Paralytic Poliomyelitis Associated With Sabin Monovalent and Bivalent Oral Polio Vaccines in Hungary

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Abstract

Historical records of patients with vaccine-associated paralytic poliomyelitis (VAPP) in Hungary during 1961–1981 were reviewed to assess the risk of VAPP after oral polio vaccine (OPV) administration. A confirmed VAPP case was defined as a diagnosis of paralytic poliomyelitis and residual paralysis at 60 days in a patient with an epidemiologic link to the vaccine. Archived poliovirus isolates were retested using polymerase chain reaction and sequencing of the viral protein 1 capsid region. This review confirmed 46 of 47 cases previously reported as VAPP. Three cases originally linked to monovalent OPV (mOPV) 3 and one case linked to mOPV1 presented after administration of bivalent OPV 1 + 3 (bOPV). The adjusted VAPP risk per million doses administered was 0.18 for mOPV1 (2 cases/11.13 million doses), 2.96 for mOPV3 (32 cases/10.81 million doses), and 12.82 for bOPV (5 cases/390,000 doses). Absence of protection from immunization with inactivated poliovirus vaccine or exposure to OPV virus from routine immunization and recent injections could explain the higher relative risk of VAPP in Hungarian children. In polio-endemic areas in which mOPV3 and bOPV are needed to achieve eradication, the higher risk of VAPP would be offset by the high risk of paralysis due to wild poliovirus and higher per-dose efficacy of mOPV3 and bOPV compared with trivalent OPV.

Keywords: adverse effects, poliomyelitis, poliovirus vaccine, oral

Topic: poliomyelitis, hungary, paralysis, poliovirus vaccine, oral, vaccines, poliovirus, paralytic poliomyelitis

Issue Section: ORIGINAL CONTRIBUTIONS

Oral poliovirus vaccine (OPV) has been the primary tool used to eradicate poliovirus. The trivalent oral poliovirus vaccine (tOPV), which contains Sabin vaccine strains of the 3 poliovirus serotypes, replaced monovalent vaccines (mOPVs) in the 1960s because it could confer immunity to more than one poliovirus serotype with a single dose (1, 2). Widespread use of tOPV eradicated type 2 wild poliovirus (WPV) in 1999 and has eliminated indigenous transmission of WPV types 1 and 3 from all countries except India, Pakistan, Afghanistan, and Nigeria (3). Since 2005, the Global Polio Eradication Initiative has shifted to the use of monovalent vaccines (mOPV1 and mOPV3), and in 2010 to bivalent OPV1 + 3 (bOPV) in areas with ongoing WPV transmission, because of their having higher efficacy than tOPV in conferring immunity to corresponding WPV serotypes (4–6).

Studies from Hungary, the United States, and the former East Germany have suggested that mOPV3 is associated with a higher risk of vaccine-associated paralytic poliomyelitis (VAPP) than are other vaccine formulations (7–10). However, reports of VAPP risk after mOPV3 administration are scarce because of the short duration of mOPV use, and the reported absolute and relative risks for VAPP varied widely by country partly because of differences in case definitions, surveillance sensitivity, and presence of risk factors such as intramuscular injection or immunodeficiency (7–20). Some VAPP cases reported during the early use of mOPVs could also have been from WPV infection, as laboratory tests available before the development of molecular techniques could not consistently distinguish WPVs from Sabin vaccine-related strains (21, 22). Further clarification of the relative risks and benefits of different OPV formulations is important, considering new widespread use of mOPV3 and bOPV in endemic countries (3, 23).

In the present study, we sought to determine whether the published high rates of VAPP associated with mOPV3 in Hungary (3.24 cases per million doses) (7) could be confirmed and whether VAPP rates

in Hungary were representative of those reported in other countries in which mOPV3 had been used.

We reviewed historical records of VAPP cases from 1961 to 1981 that were archived at the Hungarian National Center for Epidemiology, Budapest, Hungary, and used polymerase chain reaction (PCR) and nucleotide sequencing to analyze archived poliovirus isolates from VAPP cases reported during 1961–1967. We also reviewed published literature on VAPP cases that occurred after administration of OPV globally and in-country reports that described VAPP cases associated with OPV use from the former Union of Soviet Socialist Republics (USSR) and selected countries of Eastern Europe during 1959–1960.

