanenkova N, Combiescu M, Aubert-Combiescu A, Seghier M, Caro V, Crainic R, Delpeyroux F. Genomic features of intertypic recombinant sabin poliovirus strains excreted by primary vaccinees. Journal of Virology 2001;75(13):5740–5751 [PubMed: 11390576]
54. Liu HM, Zheng DP, Zhang LB, Oberste MS, Kew OM, Pallansch MA. Serial recombination during circulation of type 1 wild-vaccine recombinant polioviruses in China. Journal of Virology 2003;77(20):10994–11005 [PubMed: 14512548]
55. Guillot S, Caro V, Cuervo N, Korotkova E, Combiescu M, Persu A, Aubert-Combiescu A, Delpeyroux F, Crainic R. Natural genetic exchanges between vaccine and wild poliovirus strains in humans. Journal of Virology 2000;74(18):8434–8443 [PubMed: 10954543]
56. Rousset D, Rakoto-Andrianarivelo M, Razafindratsimandresy R, Randriamanalina B, Guillot S, Balanant J, Mauclere P, Delpeyroux F. Recombinant vaccine-derived poliovirus in Madagascar. Emerging Infectious Diseases 2003;9(7):885–887 [PubMed: 12899139]
57. Shimizu H, Thorley B, Paladin FJ, Brussen KA, Stambos V, Yuen L, Utama A, Tano Y, Arita M, Yoshida H, Yoneyama T, Benegas A, Roesel S, Pallansch MA, Kew OM, Miyamura T. Circulation of type 1 vaccine-derived poliovirus in the Philippines in 2001. Journal of Virology 2004;78(24):13512–13521 [PubMed: 15564462]
58. Domingo E, Escarmis C, Sevilla N, Moya A, Elena SF, Quer J, Novella IS, Holland JJ. Basic concepts in RNA virus evolution. Faseb Journal 1996;10(8):859–864 [PubMed: 8666162]
59. Agol VI. Molecular mechanisms of poliovirus variation and evolution. Current Topics in Microbiology and Immunology 2006;299:211–259 [PubMed: 16568901]
60. Pfeiffer JK, Kirkegaard K. Bottleneck-mediated quasispecies restriction during spread of an RNA virus from inoculation site to brain. Proceedings of the National Academy of Sciences of the United States of America 2006;103(14):5520–5525 [PubMed: 16567621]
61. Vignuzzi M, Stone JK, Arnold JJ, Cameron CE, Andino R. Quasispecies diversity determines pathogenesis through cooperative interactions in a viral population. Nature 2006;439(7074):344–348 [PubMed: 16327776]
62. World Health Organization. WHO expert committee on biological standardization - thirty-third report. Geneva, Switzerland; 1983.
63. Reed LJ, Muench H. A simple method of estimating fifty per cent endpoints. American Journal of Epidemiology 1938;27(3):493–497
64. Domingo E, Biebricher CK, Eigen M, Holland JJ, Corporation E. Quasispecies and RNA virus evolution: Principles and consequences. Austin, TX: Landes Bioscience; 2001.
65. Nathanson N, Kew OM. From emergence to eradication: The epidemiology of poliomyelitis deconstructed. American Journal of Epidemiology 2010;172(11): 1213–1229 [PubMed: 20978089]
66. Bernier RH. Some observations on poliomyelitis lameness surveys. Reviews of Infectious Diseases 1984;6 Suppl 2:S371–S375 [PubMed: 6740075]
67. Shelokov A, Habel K, McKinstry DW. Relation of poliomyelitis virus types to clinical disease and geographic distribution: A preliminary report. Annals of the New York Academy of Science 1955;61(4):998–1004
68. Alexander LN, Seward JF, Santibanez TA, Pallansch MA, Kew OM, Prevots DR, Strebel PM, Cono J, Wharton M, Orenstein WA, Sutter RW. Vaccine policy changes and epidemiology of poliomyelitis in the United States. Journal of the American Medical Association 2004;292(14):1696–1701 [PubMed: 15479934]
69. Nkowane BM, Wassilak SGF, Orenstein WA, Bart KJ, Schonberger LB, Hinman AR, Kew OM. Vaccine-associated paralytic poliomyelitis. United States: 1973 through 1984. Journal of the American Medical Association 1987;267(10):1335–40
70. Strebel PM, Sutter RW, Cochi SL, Biellik RJ, Brink EW, Kew OM, Pallansch MA, Orenstein WA, Hinman AR. Epidemiology of poliomyelitis in the United States one decade after the last reported case of indigenous wild virus-associated disease. Clinical Infectious Diseases 1992;14:568–79 [PubMed: 1554844]
71. Kohler KA, Banerjee K, Gary Hlady W, Andrus JK, Sutter RW. Vaccine-associated paralytic poliomyelitis in India during 1999: Decreased risk despite massive use of oral polio vaccine. Bulletin of the World Health Organization 2002;80(3):210–6 [PubMed: 11984607]

