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Review

New insights into physiopathology of immunodeficiency-associated vaccine-derived poliovirus infection; systematic review of over 5 decades of data

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ABSTRACT

Widespread administration of oral poliovirus vaccine (OPV) has decreased global incidence of poliomyelitis by ≈99.9%. However, the emergence of vaccine-derived polioviruses (VDPVs) is threatening polio-eradication program. Primary immunodeficiency (PID) patients are at higher risks of vaccine-associated paralytic poliomyelitis (VAPP) and prolonged excretion of immunodeficiency-associated VDPV (iVDPV).

We searched Embase, Medline, Science direct, Scopus, Web of Science, and CDC and WHO databases by 30 September 2016, for all reports of iVDPV cases. Patient-level data were extracted form eligible studies. Data on immunization coverage and income-level of countries were extracted from WHO/UNICEF and the WORLD BANK databases, respectively. We assessed bivariate associations between immunological, clinical, and virological parameters, and exploited multivariable modeling to identify independent determinants of poliovirus evolution and patients' outcomes. Study protocol was registered with PROSPERO (CRD42016052931).

4329 duplicate-removed titles were screened. A total of 107 iVDPV cases were identified from 68 eligible articles. The majority of cases were from higher income countries with high polio-immunization coverage. 74 (69.81%) patients developed VAPP. Combined immunodeficiency patients showed lower rates of VAPP ($p < .001$) and infection clearance ($p = .02$), compared to humoral immunodeficiency patients. The rate of poliovirus genomic evolution was higher at early stages of replication, decreasing over time until reaching a steady state. Independent of replication duration, higher extent ($p = .04$) and rates ($p = .03$) of genome divergence contributed to a less likelihood of virus clearance. PID type ($p < .001$), VAPP occurrence ($p = .008$), and income-level of country ($p = .04$) independently influenced patients' survival.

With the use of OPV, new iVDPVs will emerge independent of the rate of immunization coverage. Inherent features of PIDs contribute to the clinical course of iVDPV infection and virus evolution. This finding could shed further light on poliomyelitis pathogenesis and iVDPV evolution pattern. It also has implications for public health, the polio eradication effort and the development of effective antiviral interventions.

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1. Introduction

Since the foundation of Global Polio Eradication Initiative, billions of oral poliovirus vaccine (OPV) doses have been administered as the mainstay of polio-eradication strategy due to lower cost, ease of administration, and the ability to induce intestinal immunity and passively immunize contacts in areas of poor sanitation. This has led to ≈99.9% decreased in annual incidence of wild-type poliomyelitis from 350,000 cases in 1988 to 35 cases in 2016. However, emergence of neurovirulent vaccine-derived polioviruses (VDPVs) has raised concerns regarding continued OPV use [1–3].

Normally, attenuated viruses replicate in the gastrointestinal (GI) tract of OPV recipients for a short period and disappear in 2–6 weeks after OPV exposure [4]. In rare situations, particularly in immunocompromised patients, vaccine-polioviruses are not cleared from GI tract and continue to replicate for prolonged durations. The unstable genome of OPV strains is susceptible to spontaneous mutations, occurring to ∼1–2% of nucleotides in viral protein 1 (VP1) region per each year of replication. Revertant substitutions in modified genes of OPV strains, in very rare instances (1 in every 2.7 million doses) recover neurovirulent potential resulting in vaccine-associated paralytic poliomyelitis (VAPP) [2,5–7]. VDPVs are defined as poliovirus serotypes 1&3 with >1%, and serotype 2 with >0.6% divergence in VP1 coding region from the parental OPV strains [8].

Primary immunodeficiency (PID) patient are at ∼3000-fold increased risk of VAPP, and may chronically excrete immunodeficiency-associated VDPVs (iVDPVs) in stool. iVDPV emergence is a major challenge for the polio-eradication program. Vaccine viruses may also continue replication by infecting several healthy hosts, through person to person transmission in under-immunized communities, and attain genetic drift to meet the definition of circulating-VDPVs [2]. Ambiguous VDPVs are isolates from either immunocompetent individuals or the environmental samples, without any evidence of community circulation [2]. In addition to the risk that all 3 VDPV categories pose to the current eradication efforts, a silent excretion of divergent viruses by PID patients presents a long-term risk of polio-outbreak after OPV cessation [2,5,8,9]. A literature review on this topic is provided in Supplementary Background.

Despite the passage of more than 54 years from identifying the first iVDPV patient in 1962, most of our understandings about different aspects of iVDPV infection have come from case studies, each presenting a limited number of patients. Previous review studies provided valuable findings regarding the epidemiological aspects of the infection. However, they lacked in-depth analysis of clinical and immunological parameters [10,11]. We conducted this systematic review of iVDPV cases and analyzed the associations between clinical, immunological and virological variables to identify factors which determine presentations and outcomes of these patients, as well as the pattern of iVDPV genomic evolution.