MATERIALS AND METHODS

Literature review

We conducted a review of articles in which VAPP risk had been reported by using electronic search software (Medline Ovid 1950–2005) and applying the keyword "vaccine-associated paralytic poliomyelitis." Studies that used an adequate surveillance system to identify VAPP cases and reported VAPP with mOPV formulations were prioritized (7–20, 24). Additionally, we searched for VAPP cases reported during the years of mOPV use in former USSR and Eastern European countries archived at the USSR Medical Academy of Science in Moscow (25).

Investigators in Hungary reviewed in-country reports, published literature, symposium transcripts, and vaccine distribution records available at the Hungarian National Center for Epidemiology to record data on polio campaigns conducted during 1961–1981, including the type of vaccine and number of doses distributed, dates of campaigns, and targeted age groups (7, 18, 26–28). Published reports and symposia transcripts were used to complement information on VAPP cases reported during this period (29–34).

Case identification methods in Hungary, 1961–1981

During the period of 1961–1981, Hungary had a population of approximately 10 million people divided administratively into 20 districts. Primary health care, including vaccination, was provided through dispensaries staffed by physicians and nurses who reported all suspected cases of paralytic poliomyelitis to the District Preventive Medicine Center. The government compensation for reported cases that was instituted in 1962 encouraged caregivers to pursue full investigation of suspected cases. These cases were initially investigated by a public health official, and if the initial clinical diagnosis was consistent with paralytic poliomyelitis, the patient was referred to the Central Hospital of Infectious Diseases, St. Laszlo, Budapest, for neurologic and virologic evaluation. Blood and stool samples were collected from all patients; cerebrospinal fluid samples were occasionally collected.

Cases were confirmed as paralytic poliomyelitis if neurologic signs and symptoms were compatible and paralysis persisted for at least 60 days after onset. Using epidemiologic criteria (i.e., vaccine receipt, contact with vaccine, or link to WPV cases) and laboratory criteria (i.e., poliovirus detected by culture or increase in homotypic neutralizing antibody titers), cases were classified as WPV-associated, vaccine-associated (recipient or contact), or undetermined (7).

Poliovirus isolation was originally performed in primary monkey kidney cells. Isolates were characterized as "vaccine-like" or "nonvaccine-like" using a combination of the then-standard methods of serodifferentiation assays and tests for phenotypic markers ("T marker," "d marker") and growth characteristics in different media (7, 21, 27, 29).

Case identification methods during recent review

We compiled clinical and epidemiologic information on patients with suspected paralytic poliomyelitis reported in Hungary during 1961–1981 using case reports, case investigation, and laboratory forms archived in the Hungarian National Center for Epidemiology. Dates of paralysis onset were compared with dates of campaigns recorded in sources cited above.

A case of paralysis was classified as suspected VAPP if the patient had a confirmed diagnosis of paralytic poliomyelitis in archived clinical records and residual paralysis at 60 days and an epidemiologic link with the vaccine was identified. Cases were further classified as confirmed VAPP if isolation of vaccine virus (and no WPV) from stools or polio antibody seroconversion to the same serotype as the vaccine virus received was demonstrated; possible VAPP if no vaccine virus isolation or seroconversion results were available; recipient VAPP if paralysis onset was within 4–40 days of receipt of the vaccine; or contact VAPP if paralysis onset was within 4–75 days of contact with the vaccine or the OPV campaign in their area. These definitions are similar to those used in Hungary during 1961–1981 and were used by the World Health Organization in other countries (13, 14, 35). Clinical information reported with case investigation forms was used to determine the presence of risk factors among persons with confirmed VAPP.

Molecular characterization of archived poliovirus isolates

Molecular characterization of poliovirus isolates from 15 suspected VAPP patients and 5 suspected WPV patients reported from 1960 to 1967 was performed at the laboratories of the Hungarian National Center for Epidemiology and the Centers for Disease Control and Prevention, Atlanta, Georgia. After reculture of isolates in mouse L cells expressing the human poliovirus receptor (36) and RD cells (37), polioviruses were identified using PCR (38, 39), followed by sequencing of the viral protein 1 region (approximately 900 nucleotides) and the partial 5′-untranslated region containing the major determinants of the attenuated phenotype (approximately 370 nucleotides) (40, 41).