72. Cáceres VM, Sutter RW. Sabin monovalent oral polio vaccines: Review of past experiences and their potential use after polio eradication. Clinical Infectious Diseases 2001;33(4):531–541 [PubMed: 11462191]
73. Dömök I Experiences associated with the use of live poliovirus vaccine in Hungary, 1959–1982. Reviews of Infectious Diseases 1984;6(Suppl 2):S413–S418 [PubMed: 6740083]
74. Estívariz CF, Molnár Z, Venczel L, Kapusinszky B, Zingeser JA, Lipskaya GY, Kew OM, Berencsi G, Csohán Á. Paralytic poliomyelitis associated with Sabin monovalent and bivalent oral polio vaccines in Hungary. American Journal of Epidemiology 2011;174(3):316–325 [PubMed: 21685412]
75. Nomoto A, Omata T, Toyoda H, Kuge S, Horie H, Kataoka Y, Genba Y, Nakano Y, Imura N. Complete nucleotide sequence of the attenuated poliovirus Sabin 1 strain genome. Proceedings of the National Academy of Sciences of the United States of America 1982;79(19):5793–5797 [PubMed: 6310545]
76. Stanway G, Hughes PJ, Mountford RC, Reeve P, Minor PD, Schild GC, Almond JW. Comparison of the complete nucleotide sequences of the genomes of the neurovirulent poliovirus P3/Leon/37 and its attenuated Sabin vaccine derivative P3/Leon 12a1b. Proceedings of the National Academy of Sciences of the United States of America 1984;81(5):1539–1543 [PubMed: 6324200]
77. Bouchard MJ, Lam DH, Racaniello VR. Determinants of attenuation and temperature sensitivity in the type 1 poliovirus Sabin vaccine. Journal of Virology 1995;69(8):4972–4978 [PubMed: 7609067]
78. Horie H, Koike S, Kurata T, Sato-Yoshida Y, Ise I, Ota Y, Abe S, Hioki K, Kato H, Taya C, Nomura T, Hashizume S, Yonekawa H, Nomoto A. Transgenic mice carrying the human poliovirus receptor: New animal models for study of poliovirus neurovirulence. Journal of Virology 1994;68(2):681–688 [PubMed: 8289371]
79. Kawamura N, Kohara M, Abe S, Komatsu T, Tago K, Arita M, Nomoto A. Determinants in the 5' noncoding region of poliovirus Sabin 1 RNA that influence the attenuation phenotype. Journal of Virology 1989;63(3):1302–1309 [PubMed: 2536835]
80. Martin A, Benichou D, Couderc T, Hogle JM, Wychowski C, Van der Werf S, Girard M. Use of type 1/type 2 chimeric polioviruses to study determinants of poliovirus type 1 neurovirulence in a mouse model. Virology 1991;180(2):648–658 [PubMed: 1846492]
81. Omata T, Kohara M, Kuge S, Komatsu T, Abe S, Semler BL, Kameda A, Itoh H, Arita M, Wimmer E, Nomoto A. Genetic analysis of the attenuation phenotype of poliovirus type 1. Journal of Virology 1986;58(2):348–358 [PubMed: 3009852]
82. Tardy-Panit M, Blondel B, Martin A, Tekaia F, Horaud F, Delpeyroux F. A mutation in the RNA polymerase of poliovirus type 1 contributes to attenuation in mice. Journal of Virology 1993;67(8):4630–4638 [PubMed: 8392604]
83. Tatem JM, Weeks-Levy C, Georgiu A, DiMichele SJ, Gorgacz EJ, Racaniello VR, Cano FR, Mento SJ. A mutation present in the amino terminus of Sabin 3 poliovirus VP1 protein is attenuating. Journal of Virology 1992;66(5):3194–3197 [PubMed: 1313923]
84. Westrop GD, Wareham KA, Evans DM, Dunn G, Minor PD, Magrath DI, Taffs F, Marsden S, Skinner MA, Schild GC, Almond JW. Genetic basis of attenuation of the Sabin type 3 oral poliovirus vaccine. Journal of Virology 1989;63(3):1338–1344 [PubMed: 2536836]
85. Christodoulou C, Colbere-Garapin F, Macadam A, Taffs LF, Marsden S, Minor P, Horaud F. Mapping of mutations associated with neurovirulence in monkeys infected with Sabin 1 poliovirus revertants selected at high temperature. Journal of Virology 1990;64(10):4922–4929 [PubMed: 2168976]
86. Dunn G, Begg NT, Cammack N, Minor PD. Virus excretion and mutation by infants following primary vaccination with live oral poliovaccine from two sources. Journal of Medical Virology 1990;32(2):92–95 [PubMed: 2177777]
87. Macadam AJ, Arnold C, Howlett J, John A, Marsden S, Taffs F, Reeve P, Hamada N, Wareham K, Almond J, Cammack N, Minor PD. Reversion of the attenuated and temperature-sensitive phenotypes of the Sabin type 3 strain of poliovirus in vaccinees. Virology 1989;172(2):408–414 [PubMed: 2552655]

88. Minor PD, Dunn G. The effect of sequences in the 5' non-coding region on the replication of polioviruses in the human gut. Journal of General Virology 1988;69 (Pt 5): 1091–1096

89. Minor PD, John A, Ferguson M, Icenogle JP. Antigenic and molecular evolution of the vaccine strain of type 3 poliovirus during the period of excretion by a primary vaccinee. Journal of General Virology 1986;67 (Pt 4):693–706

90. Cann AJ, Stanway G, Hughes PJ, Minor PD, Evans DM, Schild GC, Almond JW. Reversion to neurovirulence of the live-attenuated Sabin type 3 oral poliovirus vaccine. Nucleic Acids Research 1984;12(20):7787–7792 [PubMed: 6093054]

91. Li J, Zhang LB, Yoneyama T, Yoshida H, Shimizu H, Yoshii K, Hara M, Nomura T, Yoshikura H, Miyamura T, Hagiwara A. Genetic basis of the neurovirulence of type 1 polioviruses isolated from vaccine-associated paralytic patients. Archives of Virology 1996;141(6):1047–1054 [PubMed: 8712922]

92. Lipskaya GY, Muzychenko AR, Kutitova OK, Maslova SV, Equestre M, Drozdov SG, Bercoff RP, Agol VI. Frequent isolation of intertypic poliovirus recombinants with serotype 2 specificity from vaccine-associated polio cases. Journal of Medical Virology 1991;35(4):290–296 [PubMed: 1666406]

93. Otelea D, Guillot S, Furione M, Combiescu AA, Balanant J, Candrea A, Crainic R. Genomic modifications in naturally occurring neurovirulent revertants of Sabin 1 polioviruses. Developments in Biolological Standardization 1993;78:33–38

94. Friedrich F, Filippis AM, Ferreira FC, Oliveira MJ, Schatzmayr HG, Da-Silva EE. Poliovirus type 1 isolated from a vaccine-associated case of paralytic poliomyelitis in Brazil. Brazilian Journal of Medical and Biological Research 1996;29(1):15–18 [PubMed: 8731326]

95. Friedrich F, Filippis AM, Ferreira FC, Schatzmayr HG, Da Silva EE. Genomic characterization of type 1 Sabin-related polioviruses isolated in Brazil. Acta Virologica 1995;39(1):23–29 [PubMed: 7572466]

96. Furione M, Guillot S, Otelea D, Balanant J, Candrea A, Crainic R. Polioviruses with natural recombinant genomes isolated from vaccine-associated paralytic poliomyelitis. Virology 1993;196(1):199–208 [PubMed: 8102826]

97. Georgescu M-M, Balanant J, Macadam A, Otelea D, Combiescu M, Combiescu AA, Crainic R, Delpeyroux F. Evolution of the Sabin type 1 poliovirus in humans: Characterization of strains isolated from patients with vaccine-associated paralytic poliomyelitis. Journal of Virology 1997;71(10):7758–7768 [PubMed: 9311861]

98. Georgescu MM, Delpeyroux F, Crainic R. Tripartite genome organization of a natural type 2 vaccine/nonvaccine recombinant poliovirus. Journal of General Virology 1995;76 (Pt 9):2343–2348

99. Kapusinszky B, Molnar Z, Szomor KN, Berencsi G. Molecular characterization of poliovirus isolates from children who contracted vaccine-associated paralytic poliomyelitis (VAPP) following administration of monovalent type 3 oral poliovirus vaccine in the 1960s in Hungary. FEMS Immunology & Medical Microbiology 2010;58(2):211–217 [PubMed: 19863665]

100. Liang X, Zhang Y, Xu W, Wen N, Zuo S, Lee LA, Yu J. An outbreak of poliomyelitis caused by type 1 vaccine-derived poliovirus in China. Journal of Infectious Diseases 2006; 194(5): 545–551

