SUPPLEMENT ARTICLE

Vaccine-Derived Polioviruses

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The attenuated oral poliovirus vaccine (OPV) has many properties favoring its use in polio eradication: ease of administration, efficient induction of intestinal immunity, induction of durable humoral immunity, and low cost. Despite these advantages, OPV has the disadvantage of genetic instability, resulting in rare and sporadic cases of vaccine-associated paralytic poliomyelitis (VAPP) and the emergence of genetically divergent vaccine-derived polioviruses (VDPVs). Whereas VAPP is an adverse event following exposure to OPV, VDPVs are polioviruses whose genetic properties indicate prolonged replication or transmission. Three categories of VDPVs are recognized: (1) circulating VDPVs (cVDPVs) from outbreaks in settings of low OPV coverage, (2) immunodeficiency-associated VDPVs (iVDPVs) from individuals with primary immunodeficiencies, and (3) ambiguous VDPVs (aVDPVs), which cannot be definitively assigned to either of the first 2 categories. Because most VDPVs are type 2, the World Health Organization's plans call for coordinated worldwide replacement of trivalent OPV with bivalent OPV containing poliovirus types 1 and 3.

Keywords. poliovirus; vaccine-derived poliovirus; VDPV; oral poliovirus vaccine; OPV; poliomyelitis

The oral poliovirus vaccine (OPV) developed by Albert Sabin and colleagues is nearly ideal for use in polio eradication [1]. This inexpensive vaccine is easily administered by mouth, facilitating its widespread use. OPV induces intestinal immunity, making recent OPV recipients resistant to infection by wild polioviruses and effectively blocking wild poliovirus transmission when used in mass campaigns. It provides long-term protection against poliomyelitis through durable humoral immunity. OPV virus can spread to and immunize unvaccinated contacts of vaccine recipients, increasing the impact of OPV beyond its recipients. Through effective use of this excellent vaccine, the World Health Organization's (WHO's) Global Polio Eradication Initiative has brought wild polioviruses to the threshold of eradication [2, 3].

Despite its many advantages, use of OPV carries certain liabilities [1, 4]. The first, the rare occurrence of cases of vaccine-associated paralytic poliomyelitis (VAPP) among OPV recipients and their contacts, was recognized soon after licensure and widespread use of OPV in the early 1960s [5]. The second, recognized more recently [6–9], is the emergence of genetically divergent vaccine-derived polioviruses (VDPVs), either during prolonged infection in persons with primary immunodeficiency disorders or during outbreaks in settings with low rates of OPV coverage [4, 10, 11].

VDPVs are of particular interest because of their implications for current and future strategies for global polio eradication [4, 10, 12, 13]. VDPVs can cause paralytic polio in humans and have the potential for sustained circulation. The clinical signs and severity of paralysis associated with VDPV and wild poliovirus infections are indistinguishable. VDPVs resemble wild polioviruses phenotypically [4, 10, 14] and differ genetically from the majority of vaccine-related poliovirus isolates. In this brief review, we describe the categories of VDPVs, update current knowledge of VDPV infections and outbreaks of VDPV infections, and consider the WHO strategy to mitigate current and future risks of VDPV emergence.

VAPP AND VDPVs

VAPP is an adverse event following exposure to OPV [1, 15]. VDPVs, by contrast, are polioviruses that have atypical genetic properties indicative of prolonged replication or circulation [4]. VAPP is sporadic and rare,

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occurring at similarly low rates in most countries that use OPV [1, 4]. In the United States, the risk of VAPP was approximately 1 case per 900 000 first doses distributed [15]. Among immunologically normal individuals, the risk of VAPP declines sharply (approximately 25-fold) with subsequent doses [15]. Persons with primary immunodeficiency disorders (PIDs; ie, B-cell defects in antibody production) are at much higher risk (by approximately 3000-fold) of VAPP [1, 4, 15], but VAPP is rare even in this group [11, 16]. A small number of individuals with PIDs who are exposed to OPV may have prolonged infections lasting >6 months [4] and excrete virus derived from the vaccine for periods substantially longer than the 4–6 weeks typical for immunologically normal OPV recipients [17]. Most cases of VAPP occur in OPV recipients or their close contacts; only a small fraction of VAPP cases are described as community acquired, and there is very little evidence of vaccine virus circulation from VAPP cases [15]. Quite distinct from VAPP are VDPVs from outbreaks or from individuals with PIDs.