RESULTS

Use of polio vaccines in Hungary, 1957–2010

In Hungary, mass vaccination campaigns in which the Salk inactivated poliovirus vaccine (IPV) was used were conducted in 1957–1959, and by 1959, nearly 90% of the population under 18 years of age

had received 3 or more doses of IPV. From 1959 to 1961, tOPV, bOPV, and mOPV types 1, 2, and 3 were administered in campaigns targeted to children aged 3 months to 15 years. From 1962 to 1991, only mOPVs were used, and campaigns were targeted to children aged 2 months to 3 years. mOPVs were administered annually in 3 successive countrywide campaigns at 5- to 8-week intervals, with the schedule mOPV1, mOPV3, and mOPV2. From 1959 to 1977, campaigns were conducted during the winter (December through March), and from 1977 to 1991 they were shifted to autumn (September through December) to avoid coinciding with the influenza season. In 1992, campaigns were replaced by a routine sequential vaccination schedule with IPV and tOPV, and since 2006 only IPV has been administered.

Monovalent Sabin OPV preparations were provided in bulk by the Chumakov Institute in Moscow for all campaigns conducted from 1959 to 1991. At the National Institute of Public Health in Budapest, Hungary, bulk OPV preparations were diluted to a concentration of approximately $1–3 \times 10^5$ median tissue culture infective dose and tested for viability in cell cultures, chemical purity, and toxicity. The vaccine was packaged in 10-dose vials and distributed statewide for administration during the campaigns.

Review and reclassification of VAPP cases reported from 1961 to 1981

Between 1961 and 1981, 57 paralytic poliomyelitis cases were reported to the Department of Communicable Diseases of the National Institute of Hygiene in Budapest, Hungary. Dömök's report (7) classified 47 of these cases as VAPP: 34 recipient cases and 13 contact cases (Table 1). After reviewing the available clinical and epidemiologic information using the study definition, we excluded 1 of these cases because the child had no residual paralysis. Two cases considered by Dömök to be VAPP recipient cases were reclassified as VAPP contact cases because more than 40 days had elapsed between vaccine receipt and paralysis onset but a contact vaccine was identified (Table 2).

Table 1.

Risk of Vaccine-Associated Paralytic Poliomyelitis per Million Vaccine Doses as Published by Dömök and After Review of Historical Data, Hungary, 1961–1984

Type of Vaccine	Million Doses Given	Classification by Dömök et al.[a]			
		Total No. of Cases	No. of Recipient Cases	No. of Contact Cases	F
mOPV1	11.13[a]	3	3	0	0
mOPV2	10.64[a]	7	2	5	0
mOPV3	10.81[a]	35	27	8	3
bOPV	0.39[b]	1	1	0	2
tOPV	1.70[b]	1	1	0	0

Abbreviations: bOPV, bivalent oral poliovirus vaccine types 1+ 3; mOPV1, monovalent oral poliovirus vaccine type 1; mOPV2, monovalent oral poliovirus vaccine type 2; mOPV3, monovalent oral poliovirus vaccine type 3; tOPV, trivalent oral poliovirus vaccine.

a As per information provided in reference 7.

b Source was reference 28.

Table 2.

Reported Risk of Vaccine-Associated Paralytic Poliomyelitis by Country, 1960–2002

Author(s) (Reference), Country or Region	Year(s)	Vaccine Type	Vaccine Doses (million)	Total N
Dömök, 1984 (7), Hungary	1961–1982	mOPV 1	11.1	3