101. Cherkasova EA, Korotkova EA, Yakovenko ML, Ivanova OE, Eremeeva TP, Chumakov KM, Agol VI. Long-term circulation of vaccine-derived poliovirus that causes paralytic disease. Journal of General Virology 2002;76(23):6791–6799

102. Bellmunt A, May G, Zell R, Pring-Akerblom P, Verhagen W, Heim A. Evolution of poliovirus type i during 5.5 years of prolonged enteral replication in an immunodeficient patient. Virology 1999;265(2):178–184 [PubMed: 10600590]

103. Buttinelli G, Donati V, Fiore S, Marturano J, Plebani A, Balestri P, Soresina AR, Vivarelli R, Delpeyroux F, Martin J, Fiore L. Nucleotide variation in Sabin type 2 poliovirus from an immunodeficient patient with poliomyelitis. Journal of General Virology 2003;84(Pt 5):1215–1221

104. Kew OM, Sutter RW, Nottay BK, McDonough MJ, Prevots DR, Quick L, Pallansch MA. Prolonged replication of a type 1 vaccine-derived poliovirus in an immunodeficient patient. Journal of Clinical Microbiology 1998;36(10):2893–2899 [PubMed: 9738040]

105. Martín J, Dunn G, Hull R, Patel V, Minor PD. Evolution of the Sabin strain of type 3 poliovirus in an immunodeficient patient during the entire 637-day period of virus excretion. Journal of Virology 2000;74(7):3001–3010 [PubMed: 10708414]
106. Gavrilin GV, Cherkasova EA, Lipskaya GY, Kew OM, Agol VI. Evolution of circulating wild poliovirus and of vaccine-derived poliovirus in an immunodeficient patient: A unifying model. Journal of Virology 2000;74(16):7381–7390 [PubMed: 10906191]
107. Contreras G, Dimock K, Furesz J, Gardell C, Hazlett D, Karpinski K, McCorkle G, Wu L. Genetic characterization of Sabin types 1 and 3 poliovaccine virus following serial passage in the human intestinal tract. Biologicals 1992;20(1):15–26 [PubMed: 1319179]
108. Lu Z, Rezapkin GV, Douthitt MP, Ran Y, Asher DM, Levenbook IS, Chumakov KM. Limited genetic changes in the Sabin 1 strain of poliovirus occurring in the central nervous system of monkeys. Journal of General Virology 1996;77 (Pt 2):273–280
109. Rezapkin GV, Chumakov KM, Lu Z, Ran Y, Dragunsky EM, Levenbook IS. Microevolution of Sabin 1 strain in vitro and genetic stability of oral poliovirus vaccine. Virology 1994;202(1):370–378 [PubMed: 8009849]
110. Assaad F, Cockburn W. The relation between acute persisting spinal paralysis and poliomyelitis vaccine—results of a ten-year enquiry. Bulletin of the World Health Organization 1982;60:231–242 [PubMed: 6980734]
111. McGoldrick A, Macadam AJ, Dunn G, Rowe A, Burlison J, Minor PD, Meredith J, Evans DJ, Almond JW. Role of mutations G-480 and C-6203 in the attenuation phenotype of Sabin type 1 poliovirus. Journal of Virology 1995;69(12):7601–7605 [PubMed: 7494267]
112. Laassri M, Lottenbach K, Belshe R, Rennels M, Plotkin S, Chumakov K. Analysis of reversions in the 5'-untranslated region of attenuated poliovirus after sequential administration of inactivated and oral poliovirus vaccines. Journal of Infectious Diseases 2006;193(10):1344–1349
113. Yang C-F, Chen H-Y, Jorba J, Sun H-C, Yang S-J, Lee H-C, Huang Y-C, Lin T-Y, Chen P-J, Shimizu H, Nishimura Y, Utama A, Pallansch MA, Miyamura T, Kew OM, Yang J-Y. Intratypic recombination among lineages of type 1 vaccine-derived poliovirus emerging during chronic infection of an immunodeficient patient. Journal of Virology 2005;79(20):12623–12634 [PubMed: 16188964]
114. Pavilanis V, Lussier G, Foley AR, Charbonneau JH, Difranco E, Dubreuil R. A study of Sabin type 1 oral vaccine virus during five human passages. Revue Canadienne de Biologie 1964;23:265–276 [PubMed: 14237159]
115. Minor PD, Dunn G, Ramsay ME, Brown D. Effect of different immunisation schedules on the excretion and reversion of oral poliovaccine strains. Journal of Medical Virology 2005;75(1):153–160 [PubMed: 15543587]
116. Matsuura K, Ishikura M, Yoshida H, Nakayama T, Hasegawa S, Ando S, Horie H, Miyamura T, Kitamura T. Assessment of poliovirus eradication in Japan: Genomic analysis of polioviruses isolated from river water and sewage in toyama prefecture. Applied and Environmental Microbiology 2000;66(11):5087–5091 [PubMed: 11055968]
117. Yoshida H, Horie H, Matsuura K, Kitamura T, Hashizume S, Miyamura T. Prevalence of vaccine-derived polioviruses in the environment. Journal of General Virology 2002;83(Pt 5):1107–1111
118. Dane DS, Dick GWA, Briggs M, Nelson R, McAlister J, Conolly JH, Haire M, McKeown CMB. Vaccination against poliomyelitis with live virus vaccines: 6. Changes in Sabin type II oral vaccine virus after human passage British Medical Journal 1961;2(5247):259–265 [PubMed: 13719566]
119. Weeks-Levy C, Tatem JM, DiMichele SJ, Waterfield W, Georgiu AF, Mento SJ. Identification and characterization of a new base substitution in the vaccine strain of Sabin 3 poliovirus. Virology 1991;185(2):934–937 [PubMed: 1660210]
120. Evans DM, Dunn G, Minor PD, Schild GC, Cann AJ, Stanway G, Almond JW, Currey K, Maizel JV Jr. Increased neurovirulence associated with a single nucleotide change in a noncoding region of the Sabin type 3 poliovaccine genome. Nature 1985;314(6011):548–550 [PubMed: 2986004]
121. Fine PE, Carneiro IA. Transmissibility and persistence of oral polio vaccine viruses: Implications for the global poliomyelitis eradication initiative. American Journal of Epidemiology 1999;150(10):1001–1021 [PubMed: 10568615]

122. Kew OM, Mulders MN, Lipskaya GY, da Silva EE, Pallansch MA. Molecular epidemiology of polioviruses. Seminars in Virology 1995;6:401–414

123. van der Sanden S, Pallansch MA, van de Kassteele J, El-Sayed N, Sutter RW, Koopmans M, van der Avoort HGAM. Shedding of vaccine viruses with increased antigenic and genetic divergence after vaccination of newborns with monovalent type 1 oral poliovirus vaccine. Journal of Virology 2009;83(17):8693–8704 [PubMed: 19515771]

124. Duintjer Tebbens RJ, Pallansch MA, Kalkowska DA, Wassilak SG, Cochi SL, Thompson KM. Characterizing poliovirus transmission and evolution: Insights from modeling experiences with wild and vaccine-related polioviruses (submitted to Risk Analysis).