CATEGORIES OF VDPVs

Polioviruses can be definitively categorized by the sequence properties of their genomes. Sequences encoding the major capsid protein, VP1 (approximately 900 nucleotides, or approximately 12% of the poliovirus genome), are routinely determined for poliovirus surveillance by the Global Polio Laboratory Network (GPLN). Within each of the 3 poliovirus serotypes are 2 broad categories of poliovirus isolates: (1) wild polioviruses, defined as polioviruses with no genetic evidence of derivation from any vaccine strain and demonstrated capability of continuous person-to-person transmission, and (2) vaccine-related polioviruses. For the purposes of poliovirus surveillance, vaccine-related polioviruses are further divided into 2 categories: (1) OPV-like isolates, which have limited divergence from their parental OPV strains and are ubiquitous wherever OPV is used, and (2) VDPV isolates, whose higher level of VP1 sequence divergence from their parental OPV strains (>1% [types 1 and 3] or >0.6% [type 2]) indicates prolonged replication (or transmission) of the vaccine virus. Finally, VDPVs are categorized as (1) circulating VDPVs (cVDPVs), when there is evidence of person-to-person transmission in the community; (2) immunodeficiency-associated VDPVs (iVDPVs), which are isolated from persons with PIDs who have prolonged VDPV infections; and (3) ambiguous VDPVs (aVDPVs), which are either clinical isolates from persons with no known immunodeficiency or sewage isolates whose ultimate source is unknown [10]. The terminology can be confusing, because in principle all clinical and environmental vaccine-related poliovirus isolates can be considered to be vaccine derived. However, the term "VDPV" is specifically reserved for isolates whose extent of sequence divergence from the parental OPV strains indicates prolonged replication or transmission. The definitions follow from the poliovirus molecular clock, which ticks at an overall rate in which approximately 1% of nucleotides undergo substitution per year [18, 19]. Thus, vaccine-related viruses that differ from the corresponding OPV strain by >1% of nucleotide positions are estimated to have replicated in 1 or more persons for at least 1 year after administration of an OPV dose. The demarcation for type 2 VDPVs (VDPV2s) was lowered to 0.6% to increase the sensitivity for early detection of cVDPV2 outbreaks [10, 19].

The definitions for VDPVs are based exclusively on the estimated duration of replication and not on their phenotypic properties. It is likely that many OPV-like isolates have recovered the capacity for higher neurovirulence and, possibly, increased transmissibility. The small number of substitutions controlling neurovirulence are frequently found to have reverted in many OPV-like isolates (and in virtually all VDPVs), especially among isolates of types 2 and 3 [20–22]. Because the critical attenuating mutations in the Sabin strains also affect fitness for virus replication in the human intestine [20], it is believed (but not rigorously testable) that revertants at these sites have increased fitness for person-to-person transmission [14, 19]. However, spread of OPV-related virus is normally limited by high population immunity, and VDPVs represent viruses whose potentials for prolonged replication or transmission have been actualized, as demonstrated by their genetic properties.

RELATIVE PUBLIC HEALTH IMPORTANCE OF cVDPVs, iVDPVs, AND aVDPVs

The 3 categories of VDPVs differ in their public health importance. Circulating VDPVs pose the same public health threat as wild polioviruses because they have recovered the biological properties of wild polioviruses, have the potential to reestablish endemicity in settings of low (ie, type-specific) polio vaccine coverage [19, 23], and require the same control measures. Immunodeficiency-associated VDPVs may be excreted by individuals with PIDs for many years with no apparent paralytic signs [24, 25]. However, individuals infected with iVDPVs are at risk of developing paralytic poliomyelitis [6, 7, 25] and may infect others, presenting the potential risk of outbreaks [26]. Ambiguous VDPVs are heterogeneous: some are cVDPVs for which only 1 case isolate had yet been obtained, whereas others, such as highly divergent sewage isolates from developed countries, are probably iVDPVs.

VIROLOGIC TESTING FOR VDPVs

All poliovirus isolates are characterized by laboratories of the GPLN [27]. Viruses isolated in cell culture [28] are identified by real-time reverse-transcription polymerase chain reaction (rRT-PCR) assays that use enterovirus-specific and poliovirus group–specific, serotype-specific, and Sabin strain–specific

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primer sets [28, 29]. Vaccine-related poliovirus isolates are further screened for VDPVs by using a rRT-PCR assay targeting sequences that typically revert during replication of OPV in the human intestine [30]. The rRT-PCR VDPV assay is designed to maximize sensitivity for VDPV detection, so some OPV-like isolates are flagged as candidate VDPVs. The molecular assays have largely replaced a screening method previously used by the GPLN [31] that was based on the observation that VDPVs are typically more antigenically divergent than OPV-like isolates. Vaccine-related isolates (identified by molecular assays) that were found to have so-called non–vaccine-like antigenic properties were described as yielding discordant results and were candidate VDPVs [31]. Routine sequencing of the VP1 region of all candidate VDPV isolates is necessary for definitive identification of VDPVs.