2. Methods

This systematic review has been registered with PROSPERO (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID = CRD42016052931). We conducted a systematic search of CDC and WHO websites and electronic databases: Embase, Medline, Science direct, Scopus, and Web of Science till 30 September 2016, to find articles describing at least 1 immunodeficient patients who shed VDPV. We designed a sensitive search strategy using the key words "poliomyelitis", "oral poliovirus vaccine", "vaccine-derived poliovirus", "immunodeficiency", and their related terms. No restrictions were considered for study design and publication time. Articles in English and French were included. Study selection and quality assessment were performed by 2 reviewers. The quality of articles was not a matter of exclusion and was used when there was an inconsistency in results between papers, with the highest quality paper being used when different articles referred to the same cases.

Two reviewers independently extracted patient-level data in terms of epidemiological data, patients' characteristics, and features of iVDPV infection. Possible discrepancies were resolved by consensus or consulting a third reviewer.

Data on polio-immunization coverage and income-level of countries were extracted from WHO [12] and the World-Bank [13] databases, respectively. When available, the interval between presumed infective OPV dose and the latest positive stool specimen was calculated to estimate total virus replication time. Otherwise, results of phylogenetic analysis of poliovirus RNA reported by original case-studies were considered for this estimation. This was in line with the most recent strategy used by CDC/WHO to estimate this duration [11,14]. We defined "iVDPV detection speed" as an index of how quickly excretion was documented, which was calculated as the duration of virus shedding under observation divided by the total virus replication time. "Virus evolution rate" was defined as the maximum percent VP1 divergence divided by the total virus replication time. PIDs were categorized into 2 groups of predominantly antibody deficiencies (PADs) and combined immunodeficiencies (CIDs) based on International Union of Immunological Societies (IUIS) classification [15]. After summarizing the descriptive results, bi-variate and multivariable analyses

were performed to unravel potential associations. *P* values < .05 were considered statistically significant.

Detailed description of review protocol, search strings, variable definitions, statistical analyses, and multivariable model building is provided in the Supplementary Methods.

3. Results

Among 4329 titles screened, 283 articles were assessed in full-text. Sixty-eight articles met the inclusion criteria for data extraction (Supplementary Figure). Detailed properties of included articles and reasons for study exclusion are presented in the Supplement (Results, Tables 2&3).

3.1. Descriptive findings

A total of 107 iVDPV cases were reported during January 1962 to May 2016. Nearly half of patients (n = 54, 50.47%) were documented 2011–2016. The highest frequency of cases reported were from Iran (n = 20, 18.5%), the United States (n = 12, 11.2%), Egypt (n = 9, 8.3%), China and India (n = 8, 7.4%, for each). Among 106 cases with data, 68 cases (64.1%) were reported from high-income and upper middle-income countries. Sixty iVDPV cases (58.2% of 103 cases with data) emerged in countries with ≥95% polio-immunization coverage.

We identified 6 cases not reported in WHO/CDC annual updates. Two patients from Italy and the United States, respectively, shed 0.88% and 0.9% divergent viruses, consistent with the most recent definition of iVDPV2 (≥0.6% VP1 divergence) [5,16]. Four other cases were from Iran, Belarus, Russia and Tunisia [9,17–20].

Characteristics of patients are summarized in Table 1. The majority of patients had PADs. In nearly 60% of patients, PID was detected following iVDPV detection. Thirty-two patients (30.19%) never had paralysis, 20 of whom (62.5%) were identified after 2011. Among 25 patients with data on site of paralysis, 7 cases (28.0%) developed bulbar poliomyelitis [5,19,21–25]. Three of them died from respiratory paralysis [5,19,23]. Twenty-six of 29 cases with available records (89.6%) received the first OPV dose before 6 months age (58.6% at birth). Three patients never received OPV and the route of infections was suspected to be transmission from OPV recipients or unimmunized secondarily infected contacts [9,26,27]. Among 56 cases with data, 35 patients (62.5%) stopped virus excretion upon the latest follow-up, with a median shedding duration of 5.5 months after diagnosis. Documented immunoglobulin replacement therapy was reported in 43.33%, 14.63%, and 17.07% of patients from high-income, upper-middle income, and lower-income countries, respectively (total = 31 patients). This data was missing for rest of the patients. Four patients were reported to receive hematopoietic stem-cell transplantation (HSCT), which resulted in clearance of infection in 3 of them [14,26,28].

One hundred and thirteen iVDPVs were isolated from 107 patients (Fig. 1). iVDPV2 was the most prevalent serotype (69.03%). Six patients shed 2 different virus serotypes [2,8,9,29]. Seven isolates (6.19%) were intertypic recombinant iVDPVs [9,19,21,30,31]. Concurrent infection with multiple lineages of one iVDPVs serotype was reported in 5 cases [22,24,26,32,33]. Nine patients shed highly diverged iVDPVs, estimated to have replicated for ≥5 years [6,14,23,25,34–37]. Properties of iVDPV infections are summarized in Table 2.