125. Fine PEM, Carneiro IAM. Transmissibility and persistence of oral poliovirus vaccine viruses: Implications for the global poliomyelitis eradication initiative. London: Infectious Disease Epidemiology Unit, Department of Infectious and Tropical Diseases, London School of Hygiene; 1998 5.

126. Sutter RW, Suleiman AJM, Malankar PG, Mehta FR, Medany MA, Arif MAM, Linkins RW, Pallansch MA, ElBualy MS, Robertson SE. Sequential use of inactivated poliovirus vaccine followed by oral poliovirus vaccine in Oman. Journal of Infectious Diseases 1997;175:S235–S240

127. Centers for Disease Control and Prevention. Update on vaccine-derived polioviruses--worldwide, January 2006-August 2007. Morbidity and Mortality Weekly Report 2007;56(38):996–1001 [PubMed: 17898693]

128. Centers for Disease Control and Prevention. Update on vaccine-derived polioviruses. Morbidity and Mortality Weekly Report 2006;55(40):1093–1097 [PubMed: 17035927]

129. Yan D, Li L, Zhu S, Zhang Y, An J, Wang D, Wen N, Jorba J, Liu W, Zhong G, Huang L, Kew O, Liang X, Xu W. Emergence and localized circulation of a vaccine-derived poliovirus in an isolated mountain community in Guangxi, China. Journal of Clinical Microbiology 2010;48(9):3274–3280 [PubMed: 20631095]

130. Rakoto-Andrianarivelo M, Gumede N, Jegouic S, Balanant J, Andriamamonjy SN, Rabemanantsoa S, Birmingham M, Randriamanalina B, Nkolomoni L, Venter M, Schoub BD, Delpeyroux F, Reynes JM. Reemergence of recombinant vaccine-derived poliovirus outbreak in Madagascar. J Infect Dis 2008;197(10):1427–35 [PubMed: 18419577]

131. Joffret ML, Jegouic S, Bessaud M, Balanant J, Tran C, Caro V, Holmblat B, Razafindratsimandresy R, Reynes JM, Rakoto-Andrianarivelo M, Delpeyroux F. Common and diverse features of cocirculating type 2 and 3 recombinant vaccine-derived polioviruses isolated from patients with poliomyelitis and healthy children. Journal of Infectious Diseases 2012;205(9):1363–1373

132. Combelas N, Holmblat B, Joffret ML, Colbere-Garapin F, Delpeyroux F. Recombination between poliovirus and coxsackie A viruses of species C: A model of viral genetic plasticity and emergence. Viruses 2012;3(8):1460–1484

133. Centers for Disease Control and Prevention. Laboratory surveillance for wild and vaccine-derived polioviruses, January 2003-June 2004. Morbidity and Mortality Weekly Report 2004;53(42):990–993 [PubMed: 15514582]

134. World Health Organization. Laboratory surveillance for wild and vaccine-derived polioviruses, January 2003-June 2004. Weekly Epidemiological Record 2004;79(44):393–398 [PubMed: 15625974]

135. Combiescu M, Guillot S, Persu A, Baicus A, Pitigoi D, Balanant J, Oprisan G, Crainic R, Delpeyroux F, Aubert-Combiescu A. Circulation of a type 1 recombinant vaccine-derived poliovirus strain in a limited area in Romania. Archives of Virology 2007;152(4):727–738 [PubMed: 17195957]

136. World Health Organization. Progress towards global poliomyelitis eradication - the approaching extinction of wild poliovirus type 2. Weekly Epidemiological Record 1999;74(34):286–288 [PubMed: 10511815]

137. World Health Organization. Transmission of wild poliovirus type 2 - apparent global interruption. Weekly Epidemiological Record 2001;76:95–97 [PubMed: 11315462]

138. World Health Organization. Incidence series.2012: http://www.who.int/entity/immunization_monitoring/data/incidence_series.xls. accessed April 6 2012

139. Zhang J, Zhang LB, Otten MW Jr., Jiang T, Zhang XL, Zhang RZ, Wang KA. Surveillance for polio eradication in the People's Republic of China. Journal of Infectious Diseases 1997;175 Suppl 1:S122–134

140. Jiang HF, Yan DM, Zhu SL, Wang DY, Zhang Y, Zhu H, An HQ, Xu WB, Kong XH. [analysis of genetic characteristics of type II non-wild poliovirus in mainland China, 2010]. Bing Du Xue Bao 2012;28(2):130–135 [PubMed: 22519174]

141. Zhang Y, Yan D, Zhu S, Wen N, Li L, Wang H, Liu J, Ye X, Ding Z, Wang D, Zhu H, Chen L, Hou X, An H, Liang X, Luo H, Kew O, Xu W. Type 2 vaccine-derived poliovirus from patients with acute flaccid paralysis in china: Current immunization strategy effectively prevented its sustained transmission. Journal of Infectious Diseases 2010;202(12): 1780–1788

142. Adu F, Iber J, Bukbuk D, Gumede N, Yang SJ, Jorba J, Campagnoli R, Sule WF, Yang CF, Burns C, Pallansch M, Harry T, Kew O. Isolation of recombinant type 2 vaccine-derived poliovirus (VDPV) from a Nigerian child. Virus Research 2007;127(1):17–25 [PubMed: 17449127]

143. Martín J, Odoom K, Tuite G, Dunn G, Hopewell N, Cooper G, Fitzharris C, Butler K, Hall WW, Minor PD. Long-term excretion of vaccine-derived poliovirus by a healthy child. Journal of Virology 2004;78(24):13839–13847 [PubMed: 15564492]

144. Rakoto-Andrianarivelo M, Guillot S, Iber J, Balanant J, Blondel B, Riquet F, Martin J, Kew O, Randriamanalina B, Razafinimpiasa L, Rousset D, Delpeyroux F. Co-circulation and evolution of polioviruses and species C enteroviruses in a district of Madagascar. PLoS Pathogens 2007;3(12):e191 [PubMed: 18085822]

145. World Bank. World Bank list of economies (July 2002). 2002: http://www.worldbank.org/data/databytopic/CLASS.XLS. accessed December 2002