PROPERTIES DISTINGUISHING iVDPVs AND cVDPVs

All cVDPVs and many iVDPVs share key properties, including (1) unusually high genetic divergence from their respective OPV reference strains, (2) reversion of the key genetic determinants of the attenuated and temperature-sensitive phenotypes, and (3) demonstrated capacity to cause paralytic disease in humans [4]. Circulating VDPVs can be recognized by the sequence relationships among isolates, obtained either from individuals with no known contact or from the environment, when there is evidence of shared genetic lineages [8, 19, 26, 32, 33]. Genetic lineages, typical of wild poliovirus circulation [18, 35], represent chains of transmission that may be inferred directly from the combined sequence and basic epidemiologic data (ie, date of specimen collection), and their detection does not necessarily require the appearance of paralytic cases [19, 26, 33].

Circulating VDPVs and iVDPVs usually differ in ways that reflect the different selective pressures exerted on the virus during person-to-person transmission, compared with prolonged infection in a single individual. These biological differences between isolates have permitted prediction of the likely identities of many aVDPV isolates, which were subsequently confirmed upon investigation of the associated cases [4]. Nearly all of the cVDPVs shown in Table 1 have vaccine/nonvaccine recombinant genomes, which are rare among OPV-like and iVDPV isolates [4]. Serial recombination with closely related (species C) non–poliovirus enteroviruses [47] frequently occurs during wild poliovirus circulation [48] and is an indication of person-to-person transmission. Vaccine/nonvaccine recombination appears to facilitate cVDPV emergence by replacement of attenuating sequences in a single event [14], and rates of recombination are substantially higher during the early phases of emergence than after these periods (J. Jorba, unpublished data). Nonetheless, recombination may not be obligatory for cVDPV emergence, because type 1 VDPVs (VDPV1s) circulating locally in China [33, 36] and the United States [26] had nonrecombinant genomes.

Key distinguishing features of iVDPV isolates may include (1) heterogeneity at sites of nucleotide variability within a serotype (indicative of mixed virus populations) [6, 49, 50], (2) nonrecombinant or vaccine/vaccine-recombinant genomes [4, 10], (3) more-extensive antigenic variability than typically observed with cVDPVs of the same age (divergence from OPV) [25], and (4) the occasional occurrence of heterotypic iVDPV coinfections (Table 2).

cVDPV OUTBREAKS

Among the 2 well-defined categories of VDPVs, cVDPVs are of the greatest current public health concern [13, 39, 68]. Since 2000, cVDPV outbreaks have occurred in 18 countries, with the large majority (87.1%) of reported cases associated with type 2 (Figure 1 and Table 1). Type 1 cVDPVs (11.1% of reported cases) were associated with the outbreaks in Hispaniola in 2000–2001 and Indonesia in 2005 [8, 37]. By contrast, type 3 cVDPV (cVDPV3) outbreaks are rare, accounting for only 1.8% of known cVDPV cases (Figure 1 and Table 1) [10], an unexpected finding because the type 3 OPV strain is a major contributor to VAPP in OPV recipients [4, 15]. The predominance of cVDPV2 cases after 2005 is even more striking, as type 2 accounts for 97.1% of the total (Figure 1 and Table 1). Because the case/infection ratio for wild poliovirus type 2 infection is approximately 1:2000 [69], the number of cVDPV2 infections worldwide since 2000 may be >1 million [19, 70].

During 2005–2013, a polio outbreak of 385 cases associated with cVDPV2 was reported in northern Nigeria (Figure 1 and Table 1) [39, 41, 42]. The outbreak peaked at 154 cases, in 2009, with the last case reported in December 2012. However, circulation has continued to the present, as numerous environmental isolates closely related to the Nigerian cVDPV2 AFP case isolates were detected up to February 2014. Genetic analysis resolved the outbreak into >20 independent VDPV2 emergences that occurred since 2004, at least 7 of which established circulating lineages [19, 42]. The outbreak was restricted to the northern states, where routine immunization coverage with tOPV is low and mass campaigns using tOPV were infrequent [41, 42]. Spread of cVDPV2 from northern Nigeria has been very limited, with only 6 cases in Niger and 1 case in Chad from importations (Figure 1; Table 1).

Most of the other recent cVDPV outbreaks have also been associated with type 2 (Table 1), several of which (eg, those in Afghanistan, Chad, the Democratic Republic of the Congo, Ethiopia, India, Pakistan, Somalia, and Yemen) were associated with multiple independent emergences [10, 43]. These observations were anticipated by findings in Madagascar, where successive cVDPV2 emergences occurred in the same geographic area [9, 40]. Three separate cVDPV3 emergences were detected in

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Table 1. Characteristics of Outbreaks of Circulating Vaccine-Derived Poliovirus (cVDPV), by cVDPV Serotype and Country, 2000–2013