Investigation of poliovirus excretion was reported for 516 contacts of 20 iVDPV cases. Most of the specimens were negative for iVDPVs and few contacts shed Sabin-like viruses. Five contacts of 2 CID patients shed VDPVs related to viruses isolated from the indexed patients. One healthy contact of a non-paralyzed major histocompatibility complex class II deficiency patient in Morocco excreted VDPV2 for more than 216 days [30]. In an undervaccinated community in Minnesota, VDPV1 was isolated from 4 contacts of a paralytic patient with severe combined immunodeficiency (SCID). Three other contacts had only serologic evidence of a previous infection in this outbreak [26].

Detailed characteristics of all patients and iVDPVs isolated are described in the Online Supplement (Results & Table 4).

Table 1
Clinical characteristics of iVDPV patients.

Parameters	No. cases with data (n = 107)	Results
Age, median (IQR), year		
At iVDPV detection	90	1.04 (0.67–2.58)
At PID diagnosis	33	1.09 (0.58–3)
At last follow up	36	2.12 (1.21–5.6)
VAPP to death interval, median (IQR), year	25	0.5 (0.08–2.33)
Gender, no. (%) male	85	52 (61%)
VAPP occurrence	106	
Paralyzed, no. (%)		74 (69.81%)
Non-paralyzed, no. (%)		32 (30.19%)
Site of paralysis	25	
Monoplegia, no. (%)		6 (24%)
>1 limb/bulbar, no. (%)		19 (76%)
Diagnosis precedence[a]	39	
iVDPV first, no. (%)		23 (58.97%)
PID first, no. (%)		16 (41.03%)
iVDPV shedding[b]	56	
Cleared infection, no. (%)		35 (62.5%)
Continued shedding, no. (%)		21 (37.5%)
Latest survival status[c]	68	
Survived, no (%)		29 (42.65%)
Died, no. (%)		39 (57.35%)
Primary immunodeficiencies:	107	
Predominantly antibody deficiencies		**48 (44.86%)**
AGG, no. (%)		21 (19.63%)
HGG, no. (%)		11 (10.28%)
CVID, no. (%)		16 (14.95%)
Combined immunodeficiencies		**36 (33.64%)**
SCID, no. (%)		25 (23.36%)
MHC2 and other, no. (%)		9 (8.41%)
CID with syndromic features, no. (%)		2 (1.87%)
Unspecified PID		**23 (21.50%)**

AGG: agammaglobulinemia, CID: combined immunodeficiency, CVID: common variable immunodeficiency, HGG: hypogammaglobulinemia, IQR: interquartile range, iVDPV: immunodeficiency-associate vaccine derived poliovirus, MHC2: Major histocompatibility complex class II deficiency, PID: primary immunodeficiency, SCID: severe combined immunodeficiency, VAPP: vaccine-associated paralytic poliomyelitis.

[a] Diagnosis precedence determined whether patients' PIDs were detected prior to or following the manifestation of iVDPV infection.

[b] iVDPV clearance determined that patients stopped poliovirus shedding during life.

[c] Latest survival status indicates whether the patients were alive or died by the last available document published. It may not indicate the current survival status of patients.

3.2. Analytical findings

Exploiting a comprehensive and consolidated statistical approach, we analyzed relationships between different personal, clinical, and virological properties of iVDPV cases (Supplementary Results and Tables 5&6). Among all patients reported, those with agammaglobulinemia and SCID had the most and least likelihood to develop VAPP, respectively (p = .001). Among different PADs, common variable immunodeficiency (CVID) was associated with the lowest incidence of VAPP in identified patients (p = .041)