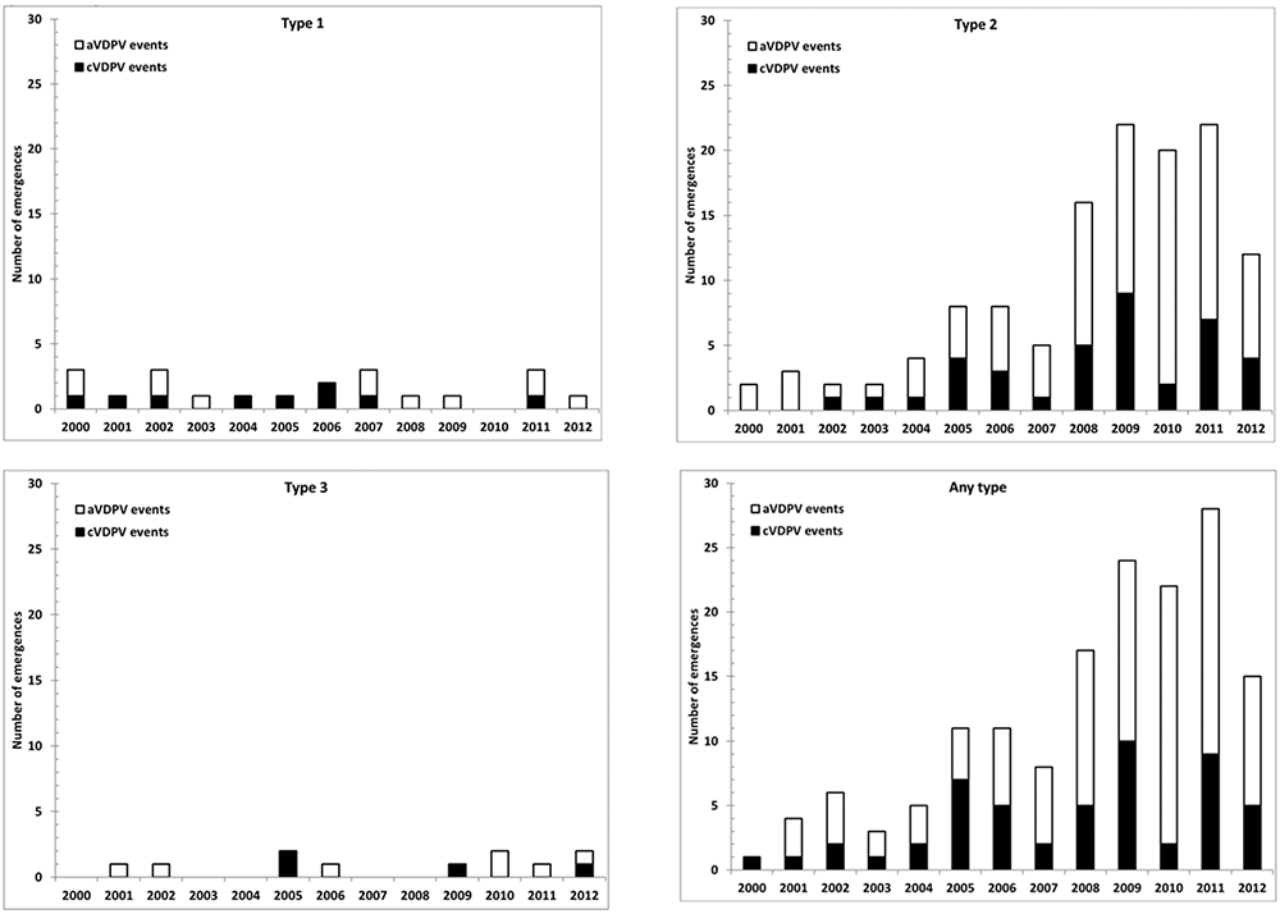

Figure 1:

Annual numbers of circulating vaccine-derived poliovirus (cVDPV) and ambiguous vaccine-derived poliovirus (aVDPV) events, by serotype.

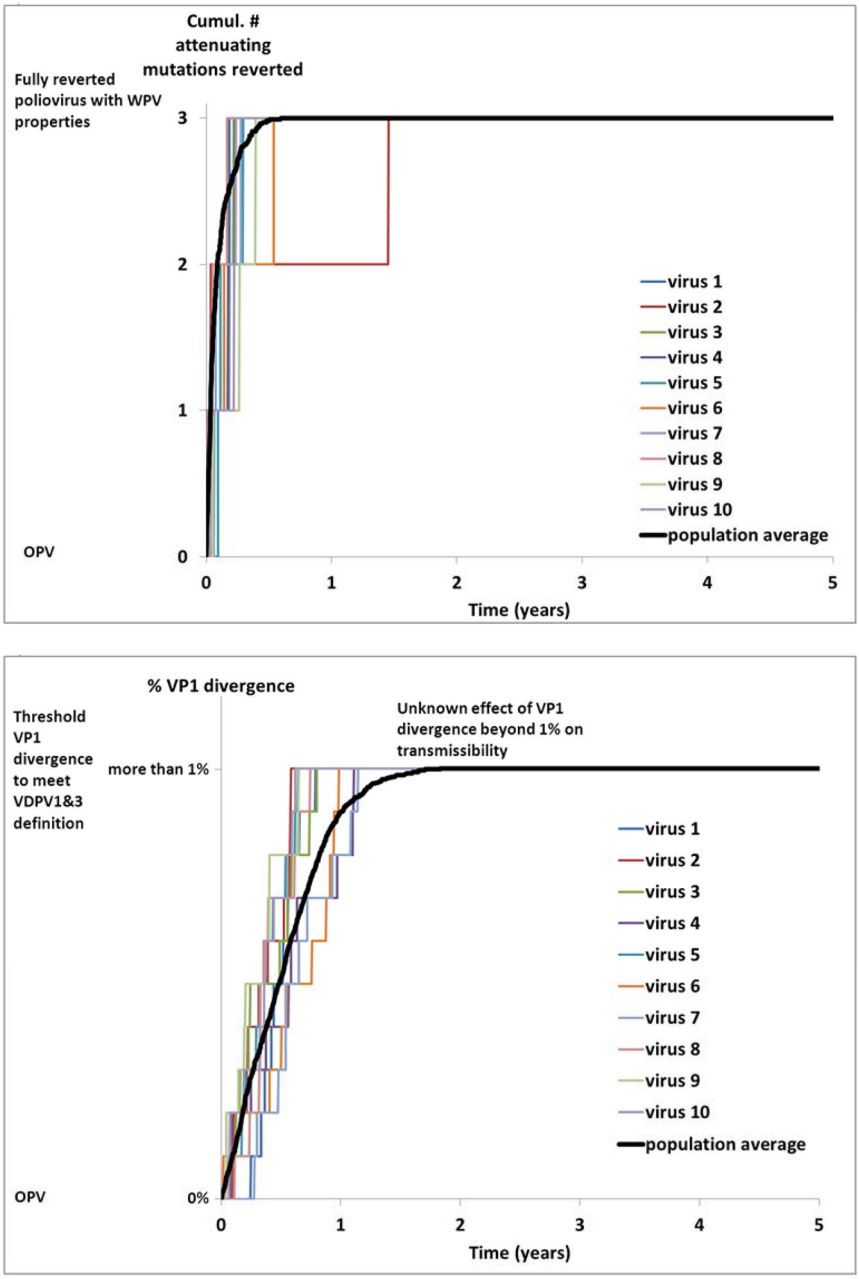

Figure 2: Two alternative formulations of the OPV evolution process. *

a) Based on reversion of a small number of key attenuating mutations

b) Based on a more gradual reversion process approximated by VP1 divergen

Acronyms: Cumul. # = cumulative number of; OPV = oral poliovirus vaccine; VDPV = vaccine-derived poliovirus; VP1 = viral protein 1 region; WPV = wild poliovirus