Serotype, Country	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013[a]	Total	VP1 Divergence, %, Range	Estimated Independent Emergences, No.	Reference(s)
cVDPV1																		
Haiti/DOR	12	9	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	21	1.9–2.6	1	[8]
Philippines	. . .	3	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	3	3.1–3.5	1	[32]
China	. . .	. . .	. . .	. . .	2	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	2	1.0–1.2	1	[36]
Indonesia	. . .	. . .	. . .	. . .	. . .	46	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	46	1.1–3.0	1	[37]
Myanmar	. . .	. . .	. . .	. . .	. . .	. . .	1	4	. . .	. . .	. . .	. . .	. . .	. . .	5	1.5–2.2	1	[38]
Mozambique	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	2	. . .	. . .	2	3.0–4.3	1	[10, 39]
cVDPV2																		
Madagascar	. . .	1	4	. . .	. . .	3	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	8	1.1–3.7	2–3	[9, 10, 40]
Nigeria	. . .	. . .	. . .	. . .	. . .	3	22	71	66	154	27	34	8	3[b]	388	0.7–7.3	>20	[19, 41, 42]
Niger	. . .	. . .	. . .	. . .	. . .	. . .	2[c]	. . .	. . .	2[c]	1[c]	1[c]	. . .	1[b]	7	0.7–5.2	. . .	[10, 38, 39]
DRC	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	13	5	18	11	17	. . .	64	0.7–3.5	>10	[10, 39, 43]
Ethiopia	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	3	1	. . .	. . .	. . .	. . .	4	0.8–1.2	1–3	[44]
Somalia	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	1	6	1	9	1	1	19	0.7–4.0	3–5	[10, 39]
India	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	15	2	. . .	. . .	. . .	17	1.3–1.6	5	[39]
Afghanistan	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	3	5	1	13[d]	3[d]	25	0.9–5.5	1–2	[39]
Chad	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	1[c]	. . .	12	4	17	0.7–2.1	2	[39]
Yemen	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	9	. . .	. . .	9	0.6–1.6	4–5	[10]
China	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	1	2	. . .	3	0.7–1.8	1	[45]
Kenya	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	3[e]	. . .	3	4.3–4.9	. . .	[45]
Pakistan	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	14	47	61	0.7–3.3	2–3	[45]
Cameroon	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	4[b]	4	1.3–2.0	. . .	[45]
cVDPV3																		
Cambodia	. . .	. . .	. . .	. . .	. . .	1	1	. . .	. . .	. . .	. . .	. . .	. . .	. . .	2	1.9–2.4	1	[38, 46]
Ethiopia	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	1	6	. . .	. . .	. . .	7	1.3–3.1	1–2	[39]
Yemen	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	3	1	4	2.0–3.0	1–2	[10]

Data are no. of reported cases of poliomyelitis, unless otherwise indicated.

Abbreviations: DOR, Dominican Republic; DRC, Democratic Republic of the Congo.

[a] Data are modified from [34] and are current as of 14 March 2014.

[b] Importation from Nigeria of cVDPV2 originating in Chad.

[c] Importation from Nigeria.

[d] Importation from Pakistan (3 cases in 2012 and 1 case in 2013).

[e] Importation from Somalia.

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Table 2. Characteristics of Infections with Prolonged Excretion of Immunodeficiency-Associated Vaccine-Derived Poliovirus (iVDPV), 1962–2013