		mOPV2	10.6	7
		mOPV3	10.8	35
		bOPV, tOPV		2
Driesel et al., 1995 (8), Germany	1960–1990	mOPV 1,2	33.33	10
		mOPV3	16.67	18
Schonberger et al., 1996 (9), United States	1961–1972	mOPV1	117.8	20
		mOPV2	111.0	4
		mOPV3	112.5	48
		tOPV	210.4	47
Nkowane et al., 1987 (11), United States	1973–1984	tOPV	274.1	105
Strebel et al., 1992 (12), United States	1980–1989	tOPV	203.5	80
World Health Organization, 1976 (13), country 4[a]	1970–1979	mOPV	14.8	18
World Health Organization, 1976 (13), country 7[a]		mOPV, tOPV	NA	164
World Health Organization, 1976 (13), country 8[a]		mOPV, tOPV	NA	165
Esteves, 1988 (14), country 4[a]	1980–1984	mOPV	4.0	2
Esteves, 1988 (14), country 7[a]		tOPV	19.5	10
Esteves, 1988 (14), country 8[a]		tOPV	8.4	305
Más Lago, 1999 (15), Cuba	1963–1996	tOPV	64	18
Andrus et al., 1995 (16), Americas	1989–1991	tOPV	431.6	205

Kohler et al., 2002 (17), India	1999	tOPV	733.4	181
Strebel et al., 1995 (18), Romania	1984–1992	tOPV	17	93
Ivanova et al., 2001 (19), Russia	1998–1999	tOPV	48	18
Samoilovich et al., 2003 (20), Belarus	1996–2002	tOPV	8.2	11

Abbreviations: mOPV1, monovalent oral poliovirus vaccine type 1; mOPV2, monovalent oral poliovirus vaccine type 2; mOPV3, monovalent oral poliovirus vaccine type 3; NA, data not available or not reported; tOPV, trivalent oral poliovirus vaccine.

a Countries were intentionally not identified in these references; the same numbers were used for the same countries in the 2 studies. Country 4 used mOPV in the order mOPV1, mOPV3, mOPV2 during 1970–1984. Country 7 used mOPV types 1, 2, and 3 during 1970–1973 and tOPV during 1974–1984. Country 8 used mOPV types 1, 2, and 3 during 1970–1978; type 1 only was used in 1979 because the other types were not available, and tOPV was used from 1980 to 1984.

Therefore, the final VAPP case count was 46, with 32 recipient cases and 14 contact cases (Table 1). Of these, 38 were considered confirmed instances of VAPP based upon isolation of vaccine-like poliovirus in stool samples (33) or demonstration of an increase in neutralizing antibody titers to the same serotype as the received vaccine (4 recipient cases and 1 contact case), and 8 were considered possible VAPP cases. One case with Sabin type 3 virus isolated in stool 84 days after the last mOPV3 round was considered a contact VAPP case despite not strictly following the case definition because that person was part of a cluster in Szabolcs-Szatmar-Bereg County during 1968.

Three cases previously linked to mOPV3 and 1 case linked to mOPV1 in Dömök's report had received bOPV according to the case investigation forms and a previous report published in 1969 (29). Therefore, the number of cases linked to bOPV was 5 instead of 1. All developed paralysis 19–26 days after receiving bOPV, and their ages were 5–11 months. Three of 4 patients for whom information was available were hospitalized with fever (1 with possible meningitis), and 1 had received intramuscular

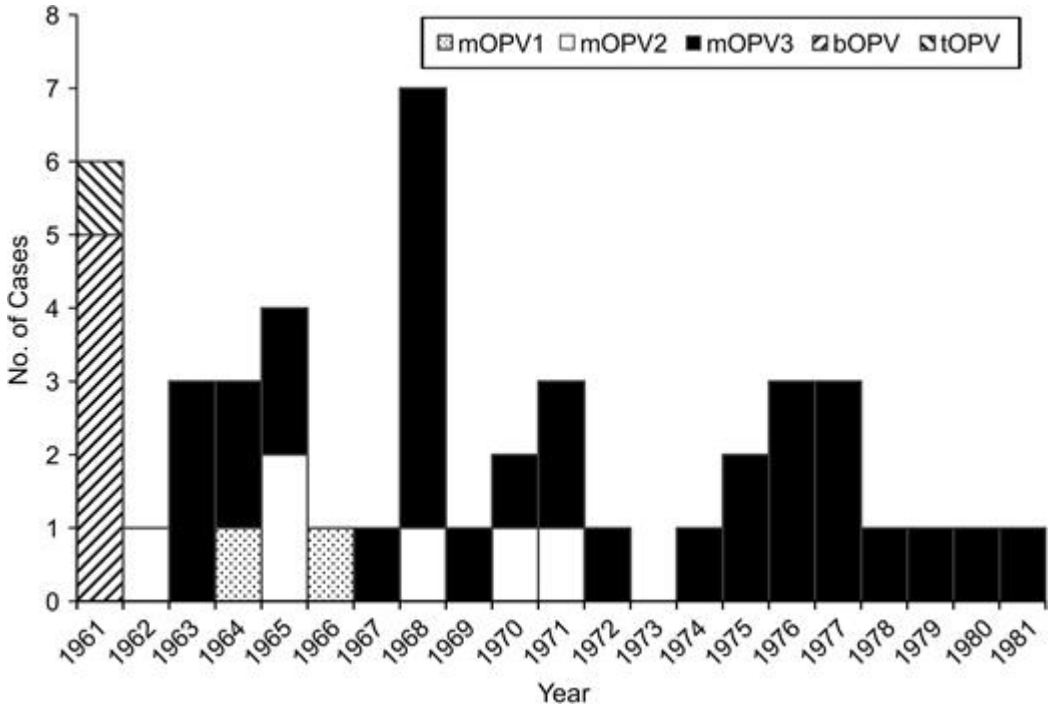
injections (information was not available for the others). Type 3 virus was isolated in 3 cases and type 1 in 1 case. No virus was isolated in 1 case classified as possible VAPP, a 7-month-old boy who had received bOPV 21 days before developing paralysis of his left leg and who had neutralizing antibodies to types 1 and 3 but in whom changes in titers were not followed.