* Both formulations assume exponentially distributed times between reversion events based on different values. Panel a assumes hypothetical average times of 14, 35, and 60 days until attenuating mutations 1, 2, and 3, respectively. Panel b assumes 10 nucleotide changes per year based on the approximate molecular clock[43] and 900 total nucleotides in the VP1 region, with divergence truncated at 1% as a potential (although uncertain) point beyond

which the virus is no longer attenuated and further divergence has only random effect on neurovirulence and transmissibility (i.e., any virus with 10 or more mutations receives a value “more than 1%” on the y-axis). In both panels, the” population average” represents the average of 100 realizations at each point in time.

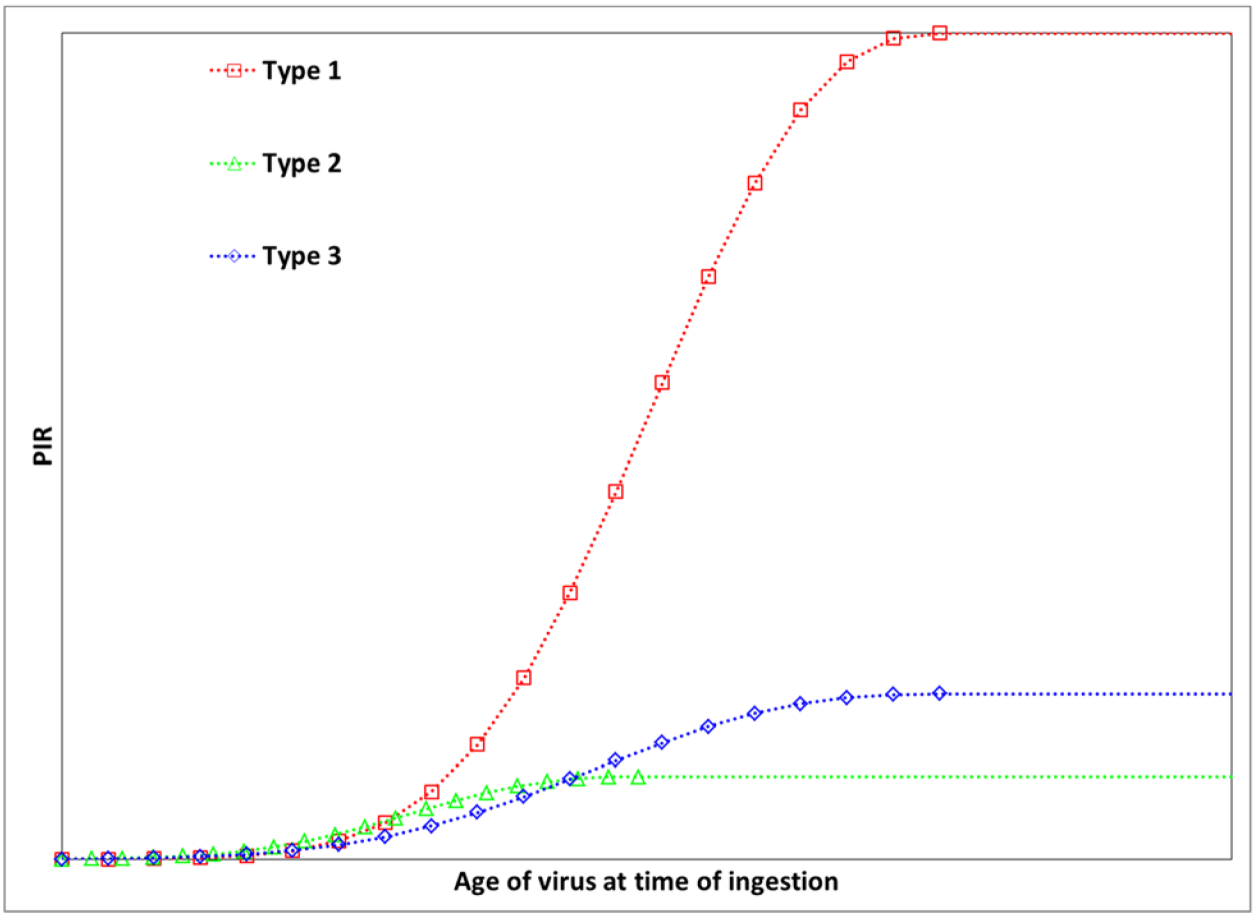

Figure 3:
Hypothetical relationship between reversion of the virus and paralysis-to-infection ratio (PIR), showing differences between serotypes in PIR due to different starting points (virus age 0, reflecting oral poliovirus vaccine) and end points (oldest virus age, reflecting fully-reverted poliovirus with assumed PIR equal to wild poliovirus) and in the speed of the reversion process.

Table 1:

Characterization of cVDPV events (2000-2012).

Country or countries	Last prior indigenous homotypic WPV isolate[a]	Sero-type	First case[b]	Last case[b]	Virologically-confirmed cases[b]	Number of isolates (maximum % divergence)[c]	Reference
Chad	<1998	2	September 12, 2012	October 20, 2012	2	2 (1.8)	(26)
Pakistan, Afghanistan	1997	2	August 30, 2012	December 8, 2012	21	19 (2.9)	(26)
Chad	<1998	2	August 4, 2012	October 17, 2012	10	10 (1.2)	(26)
Yemen	<2000	3	April 27, 2012	November 25, 2012	3	5 (3)	(26)
DR Congo	< 1998	2	14-Mar-12	After 2012	2	2 (1.2)	(41)
DR Congo	< 1998	2	26-Nov-11	After 2012	3	3 (1.6)	(41)
DR Congo	< 1998	2	04-Nov-11	After 2012	11	11 (1.4)	(41)
China	< 1985	2	October 25, 2011	March 1, 2012	3	8 (1.2)	*d*
China	< 1985	2	October 25, 2011	February 6, 2012	3	10 (1.3)	*d*
DR Congo	< 1998	2	17-Oct-11	After 2012	12	12 (1,7)	(39, 41)
Yemen	< 1998	2	24 Aug-11	12Oct11	2	2 (1.3)	(41)
Yemen	< 1998	2	08-Aug-11	05-Oct-11	2	2 (0.89)	(41)
Madagascar*	1997	2	17-May-11	18-May-11	0	3 (3.7)	(41)
Yemen	< 1998	2	8-Apr-11	26-Aug-11	6	6 (1.6)	(41)
Mozambique	1993[e]	1	10-Feb-11	02-Jun-11	2	2 (4.3)	(41)
DR Congo	< 1998	2	29Aug-10	06-Sep-10	2	2 (1.4)	(41)
DR Congo	< 1998	2	20-Apr-10	13-Oct-10	9	9 (2.1)	(41)
India	1999	2	Oct-09	Nov-09	4	3 (1.4)	(33)
India	1999	2	Oct-09	Dec-09	3	3 (1.4)	(33)
India	1999	2	Oct-09	Jan-10	3	2(1.3)	(33)
India	1999	2	Oct-09	Nov-09	2	2 (1.6)	(33)
Somalia	< 1998	2	21-Aug-09	10-Dec-11	15	> 28 (3.5)	(33, 39, 41)
DR Congo	< 1998	2	09-Aug-09	24-Sep-10	5	5 (3.5)	(41)
Afghanistan	1997	2	24-Jul-09	December 21, 2012	12	12 (4.9)	(33)
India	1999	2	14-Jun-09	Dec-10	4	4 (1.4)	(33)
Ethiopia	< 2005	3	27-Apr-09	17-May-10	6	>8 (2.8)	(33, 39)
Nigeria	≤ 1998	2	17-Apr-09	19-May-09	2	2 (2.4)	(32)
Nigeria, Niger	≤ 1998 (Nigeria)	2	18-Nov-08	18-May-10	8	8 (3.0)	(32)
Ethiopia	< 1998	2	04-Oct-08	16-Feb-09	5	5 (1.2)	(33, 39)
DR Congo	< 1998	2	29-Aug-08	25-Feb-09	5	5 (1.8)	(39, 41)