Country/Region	Year Detected	Immune Deficiency[a]	Paralysis	Serotype(s)	Maximum VP1 Divergence From Sabin Strain, %	Reference(s)
United Kingdom	1962	HGG	No	1	2.5	[51–53]
United Kingdom	1962	HGG	No	3	2.3	[49, 54]
Japan	1977	XLA	Yes	2	. . .	[55, 56]
United States	1980	AGG	Yes	2	1.3	[57]
United States	1981	CVID	Yes	1	10.0	[6]
United States	1986	XLA	Yes	2	2.0	[57]
United States	1986	CVID	No	1	5.4	[31]
	1992			2	11.8	[31]
United Kingdom	1987	CVID	No	2	4.1	[53, 58]
United States	1989	AGG	Yes	1	1.1	[57]
Germany	1990	CVID	Yes	1	8.3	[7]
United States	1990	SCID	Yes	2	1.9	[57]
United States	1991	CVID	Yes	2	1.4	[57]
Iran	1995	HGG	Yes	2	2.2	[59]
United Kingdom	1995	CVID	No	2	12.9	[24, 53]
United States	1995	SCID	Yes	2	2.1	[57]
Argentina	1998	XLA	Yes	1	2.8	[60]
Germany	2000	CVID	Yes	1	3.5	[31]
United Kingdom	2000	CVID	No	2	6.3	[53]
Taiwan	2001	CVID	Yes	1	3.5	[50]
Kazakhstan	2002	HGG	Yes	2	2.3	[31]
Kuwait	2002	MHC II	No	2	2.0	[31]
United Kingdom	2002	ICF syndrome	No	2	2.5	[53]
Peru	2003	AGG	Yes	2	1.2	[31, 61]
Thailand	2003	HGG	Yes	2	2.2	[62]
China	2005	XLA	Yes	2, 3	4.2 (type 2), 3.9 (type 3)	[31, 38]
Iran	2005	MHC II	Yes	1, 2	1.1 (type 1), 1.4 (type 2)	[59, 63]
Morocco[b]	2005	SCID	Yes	2	4	[31]
Syria	2005	HGG	Yes	2	1.3	[31, 38]
United States	2005	SCID	Yes	1	>2.3	[26]
Iran	2006	SCID	Yes	2	1.7	[59]
Iran	2006	XLA	Yes	3	2.1	[59, 64]
Kuwait	2006	SCID	Yes	3	1.2	[38]
Syria	2006	HCI	Yes	2	2.2	[38]
Tunisia[c]	2006	SCID	No	2	2.0	[31, 38]
Belarus	2007	HGG	Yes	2	1.9	[65]
Egypt	2007	SCID	Yes	3	1.1	[38]
Iran	2007	SCID	Yes	1, 2	1.7 (type 1), 1.7 (type 2)	[59]
Iran	2007	XLA	Yes	3	2.0	[59]
Russia	2007	HGG	Yes	1	1.0	[65]
Iran	2008	XLA	Yes	2	1.2	[65]
Argentina	2009	HGG	Yes	1	3.8	[44]
Colombia	2009	AGG	Yes	2	1.5	[39]
India	2009	CVID	Yes	1	6.2	[39]
United States	2009	CVID	Yes	2	12.3	[25]
Algeria	2010	HLA-DR	Yes	2	1.8	[39]
China	2011	PID	Yes	3	2.0	[39]
China	2011	PID	Yes	2	1.9	[39]
India	2010	PID	Yes	2	1.6	[39]

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Table 2 continued.

Country/Region	Year Detected	Immune Deficiency[a]	Paralysis	Serotype(s)	Maximum VP1 Divergence From Sabin Strain, %	Reference(s)
Iraq	2010	PID	Yes	2	1.2	[39]
Sri Lanka	2010	SCID	No	2	1.3	[39, 66]
Egypt	2011	PID	No	2	1.4	[10]
Egypt	2011	AGG	Yes	1	2.1	[10]
Egypt	2011	PID	Yes	3	4.2	[10]
Iran	2011	SCID	Yes	2	2.0	[10]
Iran	2011	XLA	Yes	2	2.7	[10]
Iran	2011	PID	Yes	1, 2	2.7 (type 1), 3.3 (type 2)	[10]
South Africa	2011	AGG	Yes	3	1.9	[67]
Sri Lanka	2011	CVID	Yes	3	1.9	[10, 66]
Turkey	2011	PID	No	2	1.8	[39]
West Bank	2011	SCID	No	2	1.2	[10]
China	2012	CVID	Yes	2, 3	1.4 (type 2), 1.6 (type 3)	[10]
Egypt	2012	PID	No	2	1.0	[45]
India	2012	HGG	Yes	2	2.8	[10]
Iran	2012	PID	Yes	2	1.4	[10]
Iran	2012	PID	Yes	2	1.1	[45]
Iraq	2012	PID	Yes	2	1.0	[45]
Afghanistan	2013	PID	Yes	2	0.9	[45]
China	2013	PID	Yes	3	1.3	[45]
Egypt	2013	PID	No	2	0.9	[45]
India	2013	HGG	Yes	2	0.9	[45]
Iran	2013	PID	Yes	2	0.9	[45]
Saudi Arabia[d]	2013	SCID	No	2	4.4	[45]
United States[e]	2013	SCID	Yes	1	1.1	[45]

Abbreviations: Ab, antibody; AGG, agammaglobulinemia; HCI, humoral and cellular immunodeficiency; HGG, hypogammaglobulinemia; HLA-DR, HLA-DR–associated immunodeficiency; ICF, immunodeficiency-centromeric instability-facial abnormalities; MHC II, major histocompatibility complex class II molecule deficiency; SCID, severe combined immunodeficiency; XLA, X-linked agammaglobulinemia.

[a] Common variable immunodeficiency (CVID) is most frequently associated with chronic iVDPV excretion and highly divergent iVDPV isolates.

[b] Patient treated in Spain.

[c] Patient treated in France.

[d] Patient treated in Germany.

[e] Child traveled with family to the United States after receiving 2 doses of oral polio vaccine in India.

Ethiopia in 2009–2010, and a single cVDPV1 emergence was detected in Mozambique in 2011 (Table 1).