Of the 11 paralytic cases for which VAPP was excluded, 2 had WPV type 1 (WPV1) isolated in stools, 6 were epidemiologically linked to a WPV1 outbreak in 1966–1967, 1 had adenovirus type 6 isolated in stools and cerebrospinal fluid, 1 was negative for virus isolation and had no link to vaccine, and 1 had transient paralysis.

Epidemiologic characteristics of VAPP cases in Hungary, 1961–1981

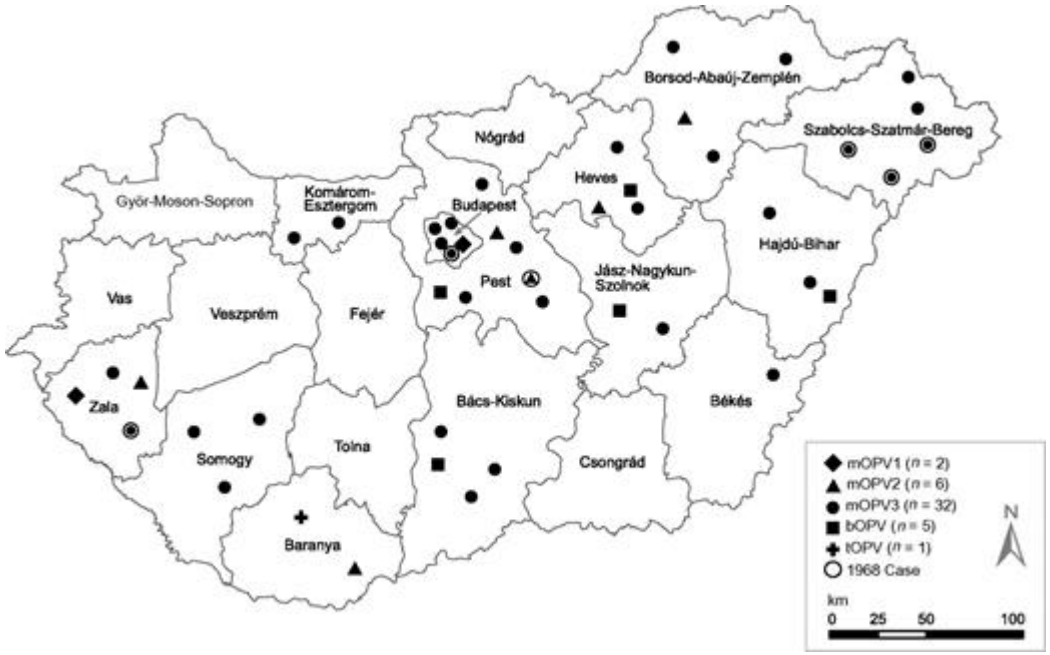
Using the revised classification and including both confirmed and possible cases, we found the risk of VAPP to be 2.96 cases per million doses for mOPV3 and 12.82 cases per million doses for bOPV compared with 3.24 cases per million doses and 2.56 cases per million doses reported previously (Table 1). During the 20-year period, 0–3 VAPP cases were reported annually, except in 1961 (6 cases) and 1968 (7 cases) (Figure 1). The cases reported in 1961 were associated with bOPV administration. During 1968, a cluster of 6 cases of type 3 VAPP with onset dates of April 4, April 6, April 24, May 4, May 30, and June 19 were reported; of these, 2 patients were institutionalized children and 3 were reported from Szabolcs-Szatmar-Bereg County (Figure 2). Although 5 of these cases could be temporally linked to a campaign with Sabin mOPV3 (March 22–24), they also coincided with an outbreak of poliomyelitis in Poland associated with distribution of the experimental USOL-D-bac type 3 mOPV in clinical trials conducted 4–6 months before (31, 32, 33). In Hungary, USOL-D-bac vaccine was administered during October 1967 to fewer than 50 institutionalized children within Budapest, and no adverse events were identified during the 2- to 3-month follow-up (34). However, we could not document a link between these 1968 VAPP cases and the USOL-D-bac vaccine trials, and archived isolates were not available for retesting.

