NEUROLOGIC COMPLICATIONS ASSOCIATED WITH ORAL POLIOVIRUS VACCINE AND GENOMIC VARIABILITY OF THE VACCINE STRAINS AFTER MULTIPLICATION IN HUMANS

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Summary. – The oral poliovirus vaccine (OPV) has been effectively used in the reduction and control of poliomyelitis cases on the planet. Despite several advantages of using the attenuated OPV strains, the rare occurrence of vaccine-associated paralytic poliomyelitis (VAPP) cases in vaccine recipients and their susceptible contacts is a disadvantage. Molecular biology studies of polioviruses isolated from stool and central nervous systém (CNS) of patients with VAPP have confirmed the vaccine origin of the isolates and demonstrated genomic modifications known or suspected to increase the neurovirulence. Similar genomic modifications have also been identified in OPV-derived strains isolated from healthy vaccinees and healthy contacts, suggesting that host factors are also involved in the establishment of poliomyelitis. Other neurologic complications such as meningitis, encephalitis, convulsions, transverse myelitis and Guillain-Barré syndrome have also been rarely associated with the use of this vaccine. The characterization of polioviruses isolated from such cases has demonstrated their OPV origin.

Key words: oral poliovirus vaccine; vaccine-associated cases; mutation; recombination

Introduction

Polioviruses (*Enterovirus* genus, *Picornaviridae* family) are the etiologic agents of poliomyelitis (Almond, 1987; Melnick 1996a,b), an acute disease of CNS of humans that may result in paralysis. These viruses multiplicate in the digestive tract and may induce paralysis provided the viral replication destroys a sufficiently large number of motor neurons in regions of CNS that control specific muscles. Poliovirus consists of an icosahedral particle composed of 60 copies of each of the four capsid proteins VP1, VP2, VP3 and VP4, surrounding the viral genome, and a single-stranded RNA of positive polarity of approximately 7500 nucleotides (nt) (Wimmet *et al.*, 1993; Wien *et al.*, 1996). The RNA molecule contains a 5'-non-coding region (NCR) of about 740 nt with a terminally linked protein VPg, a single open reading frame (ORF) coding for the structural and non-structural proteins, and a 3'-NCR of about 70 nt followed by a poly (A)-tract (Wimmer *et al.*, 1993). On the basis of antigenicity of the capsid, polioviruses are classified into three distinct serotypes designated 1, 2 and 3.

An international campaign under the leadership of the Worl Health Organization is underway to eradicate poliomyelitis from the planet by the year 2000 (Wright *et al.*, 1991; Wyatt, 1998). The number of poliomyelitis cases caused by wild poliovirus infections has been dramatically reduced by the extensive use of two available vaccines (Melnick, 1996c), the inacivated poliovirus vaccine (IPV) developed by Jonas Salk, and OPV developed by Albert Sabin. Mass immunization campaigns with OPV, the most widely used vaccine, was a major factor inluencing the

Abbreviations: aa = amino acid; CNS = central nervous system; CSF = cerebrospinal fluid; NCR = non-coding region; nt = nucleotide; IPV = inactivated poliovirus vaccine; OPV = oral poliovirus vaccine; ORF = open reading frame; PCR = polymerase chain reaction; VAPP = vaccine-associated paralytic poliomyelitis

success of eradication of wild indigenous poliovirus in the Americas (de-Quadros *et al.*, 1997). OPV has been more widely used because of its easier administration by the oral route, much lower cost – an important advantage for the developing world, ability to induce not only serum antibodies but also intestinal resistance, and the rapidity of development of a long-lasting immunity (Melnick, 1996a,c). The intestinal immunity induced by OPV has an important role in breaking the chain of circulation of wild polioviruses. All the three live attenuated poliovirus strains (Sabin 1, 2 and 3) that compose OPV were derived from wild type isolates by serial passaging in monkey tissue *in vitro* and *in vivo* under a variety of conditions, which differed for each of the three serotypes (Almond, 1987). These strains lost their neurovirulence but not the capacity to multiply in the gut, and induce a type-specific protection against subsequent infection with a neurovirulent poliovirus.