Key risk factors for cVDPV emergence and spread are (1) continued use of OPV at low rates of coverage, especially in routine immunization; (2) prior elimination of the corresponding wild poliovirus serotype; (3) emphasis on use of monovalent OPV (mOPV) and bivalent OPV (bOPV; types 1 and 3) in mass campaigns [10, 41]; and (4) insensitive AFP surveillance. Many of these risk factors exist in areas of insecurity, such as in parts of Pakistan, Afghanistan, northern Nigeria, Somalia, and Yemen, where rates of routine tOPV coverage remain low.

iVDPVs

It has long been recognized that patients with PIDs could become chronically infected when exposed to OPV [71]. However, explicit demonstration that vaccine-related poliovirus isolates from PID patients had unusual sequence properties awaited the use of oligonucleotide fingerprinting [6, 55] and genomic sequencing [6, 7, 49] as poliovirus diagnostic tests, with the extent of sequence divergence approximately proportional to the duration of the prolonged infection [6, 7, 25, 49, 50]. Not all isolates from PID patients in these studies were classified as iVDPVs; some isolates were from specimens collected early during the prolonged infection, with no subsequent specimens obtained. In other situations, either the prolonged infections had resolved spontaneously or the patient died from complications of the immunodeficiency (including fatal poliomyelitis) [57]. Prolonged iVDPV infections are independent events, and the isolates obtained from such infections trace separate pathways of divergence from the original OPV strains.

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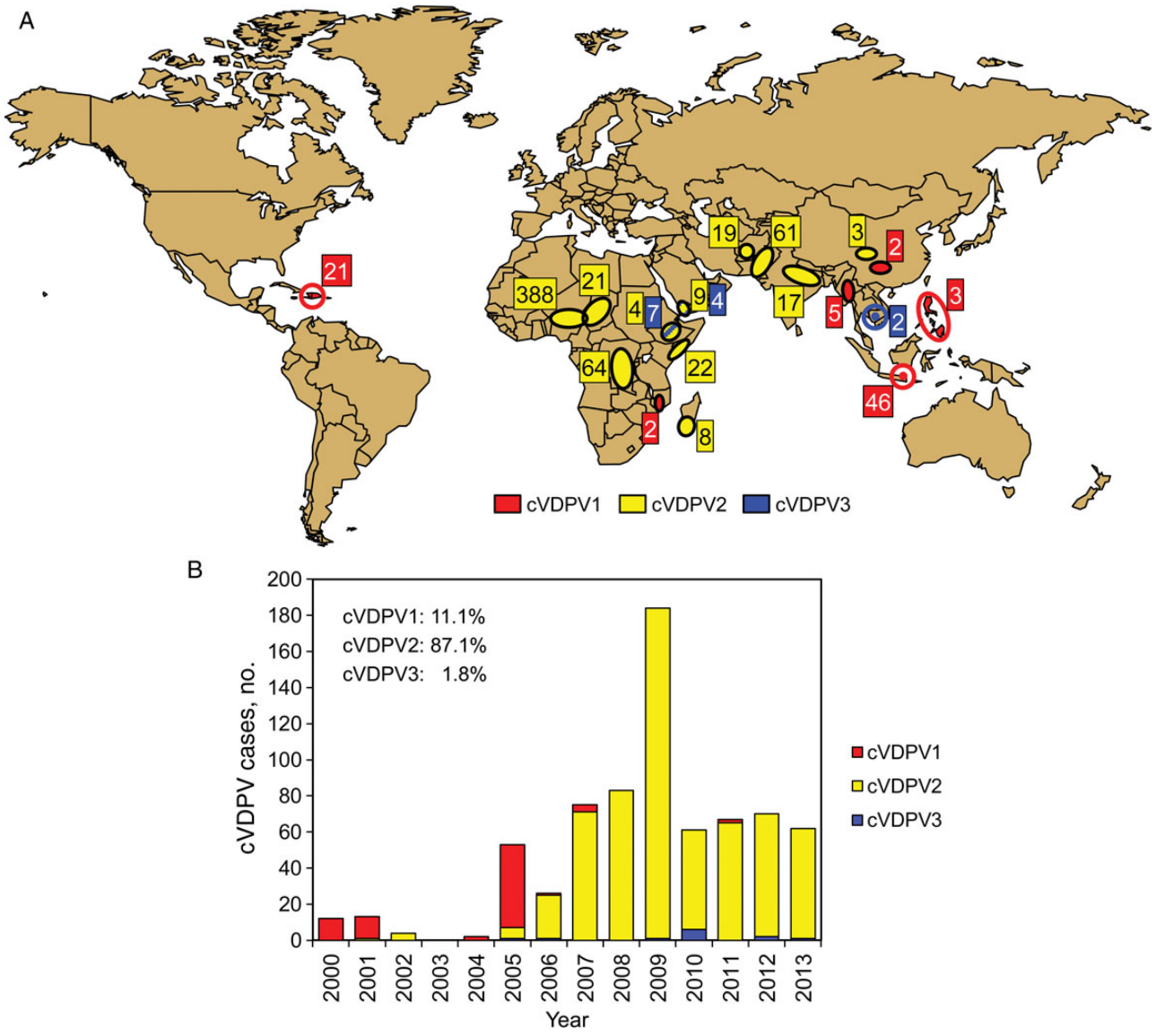