Figure 1.



Number of cases of vaccine-associated paralytic poliomyelitis by year and vaccine type, Hungary, 1961–1981. bOPV, bivalent oral poliovirus vaccine types 1 + 3; mOPV1, monovalent oral poliovirus vaccine type 1; mOPV2, monovalent oral poliovirus vaccine type 2; mOPV3, monovalent oral poliovirus vaccine type 3; tOPV, trivalent oral poliovirus vaccine.

Figure 2.



Geographic distribution of cases of vaccine-associated paralytic poliomyelitis by vaccine type, Hungary 1961–1981. bOPV, bivalent oral poliovirus vaccine types 1 + 3; mOPV1, monovalent oral poliovirus vaccine type 1; mOPV2, monovalent oral poliovirus vaccine type 2; mOPV3, monovalent oral poliovirus vaccine type 3; tOPV, trivalent oral poliovirus vaccine.

Risk factors for VAPP in Hungary

All but 1 of 32 recipient VAPP cases occurred after the patient received the first OPV dose (Table 3). Ten of 14 contact VAPP case-patients occurred after exposure to the first dose; 8 case-patients had received no OPV, and 2 had type 3 isolated in stools but had received only mOPV1. A sibling, day-care playmate, or neighbor vaccine recipient was identified as the source for 10 contact VAPP cases; a national immunization campaign was the only identified source for the remaining 4 patients.

Table 3.

Characteristics of Patients With Vaccine-Associated Paralytic Poliomyelitis Diagnosed During 1961–1981 in Hungary

Characteristic	VAPP					
	Vaccine Recipients (*n* = 32)			Contacts (*n* = 14		
	No.	%	Median (Range)	No.	%	M
Age, months			7.5 (5–25)			4
Male/total, % male	19/32	59		6/14	43	
Doses of homotypic OPVa						
0	0			10	71	
1	31	97		3	21	
2	1	4		1	7	
Days of OPV paralysis			20 (12–40)			4
Siblings <5 years of age	9/21	43		3/11	27	
Institutionalized (orphanage, day care)	7/27	26		3/13	23	
Acute non-polio-related illness 0–30 days before paralysis onset	21/28	75		13/14	93	
Hospitalization 0–30 days before paralysis onset	16/30	53		5/13	38	
Any intramuscular injection 0–30 days before paralysis onset	14/19	74		11/12	92	

Abbreviations: OPV, trivalent oral poliovirus vaccine; VAPP, vaccine-associated paralytic polio.

a Monovalent OPV of the same type as the vaccine virus was isolated in stools or trivalent OPV.

None of the children with VAPP had clinical histories compatible with primary immunodeficiency. Information on administration of intramuscular injections was not routinely recorded on the VAPP case investigation forms, and it was available for 31 of the 46 case-patients; of these, 25 (81%) had received at least 1 injection within 30 days before paralysis onset (Table 3). Of 12 cases with a known number of injections received, 5 (41%) had received 10 or more injections before paralysis. Of the 16 children with missing information on injections, 10 had been hospitalized before paralysis for illnesses or symptoms for which they probably received parenteral antimicrobial treatment: lip surgery (1), meningitis (1), pneumonia or acute respiratory infections (5), and fever (3).