Surveillance of wild poliovirus circulation (Pinheiro *et al.*, 1997; Hull and Duwdle, 1997), through isolation, serotyping and intratypic differentiation of the strains as wild or vaccine-related, is essential for the global eradication of poliomyelitis. Antigenic marker tests (van Wezel *et al.*, 1979; van-der-Avoort *et al.*, 1995) and molecular biology techniques (Balanant *et al.*, 1991; Da-Silva *et al.*, 1991; Yang *et al.*, 1991; Schweiger *et al.*, 1994; Takeda *et al.*, 1994; De *et al.*, 1995; van-der-Avoort *et al.*, 1995; Chezzi and Schoub, 1996) have been important in the identification and intratypic characterization of poliovirus strains isolated in cell cultures, and useful in epidemiological studies (Kew *et al.*, 1995; Mulders, 1997). Despite the importance of live attenuated OPV strains in the reduction of poliomyelitis cases associated with wild strains and in the circulation of these strains on the planet, a disadvantage of this vaccine is the rare occurrence of VAPP cases (Balduzzi and Glasgow, 1967; Swanson *et al.*, 1967; Stolley *et al.*, 1968; Cesario *et al.*, 1969; WHO, 1976, 1981, 1982; Basílico and Bernat, 1978; Yoneyama *et al.*, 1981; Quast *et al.*, 1993; Andrus *et al.*, 1995; Hof and Dörries, 1995). Such cases have been observed in several countries in vaccine recipients and in contacts or possible contacts of vaccine recipients (Tagaya *et al.*, 1973; Collingham *et al.*, 1978; Dömök, 1984; Kim-Farley *et al.*, 1984; Bernal *et al.*, 1987; Maass and Quast, 1987; Novello *et al.*, 1987; Frantzidou-Adamopoulou, 1992; Strebel *et al.*, 1994; Fillips *et al.*, 1994; CDCa, 1997; Fescharek *et al.*, 1997). The intratypic characterization tests used to differentiate wild from OPV-related strains have demonstrated the vaccine origin of polioviruses isolated from VAPP cases (Kew *et al.*, 1981; Minor, 1982; Mertens *et al.*, 1983; Cruickshank *et al.*, 1984; Bergeisen *et al.*, 1986; Arlazoroff *et al.*, 1987; Querfurth and Swanson, 1990; Beausoleil *et al.*, 1994; Friedrich *et al.*, 1996a). Several studies have suggested that the attenuated OPV strains may occasionally also cause other neurologic complications (Kinnunen *et al.*, 1989, 1998; Stratton *et al.*, 1994; Ehrengut, 1990, 1998; Friedrich 1997). The techniques used in poliovirus surveillance have also enabled to isolate and characterize polioviruses from cases of these neurological complications as vaccine-related (Friedrich *et al.*, 1995d, 1996c; Ehrengut, 1996).

Poliomyelitis associated with OPV

Despite the benefits of using OPV, a rare complication related to its administration is the appearance of VAPP cases (Gelfand, 1963; Henderson *et al.*, 1964; Morse *et al*, 1966; Kleiman *et al.*, 1987; Tulshinsky and Birkhead, 1993; Mashikian and Stollerman, 1994; Sullivan *et al.*, 1995; Weibel and Benor, 1996; Tate and Johnson, 1997; Mauel *et al.*, 1998). VAPP cases observed in different countries in vaccinees and their contacts have been mainly associated with the type 2 and 3 strains, and less frequently with the type 1 strain (Hopkins *et al.*, 1969; Takatsu *et al.*, 1973; Schonberger *et al.*, 1976; Smith and Wherry, 1978; Moore *et al.*, 1982; Nkowane *et al.*, 1987; Joce *et al.*, 1992; Strebel *et al.*, 1992; Prevots *et al.*, 1994). In these and other studies (Riker *et al.*, 1971; Minor, 1981; Bateman *et al.*, 1987; Furione *et al.*, 1993; Mermel *et al.*, 1993; Groom *et al.*, 1994; David and Doyle, 1997) OPV-related poliovirus strains have been isolated from VAPP cases from various organs/materials such as nasopharynx, throat, stool, urine, blood, basal ganglia, CSF, medulla, spinal cord and brain.