Figure 1. Outbreaks of circulating vaccine-derived poliovirus (cVDPV), 2000–2013. *A*, Location of cVDPV outbreaks, by serotype. The independent emergences of cVDPV2 and cVDPV3 in Ethiopia and Yemen are indicated by yellow and blue diagonal patterns. Apart from the 2000–2001 cVDPV1 outbreak involving Haiti and the Dominican Republic and the limited spread of cVDPV2 from Nigeria to Niger and Chad (and, independently, from Chad to Cameroon, Nigeria, and Niger), all other outbreaks are independent events. Some countries had successive (eg, Madagascar) or concurrent (eg, Nigeria and the Democratic Republic of the Congo) cVDPV2 outbreaks. *B*, Number, by year and serotype, and overall percentage, by serotype, of cases associated with cVDPV outbreaks, 2000–2013.

Since the introduction of OPV, in 1961, >70 persons with PIDs have been found worldwide to be excreting iVDPVs; the majority of these immunodeficiencies were detected only after onset of AFP (Table 2). Prolonged infections lasting >5 years are described as chronic [11]. Four of the iVDPV isolates from chronic excreters were highly divergent (defined as >10% VP1 sequence divergence from the parental OPV strain), suggesting that the chronic poliovirus infections had persisted for approximately ≥10 years (Table 2). PID patients with chronic infections and the most divergent isolates have common variable immunodeficiency (CVID), a group of late-onset PIDs that have multiple etiologies [72]. CVID is the most prevalent of the PIDs (approximately 1 in 50 000) [72], but only a very small proportion of CVID patients exposed to OPV become chronically infected with iVDPVs [11]. Human immunodeficiency virus (HIV) infection, which predominantly affects T cells, does not appear to elevate the risk of iVDPV infections [73, 74].

Unlike cVDPV outbreaks, prolonged iVDPV infections cannot be prevented by high OPV coverage. Nearly all reports of

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persistent iVDPV infections have been from countries with high to intermediate levels of economic development (Table 2), where the rates of vaccine coverage are high and the survival times of PID patients may be extended by treatment with intravenous immune globulin. The survival rates for persons with PIDs are probably very low in developing countries at highest risk for poliovirus spread [11, 16]. The population of prolonged iVDPV excretors is declining in developed countries because some patients have died (Table 2), some have cleared their infections, and no new iVDPV infections have been found in countries that have shifted to inactivated poliovirus vaccine (IPV). Although the prevalence of prolonged iVDPV excretors is higher than detected by AFP surveillance, it still appears to be very low [11]. The development of effective treatments to clear prolonged iVDPV infections may facilitate detection of and access to infected individuals [10, 75].

Type 2 iVDPVs are the most prevalent (64%), followed by type 1 (21%) and type 3 (15%). Some patients have heterotypic iVDPV infections, with the extent of sequence divergence of the isolates consistent with derivation from a single trivalent OPV (tOPV) source dose (Table 2) [76].

aVDPVs

Unlike the well-defined cVDPV and iVDPV categories, aVDPVs are heterogeneous (Tables 3 and 4). Some aVDPVs have diverged by just over 1% from the parental OPV strains, have no detected progeny, and may reflect the extremes of the usual distribution of vaccine-related variants in countries using OPV [10]. Detection of other aVDPVs has foreshadowed cVDPV outbreaks [10, 84], others indicate limited person-to-person spread of OPV virus in small communities with gaps in OPV coverage [4, 26, 33, 77, 78], and still others appear to indicate more-prolonged circulation (Table 3) or additional cVDPV emergences in outbreak settings [10, 19]. Most of these latter aVDPVs have vaccine/nonvaccine recombinant genomes typical of cVDPVs.

Many aVDPVs are isolated from the environment, and some have genetic and phenotypic properties typical of iVDPVs. Highly divergent aVDPVs have been detected in Israel [45,79], Estonia [45,76], Slovakia [80, 81], and Finland [44, 83], countries whose high rates of polio vaccination coverage probably prevent extensive VDPV transmission (Table 4). Some isolates appear to signal >15 years of replication [76]. Although the likely sources of these viruses are individuals with inapparent chronic iVDPV infections, none of the infected persons have yet been identified.

Other environmental VDPVs are closely related to cVDPVs isolated from patients with AFP. These can be regarded as cVDPV isolates that cannot be linked to specific infected persons. Detection of cVDPV in the environment may signal more-widespread or more-prolonged cVDPV transmission than indicated solely by the appearance of AFP cases.