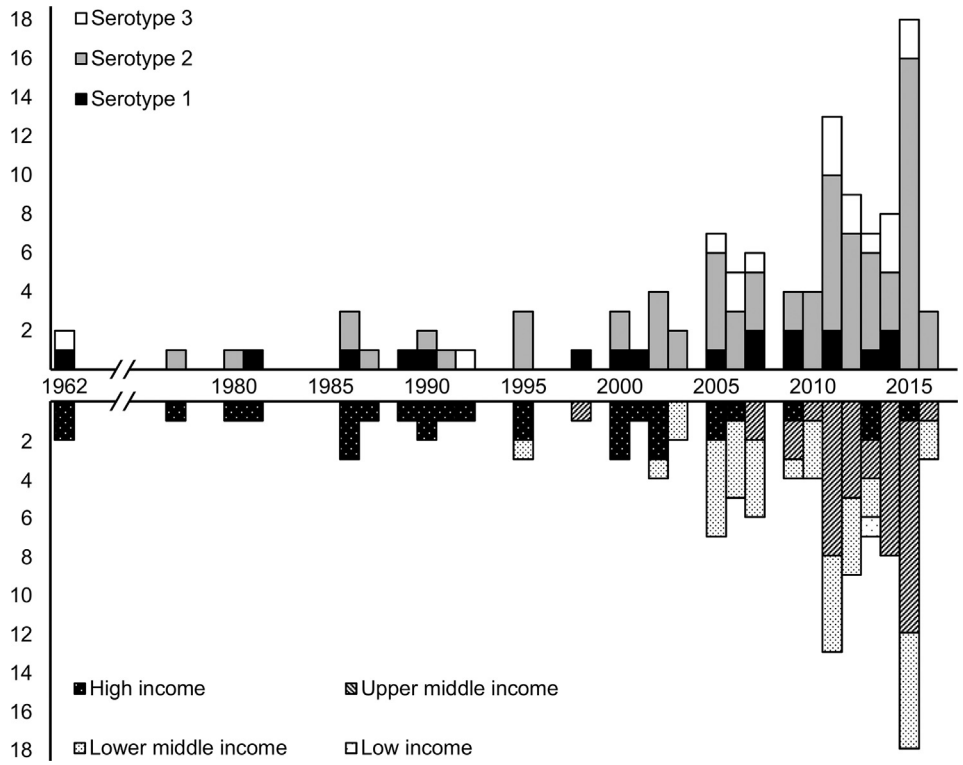


Fig. 1. Number of immunodeficiency-associated vaccine-derived polioviruses (iVDPVs) isolates detected worldwide, 1962–2016. Data stratified based on iVDPV serotype (top) and income-level of country of origin (bottom).

Table 2
Properties of iVDPV infections.

Parameters	No. isolates with data (n = 113)	Results
iVDPV serotypes	113[a]	
serotype 1	19	16.81%
serotype 2	78	69.03%
serotype 3	16	14.16%
Shedding duration in follow-up, median (IQR), year	49	0.33 (0.21–0.58)
VP1 divergence, median (IQR) %	111	1.9% (1.2–2.5%)
Virus replication time, median (IQR), year	98	1.41 (0.92–2)
Virus evolution rate, median (IQR) %/year	97	1.307 (1.11–1.86)
iVDPV detection speed, median (IQR)	49	0.28 (0.14–0.46)

IQR: interquartile range, iVDPV: immunodeficiency-associate vaccine derived poliovirus.
[a] The number of iVDPVs isolated were more that the total number of patients, because 6 patients shed 2 serotypes of poliovirus.

(Fig. 2A). Simple and multivariable analyses showed that reported CID patients were less likely to be paralyzed than reported PAD patients (OR = 0.17, p < .001). Other factors of interest did not show significant associations with VAPP presence.

Among total patients reported in our review with different PID subtypes, patients with SCID (38.46%) and CVID (54.55%) had the lowest probabilities of clearing iVDPVs prior to death/by the last documented follow-up (p = .035) (Fig. 2B). In exploring factors associated with this probability, simple logistic models revealed that reported patients with CID (odds ratio [OR] = 0.24, p = .02) and those with higher extent and rate of genome divergence (OR = 0.83, p = .04 and OR = 0.65, p = .03 per 1% increments of divergence and rate, respectively) were less likely to stop iVDPV shedding. Furthermore, patients from high (OR = 3.57, p = .04) or upper-middle (OR = 5.88, p = .03) income countries were more likely to stop shedding, compared with those reported from lower-middle income countries. After adjusting for probable confounding or suppressing effects in a multivariable logistic model, all these parameters retained their significant associations.

Simple Cox models revealed that reported CID patients (hazard ratio [HR] = 10.59, p = .003) and those who presented with paralysis (HR = 8.01, p = .04) were more likely to die by the latest documented time during iVDPV infection course. Patients from high income countries were significantly less likely to die (HR = 0.28, p = .03), compared with those reported form lower-middle income countries. In the final multivariable Cox model, PID category (p < .0001), paralysis manifestation (p = .008), and income-level of country of origin (p = .04) retained independent significant association with patients' survival (Fig. 3).

The parameter "iVDPV detection speed" was significantly higher in non-paralyzed patients rather than VAPP patients (p = .028), and in those who cleared the infection before death (p = .015). This index tended to be higher in countries with higher income levels (p = .067).

The rate of virus evolution was inversely correlated with a patients' age (r = −0.4, p = .0001). In our final multivariable linear regression model, after adjusting for the confounding effect of replication time on VP1 divergence (Fig. 4), only age at iVDPV detection (p < .001) retained a significant association with higher VP1 divergence.

4. Discussion

We systematically reviewed iVDPV cases reported worldwide during over 5 decades. The rate of case identification has strikingly