Genomic modifications of OPV strains after multiplication in humans

Although there are many advantages in using live attenuated viruses to produce conditions resembling natural infections, a general concern with live virus vaccines is the potential occurrence of genomic modifications and increase in the virulence of the viruses during multiplication in humans. Molecular biology techniques such as oligonucleotide fingerprinting, molecular hybridization, polymerase chain reaction (PCR) and nucleotide sequencing have confirmed that polioviruses isolated from stool, nasopharynx, throat, blood and CNS of VAPP cases were derived from the Sabin vaccine strains, and have demonstrated genomic modifications in these strains such as reverse mutations in attenuation determinants, suppressor mutations, mutations in antigenic sites, and genomic recombination (Fiore *et al.*, 1987; Minor *et al.*, 1989; Macadam *et al.*, 1989; Lipskaya *et al.*, 1991; Furione *et al.*, 1993; Georgescu *et al.*, 1994, 1995a,b; Friedrich 1996b). Vaccine-derived poliovirus with nucleotide substitutions can be rapidly isolated after passage in humans, probably selected by the pressure of factors such as temperature, target host cells, neutralizing antibodies, or other unknown factors (Furione *et al.*, 1993). The possibility of recombination

between the vaccine strains is favored by administration of trivalent OPV, which provides optimal conditions for multiple infection of human intestinal target cells. It has been suggested that not just mutations, but also genomic recombination could increase the neurovirulence of the Sabin vaccine strains and/or be of advantage for virus replication in humans (Lipskaya *et al.*, 1991; Furione *et al.*, 1993; Georgescu *et al.*, 1994, 1995b; Friedrich *et al.*, 1996b; Li *et al.*, 1996). Both vaccine/vaccine and vaccine/non-vaccine recombinants were detected in these studies. The selection of variants with increased neurovirulence might constitute a real problem for the vaccine safety. Molecular studies of the three Sabin poliovirus vaccine strains and comparison of these strains with the wild parental or vaccine-derived neurovirulent strains enabled to define some critical nucleotide sites of the viral genome involved in the attenuated phenotype of the vaccine strains (Macadam *et al.*, 1991, 1993). Nucleotide substitutions at these sites may account for reversion towards neurovirulence of theses viruses upon multiplication in humans. The understanding of the molecular basis of the attenuated phenotype of the vaccine strains and mechanisms of reversion to neurovirulence may allow rational improvement of vaccines and production methods, provide alternative models for vaccine safety tests on transgenic mice and/or molecular approaches (WHO, 1997; Wood and Macadam, 1997; Dragunsky *et al.*, 1997; Levenbook and Nomura, 1997), and avoid costly safety testing of vaccine pools in primates.

Genomic characterization of type 1 vaccine-derived polioviruses isolated from VAPP cases and healthy vaccinees

As the P1/Sabin strain has a greater number of attenuating mutations it has been proposed as an example explaining the higher degree of safety of his strain in comparison to the P2/Sabin and P3/Sabin vaccine strains. Reverse mutations in attenuation determinants of the P1/Sabin strain have been detected and found associated with an increase of neurovirulence of P1/Sabin-derived polioviruses isolated from stool and CNS of VAPP cases. A reverse mutation at nt 480 or a supressor mutation at nt 525, which are important for reversion to neurovirulence of the P1/Sabin strain, have been detected in almost all P1/Sabin-derived strains isolated from VAPP cases (Otelea *et al.*, 1993; Guillot *et al.*, 1994; Georgescu *et al.*, 1994; Friedrich *et al.*, 1996a; Li *et al.*, 1996; Georgescu *et al.*, 1997a). Several reverse mutations associated with the increase in neurovirulence such as those at nt 189 (5'-NCR), 935 (VP4), 2438 (VP3), 2749 (VP1), 2795 (VP1), 6203 (3Dpol), and 7441 (3'-NCR), and also additional reverse and other new mutations have also been detected in polioviruses isolated from VAPP cases (Otelea *et al.*, 1993; Li *et al.*, 1996; Georgescu *et al.*, 1997a). Two P1/Sabin-derived poliovirus strains with a recombinant genome were isolated from VAPP cases (Li *et al.*, 1996). Analysis of the 5'-NCR of P1/Sabin-derived polioviruses isolated from the stool of healthy vaccinees has also detected mutation at nt 480 or 525 (Minor and Dunn, 1988; Dunn *et al.*, 1990; Muzychenko *et al.*, 1991; Ogra *et al.*, 1991; Abraham *et al.*, 1993; Guillot *et al.*, 1994; Mallet *et al.*, 1997).