Molecular analysis of archived poliovirus isolates

We reanalyzed 18 type 3 isolates from 15 patients with VAPP (from 1960 to 1967) with diagnostic PCR and sequencing; all were type 3 Sabin-related, in agreement with the report of Dömök (7), based on serodifferentiation and phenotypic marker tests. However, only 5 isolates were from 4 VAPP cases reported during 1961–1981 (3 cases from 1961; 1 case from 1967). The other isolates were from 11 patients reported on laboratory forms to have had paralytic poliomyelitis during 1960 (8 cases) (30) or 1962 (3 cases), for whom epidemiologic or clinical data were insufficient to confirm whether they were VAPP cases and the type of vaccine to which they had been exposed. Molecular analysis also confirmed the identification by Dömök of 5 archived WPV isolates.

As reported previously (41), all isolates had the U472C mutation within the 5′-untranslated region associated with reversion to neurovirulence (42, 43), but none had more than 1% (≥10 nucleotide substitutions) viral protein 1 sequence divergence indicative of prolonged replication or circulation (44).

VAPP risk in other countries using mOPV

Simultaneous use of mOPV3 and tOPV in the same country, which would allow comparisons of VAPP risk between the different vaccines, occurred in only a few countries. In the United States, mOPVs

accounted for 92% of the polio vaccines distributed during 1961–1964, and tOPV accounted for 89% of the polio vaccines distributed during 1965–1972 (9). When we combined cases reported during both periods, we found that the risk of VAPP with mOPV3 was about 2-fold higher than the risk with tOPV (Table 2). Some countries (e.g., country 7 in Table 2) noticed a reduction in the number of cases when they switched from mOPV to tOPV, but factors such as vaccine distribution in routine immunization instead of in campaigns or variations in surveillance could also have contributed (14, 35). VAPP occurrence also decreased in country 4 between 1970–1973 and 1980–1984 despite continuous use of mOPV, and country 8 had a high number of VAPP cases during 1980–1984 (36.31 cases per million doses) despite switching from mOPV to tOPV in 1980.

Campaigns with mOPVs were conducted in the former USSR only in 1959 and 1960, and some who received vaccines during those campaigns had received IPV from 1958 to 1959. Some republics administered mOPV with the schedule mOPV1, mOPV3, mOPV2, and others provided mOPV1 followed by bOPV2 + 3 and then tOPV during the same period. A small incidence of adverse events related to OPV (<0.3 per million doses) were reported in scientific literature (24, 45) and a few possible VAPP cases were mentioned in internal reports, but many were not investigated virologically (25).

DISCUSSION

The present review of archived vaccine records, case investigation forms, and isolates from cases reported for suspected poliomyelitis in Hungary during 1961–1981 confirmed that 90% of the cases reported by Dömök as VAPP linked to mOPV3 had been correctly classified (7). In 3 cases originally linked to mOPV3 and 1 case linked to mOPV1, the case-patient had received bOPV before developing paralysis. Therefore, the risk of VAPP after mOPV3 in Hungary (2.96 per million doses administered) was slightly lower than previously reported (3.24 cases per million doses administered) (7), but still 7–8 times higher than the risks reported in the United States (0.43 per million doses) and East Germany (1.08 per million doses administered) (8, 9).