Country or countries	Last prior indigenous homotypic WPV isolate[a]	Sero-type	First case[b]	Last case[b]	Virologically-confirmed cases[b]	Number of isolates (maximum % divergence)[c]	Reference
Somalia	< 1998	2	24-Jun-08	22-Mar-09	2	>3 (2.5)	(33, 39)
DR Congo	< 1998	2	11-Feb-08	04-Jul-09	14	14 (1.8)	(39, 41)
Myanmar	2000	1	02-May-07	06-Dec-07	4	4 (2.6)	(39, 127)
Nigeria	≤ 1998	2	19-Feb-07	25-Feb-09	6	6 (3.7)	(32)
Nigeria	≤ 1998	2	04-Jul-06	19-Sep-06	2	2 (1.7)	(32)
Nigeria, Niger	≤ 1998 (Nigeria)	2	15-Jun-06	28-Jan-08	7	7 (2.4)	(32)
Nigeria, Chad, Niger	≤ 1998	2	07-May-06	24-Nov-2012	369	369 (7.2)	(32)
Myanmar*	2000	1	09-Apr-06		1	7 (1.9)	(128)
China*	1994	1	10-Mar-06	May 16, 2006	1	8 (2.2)	(127, 129)
Cambodia	< 1995	3	26-Nov-05	15-Jan-06	2	3 (2.4)	(127, 128)
DR Congo	< 1998	2	08-Jul-05	31-Aug-05	7	7 (1.0)	(39, 41)
Nigeria, Niger	≤ 1998 (Nigeria)	2	02-Jul-05	22-May-06	4	4 (2.5)	(32)
Madagascar	1997	2	13-Jun-05	14-Aug-05	4	>7 (2.7)	(128, 130, 131)
Indonesia	1995	1	09-Jun-05	26-Oct-05	46	≥45 (~3.0)	(16)
Madagascar*	< 2000	3	09-Apr-05	May-05	1	8 (1.8)	(128, 130-132)
DR Congo	< 1998	2	01-Jan-05	09-Sep-05	2	2 (1.9)	(39, 41)
China	1994	1	13-Jun-04	11-Jul-04	2	4 (1.2)	(100, 128, 133)
Laos*	< 1990	2	2004		1	3 (1.1)	(18, 128)
Kazakhstan*	< 1985	2	2003		1	2 (2.3)	(18, 134)
Romania*	< 1996	1	Jul-02		1	8 (1.3)	(18, 128, 135)
Madagascar	1997	2	Mar-02	Apr-02	4	6 (3.0)	(18, 56, 128)
Philippines	1993	1	15-Mar-01	26-Jul-01	3	4 (3.5)	(57)
Haiti, Dominican Republic	1989 (Haiti)	1	12-Jul-00	12-Jul-01	21	31 (2.6)	(15)

Acronyms: cVDPV = circulating vaccine-derived poliovirus; VP1 = viral protein 1; WPV1, WPV2 = wild poliovirus type 1, 2, respectively

Notes:

Events with an asterisk after the country indicate events with more than 1 isolate that are not at close contact, but fewer than 2 paralytic cases that would classify as aVDPV according to the prior definition, but that classify as cVDPV according to the recently updated definition.(41)

[a] Based on WHO 1999(136) and WHO 2001(137) for type 2 and various other sources for specific places(15, 16, 25, 57, 138, 139)

[b] Includes AFP cases virologically confirmed through isolation of virus from close contacts ("Last case" left blank if only one virologically-confirmed case occurred)

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

[d] Xu, 2013 (private communication)

[e] Serotype of last WPV-confirmed case unknown

Table 2:

Characterization of aVDPV events 2000-2012 (excluding environmental isolates).

Year	Country	Serotype	Number of independent emergence events	First case (or first isolate if no cases)[a]	Last case[a]	Virologically-confirmed cases[a]	Number of isolates (maximum % divergence)[b]	Reference
2012	China	2	2	January 20, 2012	March 6, 2012	2	3 (0.8)	*c*
2012	Myanmar[d]	1	1	June 1, 2012		1	2 (2.3)	*c*
2012	Nigeria	2	1	31-May-12		1	1 (0.66)	(32)
2012	South Sudan	2	1	24-Feb-12		1	1 (1.1)	(41)
2012	Sudan	2	1	01-Apr-12		1	1 (0.66)	(41)
2012	Vietnam	2	1	14-Feb-12		1	1 (0.66)	(41)
2012	Yemen	3	1	27-Apr-12		1	1 (2.3)	(41)
2012	Yemen	2	2	02-Feb-12		2	2 (2.3)	(41)
2011	Argentina	1	1	15-May-11		1	1 (1.1)	(41)
2011	Burundi	2	1	15-Dec-11		1	1 (0.66)	(41)
2011	China	2	3	January 20, 2011	September 15, 2011	3	4 (1.1)	*c*
2011	China	1	1	April 24, 2011		1	1 (1.1)	*c*
2011	DR Congo	2	1	20-Dec-11		1	1 (0.78)	(33, 41)
2011	India	3	1	07-Oct-11		1	1 (1.5)	(41)
2011	India	2	5	27-Jan-11	25-Nov-11	5	5 (1.1)	(41)
2011	Madagascar	2	1	2011		0	1 (0.66)	(41)
2011	Nigeria	2	2	15-Feb-11	12-Nov-11	1	2 (0.66-1.2)	(32)
2011	Peru	2	1	11-Apr-11		1	1 (2.2)	(41)
2011	Sudan	2	1	2011		1	1 (0.66)	
2011	Yemen	2	1	21-Sep-11		1	1 (1.0)	(41)
2010	China	2	3	February 23, 2010	November 30, 2010	3	3 (1.0)	(33, 140)
2010	China	3	1	June 24, 2010		1	2 (1.2)	(33)
2010	DR Congo	2	5	01-Mar-10	25-Jun-10	5	5 (1.4)	(33)
2010	Ethiopia	3	1	04-Nov-10		1	1 (2.2)	
2010	India	2	5	Jan-10	Dec-10	3	5 (1.0)	(33)
2010	Myanmar	2	1	06-Dec-10		1	1 (0.8)	(33)
2010	Somalia	2	1	18-Aug-10		1	1 (0.66)	(33)
2010	Syria	2	1	02-Feb-10		1	1 (1.4)	(33)
2010	Tajikistan	2	1	02-Apr-10		1	1 (1.3)	(33)
2010	Turkey	2	1	16-Dec-10		0	1 (1.5)	(33)
2009	Afghanistan	2	1	22-Nov-09		1	1 (1.4)	(33)