INDEPENDENCE OF iVDPVs AND cVDPVs

The first reports of highly divergent iVDPVs [6, 7] and cVDPVs [8, 9, 32] appeared within a few years of each other, prompting speculation that cVDPV outbreaks may be triggered by iVDPV excretors. Although it is difficult to rule out this possibility rigorously, because the early events in cVDPV outbreaks are rarely observed, 2 key observations suggest that iVDPV infections and cVDPV outbreaks, with one possible exception [26], have been independent. First, multiple independent cVDPV emergences have occurred in settings where the expected survival times for persons with PIDs are short [19, 43, 46]. Second, the extent of amino acid substitution in the neutralizing antigenic sites is typically lower for cVDPV isolates than for iVDPV isolates of similar ages (J. Jorba, unpublished results). Past experience, however, may not be a predictor of future conditions, as iVDPVs from chronically infected individuals may present a risk for spread into the community in some settings in the post-OPV era, and additional surveillance measures may be needed to detect long-term iVDPV excretors.

VDPVs AND THE POLIO ERADICATION END GAME

The emergence of VDPVs has important implications for current and future polio immunization policies [4, 13, 41, 85]. Since

Table 3. Other Vaccine-Derived Polioviruses With Genetic Evidence of Community Circulation, 1965–2011

Country	Serotype	Year(s)	Reported Cases (Contacts), No.	VP1 Divergence, %, Range	Estimated Independent Emergences	Reference(s)
Byelorussia	2	1965–1966	0 (9)	1.6–2.1	3	[77]
Romania	1	2002	1 (7)	1.1–1.3	1	[78]
Laos	2	2004	1 (1)	1.1	1	[4]
United States	1	2005	0 (5)	2.3–2.6	1	[26]
China	1	2006	1 (6)	1.4–2.2	1	[33]
Madagascar	2	2011	0 (2)	3.3–3.7	1	[10]

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Table 4. Highly Divergent Ambiguous Vaccine-Derived Polioviruses From the Environment, 1998–2013

Country, Years Isolated	Serotype	VP1 Divergence, %	Reference(s)
Israel			[10, 39, 45, 79]
2009–2012	1	8.0–13.8	
1998–2013	2[a]	6.6–16.7	
2006–2011	2[b]	10.7–11.2	
Slovakia			[80, 81]
2003–2004	2	13.4–15.0	
Estonia			[39, 45, 76, 82]
2008–2012	2	13.5–16.2	
2002–2008	3	12.6–14.9	
Finland			[10, 39, 45, 83]
2008–2013	1	12.4–14.0	
2008–2013	2	13.0–15.5	
2008–2010	3	13.7–14.6	

[a] Group 1 aVDPV2 isolates from Israel are genetically distinct from group 2 isolates and are probably derived from 2 different chronic excreters.

[b] Group 2.

1999, all poliomyelitis cases associated with poliovirus type 2 have been associated with the continued use of tOPV. The rising incidence of cVDPV2 outbreaks and their widespread occurrence in 14 countries prompted the WHO to plan for the logistically challenging step of coordinated worldwide withdrawal of tOPV and replacement with bOPV [13]. The switch from tOPV to bOPV, targeted for April 2016, is predicated on the complete cessation of cVDPV2 transmission and will require intensification of AFP and poliovirus surveillance. Under the new strategic plan, routine immunization will be strengthened, and in countries using OPV, 1 dose of IPV will be given with the third dose of diphtheria-pertussis-tetanus vaccine [86]. Large stockpiles of type 2 mOPV (mOPV2; in addition to mOPV types 1 and 3) will be maintained, and a robust surveillance and response capacity will be established. Before tOPV withdrawal, the Global Certification Commission must validate the eradication of type 2 wild polioviruses and the elimination of cVDPV2 transmission [13]. Before validation, all wild type 2 polioviruses will have been placed under strict containment, and after tOPV withdrawal all type 2 polioviruses will be similarly contained. After the switch to bOPV, any use of the mOPV2 stockpile in outbreak response will require authorization by the director general of the WHO in accordance with the recommendations of an independent advisory group [13]. Because indefinite use of OPV is incompatible with polio eradication, implementation of the switch from tOPV to bOPV will serve as a model for global OPV cessation and withdrawal, projected for 2019.

Replacement of tOPV with bOPV will greatly reduce the risk of cVDPV2 outbreaks, and global cessation of OPV use will prevent virtually all cVDPV outbreaks and all new iVDPV infections. However, a small number of individuals with chronic iVDPV infections are likely to continue to excrete poliovirus for at least a decade after the last wild poliovirus infection and administration of the last OPV dose. Therefore, maintenance of high levels of population immunity by comprehensive coverage with IPV will be essential to protect against possible iVDPV spread in the community. In addition, it will be important to detect chronic iVDPV excretors in all countries [11] and to find effective means of clearing their infections [75].

Notes

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