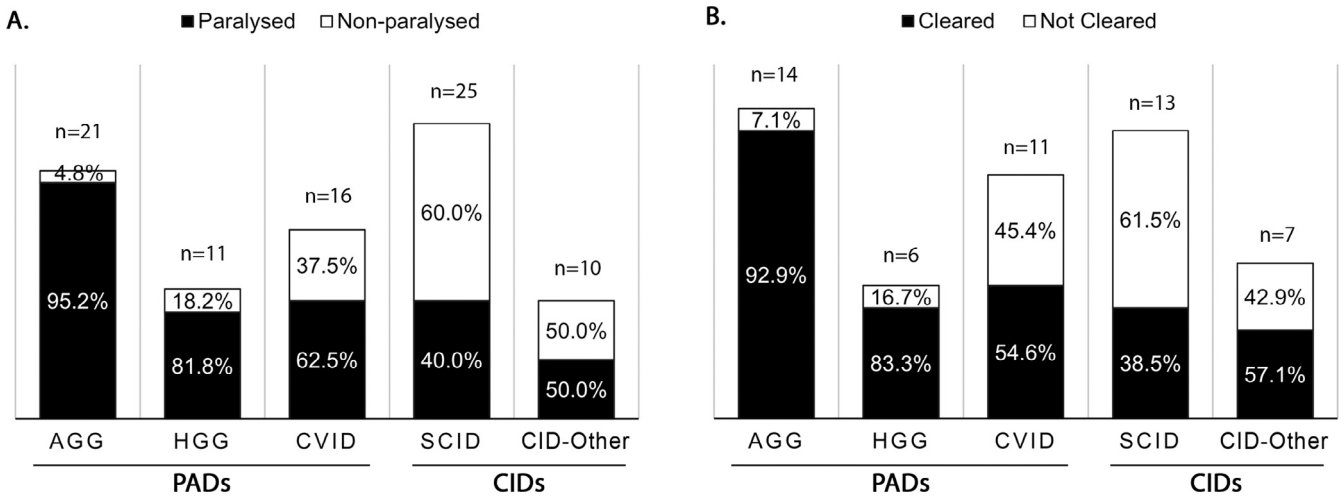


Fig. 2. Comparison of the rates of paralysis occurrence (A) and clearing poliovirus infection (B) among different types of primary immunodeficiency (PID), and between PID categories. AGG: agammaglobulinemia, HGG: hypogammaglobulinemia, CVID: common variable immunodeficiency, PAD: predominantly antibody deficiency, SCID: severe combined immunodeficiency, CID: combined immunodeficiency.

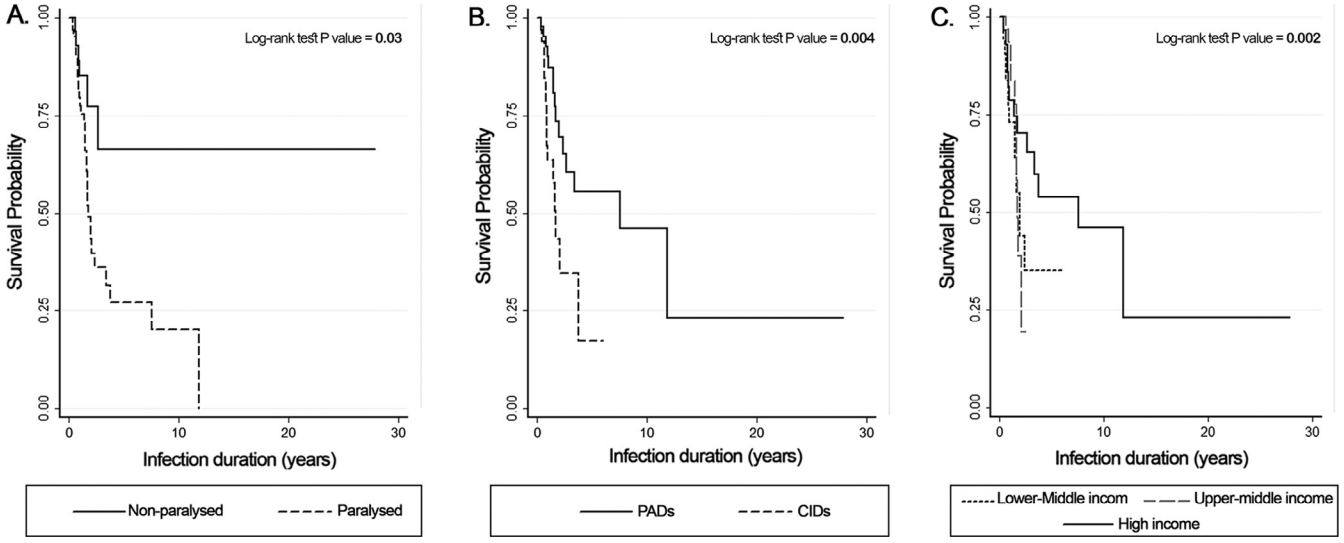


Fig. 3. Overall survival in subgroups of patients based on presence of vaccine-associated paralysis (A), category of primary immunodeficiency (B), and income-level of country of origin (C). CIDs: combined immunodeficiencies, PADs: predominantly antibody deficiencies.

accelerated since 2011, especially in developing countries, following implementation of intensified VDPV surveillance and screening studies to detect asymptomatic infection in PID patients [38–40]. Most of the patients were reported from countries with high polio-immunization coverage. The high frequency of reports from Iran and Egypt might result from high incidence of PIDs given high rates of parental consanguinity [41], sensitive acute flaccid paralysis (AFP) surveillance [9], and implementation of regional PID registry programs in these countries [42,43]. In contrast, the rate of case identification in the United States and other developed countries has not notably increased recently, due to several years of OPV discontinuation and its substitution by IPV immunization. Few recent cases reported from these countries were mostly due to case immigration and/or virus circulation in under-immunized communities. Our findings also showed that reported patients with CID, especially SCID, had a lower risks for developing VAPP, but a higher risk for persistent infection. Among those with PADs, CVID patients were more likely to have asymptomatic and prolonged infection. VAPP occurrence, income-level of countries, and PID type were independent determinants of patients' survival.