Year	Country	Serotype	Number of independent emergence events	First case (or first isolate if no cases)[a]	Last case[a]	Virologically-confirmed cases[a]	Number of isolates (maximum % divergence)[b]	Reference
2009	Central African Republic	2	1	11-Jun-09		1	1 (0.66)	
2009	China	2	1	22-Feb-09		1	1 (1.2)	(33, 39)
2009	DR Congo	2	3	26-Jun-09	31-Dec-09	3	3 (1.2)	(33)
2009	India	2	5	07-Apr-09	02-Oct-09	4	5 (1.3)	(33)
2009	India	1	1	2009		1	1 (1.1)	(33)
2009	Nigeria	2	2	17-Feb-09	15-May-09	2	2 (1.8)	(32)
2008	Angola	2	3	05-May-08	19-May-08	3	3 (1.1)	(39)
2008	Cameroon	2	1	23-Jun-08		1	1 (1.6)	
2008	Chad	2	1	10-Jul-08		1	1 (1.7)	
2008	DR Congo	2	2	19-Jan-08	06-Jul-08	2	2 (0.78)	*e*
2008	Nigeria	2	2	29-Jul-08	22-Aug-08	2	2 (2.2)	(32)
2008	Russia	1	1	Mar-08		0	1 (1.4)	(39)
2008	Somalia	2	2	27-Mar-08	05-Apr-08	2	2 (1.3)	(33, 39)
2007	China	1	1	2007		1	1 (1.1)	(127)
2007	DR Congo	2	2	16-Mar-07	15-Dec-07	2	2 (1.1-2.1)	*e*
2007	Malawi	1	1	23-Dec-07		1	1 (3.1)	(39)
2007	Nigeria	2	2	14-Jul-07	22-Oct-07	2	2 (1.0)	(32)
2006	China	3	1	Aug-06		1	1 (1.0)	(127)
2006	Nigeria	2	5	8-Jan-06	2-Nov-06	5	5 (1.2)	(32)
2005	Nigeria	2	3	14-Jul-05	23-Oct-05	3	3 (0.78)	(32)
2005	Somalia	2	1	14-Mar-05		1	1 (1.3)	*e*
2004	DR Congo	2	1	13-Oct-04		1	1 (0.66)	*e*
2004	Somalia	2	1	22-Aug-04		1	1 (1.0)	*e*
2004	China	2	1	15-Aug-04		1	1 (1.1)	(141)
2003	Latvia	2	1	2003		0	1 (NA)	(133)
2003	Mongolia	1	1	2003		0	1 (1.3)	(18, 133)
2002	China	3	1	Apr-02		1	1 (1.0)	(100)
2002	China	1	1	Jan-02		1	1 (1.1)	(100)
2002	Nigeria	2	1	09-Sep-02		1	1 (2.4)	(142)
2002	Zimbabwe	1	1	16-May-02		0	17 (1.4)[f]	(143)
2001	China	3	1	Jul-01		1	1 (1.0)	(100)
2001	Ethiopia	2	1	01-Jan-01		1	1 (0.66)	
2001	Madagascar	2	1	29-Oct-01		1	1 (1.0)	(56, 128, 132, 144)
2001	Syria	2	1	19-Feb-01		1-3	3 (1.5)	(18)

Year	Country	Serotype	Number of independent emergence events	First case (or first isolate if no cases)[a]	Last case[a]	Virologically-confirmed cases[a]	Number of isolates (maximum % divergence)[b]	Reference
2000	China	1	1	Nov-00		1	1 (1.2)	(100)
2000	Pakistan	2	1	2000		1	1 (2.3)	(18)

Acronyms: aVDPV = ambiguous vaccine-derived poliovirus; NA = not available; VP1 = viral protein 1

Notes:

[a] Includes AFP cases virologically confirmed through isolation of virus from close contacts ("Last case" left blank if only one virologically-confirmed case occurred)

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

[c] Xu, 2013 (private communication)

[d] Case exported to and reported by, China

[e] Gumede, 2012 (private communication)

[f] All isolates are from the same patient

Table 3:

Updated estimates of overall frequency of cVDPV and aVDPV events, based on prior approach.[25]

	2000-2005		2006-2011	2000-2011
	Estimates as of 1/1/2006[a]	**Updated estimates**[b]		
Average annual population size of all low- and lower middle-income OPV-using countries (in 100 millions)[c]	49	49	53	51
Number of cVDPV events	6	14	34	48
Number of cVDPV and aVDPV events	12	28	108	136
Average annual frequency of cVDPV events per 100 million people at risk	0.020	0.048	0.107	0.078
Average annual frequency of cVDPV and aVDPV events per 100 million people at risk	0.041	0.095	0.340	0.236

Acronyms: aVDPV = ambiguous vaccine-derived poliovirus; cVDPV = circulating vaccine-derived poliovirus; IPV = inactivated poliovirus vaccine

Notes:

[a] Based on cVDPV and aVDPV events identified in Table II of Duintjer Tebbens et al. (2006).[25] Given the absence of events for 1999, we changed the time period to 2000-2005, which increases the overall annual frequency compared to the previous estimate[25]

[b] Based on events in Tables 1 and 2 of this paper. See text for explanation of the different event totals compared to the prior estimates[25]

[c] We exclude upper middle and high-income countries from the population at risk given that the majority of these countries used IPV exclusively or gradually switched to IPV for routine use during 2000-2011 and because all but two events (aVDPVs in Latvia in 2003 and in Argentina in 2011, both upper middle-income countries) occurred in low- and lower middle-income countries. We use the 2002 World Bank income levels,[145] consistent with the prior analysis.[25] Changes in population size in columns reflect population growth.