Our reanalysis of 23 archived isolates from Hungary by PCR and viral protein 1 sequencing confirmed the original laboratory results reported by Dömök (7). Therefore, the high number of VAPP cases observed in Hungary was not attributable to incorrect inclusion of WPV cases. Other factors appear to have contributed to higher VAPP reporting rates in Hungary compared with other countries. First, Hungary had a sensitive polio surveillance system. Incentives were provided to parents and health-care providers for reporting and referring cases. The centralized health-care system facilitated referral of suspected cases to trained public health officials and clinicians, and samples were sent to a central laboratory staffed with experienced virologists using the most advanced techniques then available. Second, those who received vaccines in Hungary had risk factors for VAPP that were not always present in other populations. Generally, risk of VAPP is higher in persons with B-cell immunodeficiency disorders, first-dose OPV recipients, and individuals who have had intramuscular injections within 30 days of exposure to OPV (5, 12, 18, 20, 46). Receiving IPV before OPV and the presence of high levels of maternal antibodies appear to protect against VAPP (17, 46). When mOPVs were used in the United States or the former USSR, some of those vaccinated had previously received IPV (9), and a proportion could also have had natural immunity from exposure to WPV. In Hungary, between 1961 and 1981, immunization campaigns were carried out once a year in children less than 3 years of age who were highly susceptible because they had not received IPV previously, might have lost maternal antibodies at the time of the first vaccine dose, and had not been exposed to poliovirus because of the rapid elimination of WPV and the absence of routine vaccination with OPV. We could not confirm intramuscular injections as a risk factor in this investigation because of the lack of a control group. However, the high proportion of VAPP cases who received injections within 30 days of polio vaccination (80% of 50 cases with known information) and/or were hospitalized for non-polio-related illnesses before paralysis onset (49% of 43 cases) suggests that injections might also have contributed to the higher occurrence of VAPP in Hungary. The high VAPP risk reported in Romania (5.42 cases per million doses of tOPV) was unexplained for years until it was linked in 1994 to frequent use of intramuscular injections (13, 14, 18).

The present investigation showed that the highest risk of VAPP in Hungary was associated with the use of bOPV. We identified 5 cases of VAPP linked with distribution of 390,000 bOPV doses during

1961, which indicates a VAPP risk of more than 12 cases per million doses distributed. These data, reported by Dömök in 1969 (29) but not in 1984 (7), are the only sources of information about an association between VAPP and bOPV, and they were observed after provision of a very small number of doses in a single round. During 2 field trials with bOPV conducted in 1959 in Estonia (171,000 doses) and Lithuania (39,700 doses), no VAPP cases were linked to bOPV, but administration of a tOPV round after the bOPV round limited the ability to associate VAPP cases with a specific vaccine (47).

The reasons for the apparently higher risk of VAPP with bOPV observed in Hungary are not known. The interactions of Sabin strains during intestinal replication are incompletely understood and involve a complex dynamic of interference and evolution by successive nucleotide substitutions and recombination, which may result in reversion to neurovirulence but only rarely causes paralytic disease (48, 49).

There is no evidence that the high risk of VAPP associated with mOPV3 and bOPV observed in Hungary will be the same in countries with endemic circulation of WPV1 and WPV3. The risk of VAPP associated with tOPV administration in India during 1999 was 1 case per 4.1–4.6 million doses (17), lower than that observed in the United States and other developed countries (Table 2). Exposure to multiple OPV doses, high maternal antibodies when the first doses are received, and lower survival of children with immunodeficiencies could explain lower VAPP risk in India and other developing countries (16, 17). VAPP risk in Hungary may also have been overestimated in the present report because we included 9 cases that did not strictly meet the VAPP case definition and we could not exclude cases possibly linked to USOL-D-bac vaccine because isolates were not available.

The risk of VAPP in endemic countries is also offset by the much higher risks of polio from circulating WPV (approximately 1 case per 200 infections for WPV1 and approximately 1 case per 1,000 infections for WPV3) (50, 51). bOPV confers immunity against WPV1 and WPV3 more efficiently than does tOPV (6), and its use in northern India and northern Nigeria since January 2010 has reduced the number of polio cases by more than 95% during the first half of 2010 compared with 2009 (52, 53). Therefore, the risk of VAPP with bOPV or mOPV3 should be considered in the context of risk of paralysis from WPV and the potential existence of risk factors in the vaccinated populations. Tailoring the

administration of OPV vaccines to the epidemiologic conditions and surveillance for VAPP would allow assessing and optimizing the risk-benefit of these vaccines to achieve global polio eradication.

Abbreviations

bOPV bivalent oral poliovirus vaccine types 1 + 3

IPV inactivated poliovirus vaccine

mOPV monovalent oral poliovirus vaccine

PCR polymerase chain reaction

tOPV trivalent oral poliovirus vaccine

USSR Union of Soviet Socialist Republics

VAPP vaccine-associated paralytic poliomyelitis

WPV wild poliovirus

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