There were limitations to our study. We had access only to published data and specific information for some of the patients was not available. This would be expected as an inherent limitation for systematic reviews and meta-analyses utilizing individual patient data (IPD). However, these studies on IPD remain the most robust method for evidence synthesis and answering research questions [44–46]. To overcome such limitations, we exploited a sensitive approach using direct and indirect methods to retrieve parameters of interest based on all available data in the literature (Supplementary Methods & Results). Most of our data were brought together from separate case studies, with probable differences in methods of PID diagnosis. To address this inaccuracy, we included more recent articles with more detailed and higher quality information in case of duplicated reports. In addition, we conservatively omitted indefinite results. Finally, after analyzing parameters among different PID subtypes, we also classified PIDs into grosser categories based on IUIS classification [15] to minimize the effects of this heterogeneity on our analyses. We defined an explicit approach to calculate the total duration of viral replication using data on presumed infective OPV dose. A similar strategy

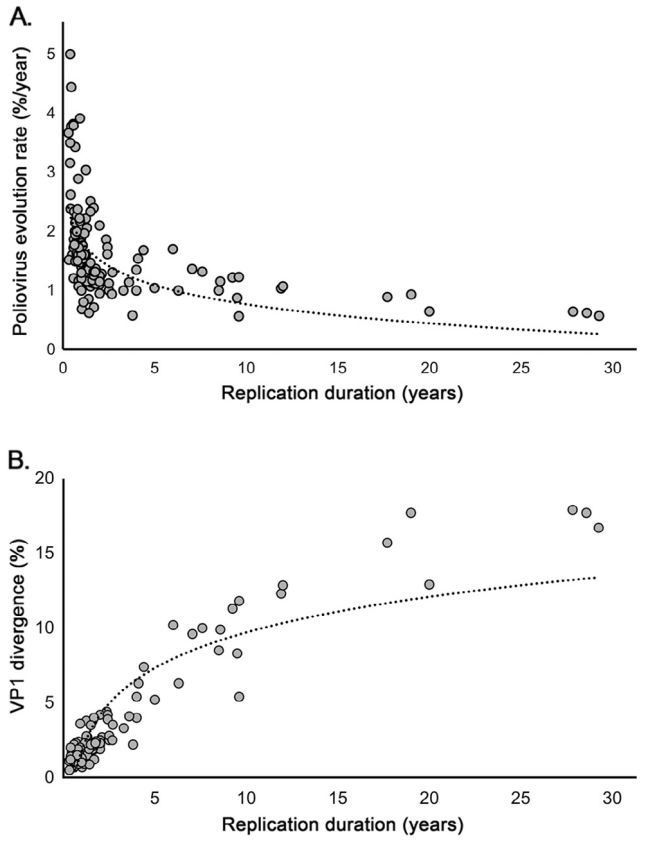


Fig. 4. Relationships of virus evolution rate (A) and viral protein 1 (VP1) divergence (B) with duration of virus replication. Logarithmic trend-lines drawn schematically unraveled the pattern of poliovirus evolution during long-term replication. Evolution rate is higher at early stages of replication and slows down gradually with a trend toward zero by increasing replication time (A). Consistently, increasing absolute VP1 divergence reached a plateau corresponding to the maximum VP1 divergence of poliovirus steady-state (B). Values for virus evolution rate and VP1 divergence were available at several time points for 8 patients.

has been used by CDC/WHO, recently [11,14]. We omitted individual patient's data from our analyses when there was evidence that the patient had acquired divergent virus from sources other than OPV (Supplementary Methods & Results).

Previous studies attempting to summarize these data have mostly focused on the epidemiology and the geographical distribution of iVDPV infection. These studies provided few analytical findings. However, many important associations between immunological, clinical, and virological parameters were not assessed [10,11]. Using a comprehensive analytic approach, we detected novel important clues in further understanding the physiopathology of iVDPV infection. Supported by an extensive literature review, an in-depth discussion of these findings was organized in separate domains of immunological and clinical aspects of the infection, and the pattern of iVDPV evolution.

4.1. Immunological aspects of response to polioviruses

Currently, humoral immunity is considered as the main protective mechanism against enteroviral infections [6]. In the absence of neutralizing antibodies in unimmunized individuals or PID patients, polioviruses can continue replication in the mucosa and lymphoid tissues of pharynx and GI tract (e.g. tonsils, Peyer's patches), and occasionally cause viremia. Motor-neurons in the brain-stem or anterior horn spine become infected following viremia or through retrograde axonal transport. Finally, viral replication causes cell destruction and paralysis [2,6,47].

Reported Patients with CIDs were significantly less likely to develop VAPP than reported PAD patients. Multivariable analysis also confirmed that PID type was the only factor predisposing to VAPP occurrence in iVDPV patients identified. Studies have also reported the susceptibility of CID patients to asymptomatic enteroviral infections [28,48,49]. Unlike PAD patients with only defective antibody production and a generally intact cell-mediated immunity, CID patients have deficiencies in both cellular and humoral immune responses [50]. Therefore, it is hypothesized that T-cell interactions with and/or cytotoxic damage to poliovirus-infected motor-neurons play a role in development of paralysis. Cytotoxic effects of CD8+ T-cells on neuronal destruction has been demonstrated in various viral infections of central nervous system [51–53]. In support, intracerebral inoculation of polioviruses in mice was reported to induce lymphocytic infiltration and tissue destruction throughout animal spinal cord [47].

CID patients are also susceptible to prolonged enteroviral infections [28,48,49,54]. In a previous study, we demonstrated a lower likelihood of clearing iVDPVs by CID patients [9]. We found this to be true also in our analysis. PAD patients, with effective cell-mediated immunity, showed higher rates of infection clearance compared with CID patients. As an explanation, interactions between cellular immunity leukocytes and poliovirus-infected cells in GI mucosa and lymphatic tissues may limit the viral replication and enhance infection clearance. This may propose a possible role of cellular immunity along with humoral immunity in clearing iVDPV infection.

In 1974, Lopez et al. described 4 poliovirus-infected SCID patients without paralysis, and discussed the possible role of cell-mediated immunity in clearing polioviral infections. Interestingly, these patients stopped poliovirus excretion only after HSCT [49]. In this review, 3 of 5 SCID patients who cleared iVDPV infection stopped excreting viruses after a successful HSCT. This clearance could be attributed to gain of both cellular and humoral function after HSCT.

None of the iVDPV-excreting patients in our review had a diagnosis of immunoglobulin-A (IgA) deficiency. In another study, vaccine poliovirus was sequentially introduced to IgA-deficient patients, and a resistance to poliovirus replication was observed in subsequent poliovirus challenges [55]. Given the absence of sufficient mucosal IgA in these patients, other types of immunoglobulins or defense mechanism may also contribute to immunity against poliovirus.

Interestingly, we observed that the incidence of VAPP and rates of iVDPV clearance varied among different PID subtypes within each category of PAD or CID patients, probably due to varying extents of cellular immunity dysfunction. In the PAD category of identified cases, agammaglobulinemic patients showed significantly higher rates of VAPP and clearance than CVID patients. CVID is a heterogeneous category of PIDs and some of these patients may have slight defects in cellular immunity [56–58]. In the CID category, reported patients with SCID were less likely to have VAPP and clear the infection than reported patients with less severe CIDs.

Altogether, our findings suggest that cellular immunity contributes to both the pathogenesis of poliomyelitis and mounting a response to clear the infection. Association between specific PID types and clinical outcomes is further discussed in Supplementary Discussion.

4.2. Clinical course and outcomes of iVDPV infection

In this review, nearly 70% of reported iVDPV excretors developed VAPP. However, we suppose that the actual proportion of iVDPV patients who do not develop paralysis would be more than 30%, considering that these patients have a less likelihood to

undergo virological testing, leading to less iVDPV detection than those who are symptomatic. The majority of asymptomatic patients have been identified since the beginning 2011, following implementation of intensified iVDPV surveillance in PID patients. In most of these patients, PID diagnosis had preceded iVDPV detection. Among VAPP patients, PID was typically diagnosed after paralytic onset/virus isolation. These observations underline the diagnostic significance of VAPP in detection of both iVDPV infection and PID, and the importance of newborn screening for PIDs before live-vaccine administration. Accordingly, we advocate immunological assessment for all patients who present vaccine-related paralysis.

The parameter "iVDPV detection speed" was two-fold higher when diagnosing asymptomatic patients through screening, compared to infection diagnosis after VAPP occurrence. It shows that VAPP is a late manifestation of iVDPV infection and patients can excrete polioviruses for a long time before diagnosis through VAPP presentation.

Higher "iVDPV detection speed" in high-income countries was probably due to exploiting screening programs. We strongly recommend screening for poliovirus excretion in asymptomatic PID patients, especially SCID cases who without HSCT are susceptible to more prolonged infections. Consistently, all the 6 iVDPV patients identified in 2 recent studies, which screened a total of 677 PID patients, had a diagnosis of CID (4 of them were SCID) [39,40]. CVID patients are another high-risk group to be screened, given their longer survival and susceptibility to log-term asymptomatic excretion. Among 9 patients with $\geq$5 years of iVDPVs shedding, 7 had CVID and 4 never had VAPP. Screening of PID patients is an inevitable piece in the puzzle of VDPV surveillance and polio-eradication program.

Patients reported from countries with higher income levels were more likely to both survive during iVDPV infection and to clear the virus. This contribution of income level to patients' outcomes might be due to poor healthcare support and/or lack of proper immunoglobulin replacement therapy in lower-income countries. Although less than one-third of patients had available immunoglobulin therapy data, this proportion was markedly higher in high-income countries. Future reports need to provide more detailed treatment data.

In addition to expected prognostic roles of features inherent to PID and economic level of countries, as a rough estimate of healthcare integrity, we found that direct consequences of poliovirus infection independently influenced the clinical course of patients. Cox model demonstrated that amongst identified cases, CID patients from lower income countries who developed VAPP had the highest likelihood to die during iVDPV infection (Fig. 3). VAPP-related muscle dysfunction may cause life-threatening impairment of vital physiologic processes. This highlights direct adverse prognostic effects of iVDPV infection in immunodeficient patients. In other words, iVDPV prevention in PID patients can notably improve their prognosis and survival. Although new drugs have shown promising effects on stopping poliovirus shedding [59], a preventive strategy to avoid OPV exposure should be in place to prevent iVDPV infection and its life-threatening complications. Most of iVDPV patients in this review received their first OPV at birth or before 6 months of age, when most of PIDs might be asymptomatic [54]. Therefore, implementing neonatal screening for PIDs and moving to all-inactivated polio-vaccine (IPV) immunization strategy would likely end iVDPV emergence and prevent VAPP and death.

4.3. Evolution of vaccine-derived poliovirus

We observed a negative association between virus evolution rate and patients' age. This rate was independent from other clinical characteristics and virus serotype. According to phylogenetic analyses, spontaneous nucleotide substitutions in VP1 region of poliovirus genome occurs at an overall rate of 1–2%/year of virus replication [32,33]. Nonetheless, we found rates of virus evolution exceeding this estimation (range: 0.5–5.0%/year) in some isolates, especially at initial stages of poliovirus replication (Fig. 4). Several studies have described high rates of poliovirus evolution [9,32]. We believe that different mechanisms other than random nucleotide substitutions contribute to the overall genomic evolution of poliovirus. Selection events during early stages of virus replication lead to additional changes in structural regions of genome that may carry unselected hitchhiker mutations and cause higher initial evolution rates [9]. Actually, selection events affect evolution process by both guiding the direction and promoting the rate of mutations. After changes are selected initially, random substitutions occur at rates closer to 1–2%/year.

Another explanation is the occurrence of intertypic and intratypic recombinations, which results in higher evolution rates. iVDPVs commonly crossover parts of genome with other vaccine serotypes [2,6]. Intratypic recombinations between multiple variants of iVDPV1 have also been described [24]. In this review, 13 patients had evidence of infection with more than one iVDPV serotype, and 5 patients shed mixed variants of poliovirus. Likewise, simultaneous co-replication of multiple lineages of iVDPVs in immunodeficient hosts has been frequently reported [24,32]. Therefore, we propose that at early stages of iVDPV evolution, and in the absence of suppressing immune activities, Sabin viruses of each serotype replicate freely in multiple lineages and have the opportunity for these genetic exchanges.

Altogether, higher rates of virus evolution observed in some iVDPV isolates may result from three mechanisms: random nucleotide substitution, selection events, and intratypic recombination. Eventually, variants of the virus that achieve higher extent of genetic alterations and better fit the host microenvironment continue to replicate for longer durations. Supporting this hypothesis, we found that regardless of replication time, both higher VP1 divergence and evolution rate associated with less likelihood of iVDPV clearance. Kew et al. also described evolution of 2 different variants of iVDPV1 in a single host, one of which became predominant subsequently and the other one disappeared [25].

Multiple-regression showed that only replication duration and a patients' age significantly correlated with higher VP1 divergence. Rate of VP1 divergence was higher at early stages of replication. Overall, we believe that vaccine polioviruses undergo genomic evolution until reaching a steady state, in which the virus best fits the host microenvironment and a balance is established between new and reverse substitutions in nucleotide sites. Supporting this explanations, viruses shed by a chronic excretor [35] showed a decrease in evolution rate over time, especially after reaching 15% drift from Sabin, which is a definition of wild-type poliovirus [2,60]. We expect this divergence will not notably increase even if the patient continues to shed iVDPVs (Supplementary Discussion).

5. Conclusion

High OPV coverage will likely result in emergence of new VAPP cases and iVDPV infections. This will impact survival of PID patients and increase the risk of outbreaks after vaccination cessation. OPV use is essential however since IPV alone will not induce sufficient mucosal immunity to prevent virus circulation in a community with existing poliovirus infections. Combined bivalent-OPV and IPV immunization should reach the maximum coverage to terminate poliovirus circulation. Transmission of iVDPVs among patients' contacts, although rare, has the potential to cause out-

breaks in under-immunized communities. In addition to AFP surveillance, monitoring chronically infected patients, screening high-risk individuals, and environmental surveillance are critical to implement as part of the endgame eradication strategy. Following certification of eradication, a switch to all-IPV immunization will be implemented which will prevent additional iVDPV emergence.

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Potential conflict of interest

Authors declare no conflict of interest.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.02.059.

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