Genomic characterization of type 2 vaccine-derived polioviruses isolated from VAPP cases, healthy contacts and healthy vaccinees

Reverse mutations in attenuation determinants of the P2/Sabin strain have been detected and found associated with an increase in neurovirulence of P2/Sabin-derived polioviruses isolated from VAPP cases. Mutations at nt 481 in the 5'-NCR and in the codon of aa 143 of the capsid protein VP1, which are important for reversion to neurovirulence of the P2/Sabin strain, were observed in almost all of the P2/Sabin-derived strains isolated from the stool and CNS of patients with VAPP (Pollard *et al.*, 1989; Equestre *et al.*, 1991; Macadam *et al.*, 1991, 1993; Muzychenko *et al.*, 1991; Friedrich *et al.*, 1995a; Guillot *et al.*, 1994; Georgescu *et al.*, 1994, 1995b, 1997b), while a mutation at nt 398 in the 5'-NCR was also frequently observed in P2/Sabin-derived strains isolated from patients with VAPP (Macadam *et al.*, 1991; Muzychenko *et al.*, 1991; Friedrich *et al.*, 1995a; Georgescu *et al.*, 1997b). Other mutations have also been detected in the genome of P2/Sabin-derived strains isolated from VAPP cases (Pollard *et al.*, 1989; Equestre *et al.*, 1991; Macadam *et al.*, 1991; Friedrich *et al.*, 1995a). P2/Sabin-derived polioviruses with a recombinant genome have been frequently isolated from patients with VAPP (Lipskaya *et al.*, 1991; Furione *et al.*, 1993; Georgescu *et al.*, 1994, 1995b, 1997b). In these studies, P2/Sabin-derived polioviruses with reverse mutations at nt 398, 481 (both in the 5'-NCR) and aa 143 (in the VP1), and with a recombinant genome were also isolated from the stool of healthy contacts of VAPP cases (Friedrich *et al.*, 1995a, 1996b). The mutations at nt 481 and aa 143 (VP1) have also been observed in strains isolated from the stool of healthy vaccinees (Minor and Dunn, 1988; Dunn *et al.*, 1990; Macadam *et al.*, 1991, 1993; Ogra *et al.*, 1991; Abraham *et al.*, 1993; Guillot *et al.*, 1994; Mallet *et al.*, 1997). Mutations have also been detected in antigenic sites of the capsid proteins of P2/Sabin-derived strains isolated from VAPP cases (Fiore *et al.*, 1987); they could act as an escape mechanism from immune response.

Genomic characterization of type 3 vaccine-derived polioviruses isolated from VAPP cases and healthy vaccinees

Reverse mutations in attenuation determinants of the P3/Sabin strain have also been observed and found

associated with an increase in neurovirulence of P3/Sabin-derived polioviruses isolated from VAPP cases. A mutation at nt 472 in 5'-NCR, important for reversion to neurovirulence, was observed in all P3/Sabin-derived strains isolated from stool and CNS of patients with VAPP (Cann *et al.*, 1984; Evans *et al.*, 1985; Macadam *et al.*, 1989; Georgescu *et al.*, 1994; Friedrich *et al.*, 1995b; Driesel *et al.*, 1995; Old *et al.*, 1997). A reverse mutation in the codon of aa 91 of the capsid protein VP3, important for reversion of the VP3/Sabin strain to neurovirulence, or suppressor mutations have also been observed in P3/Sabin-derived polioviruses isolated from stool and CNS of patients with VAPP (Macadam *et al.*, 1989; Minor *et al.*, 1989; Driesel *et al.*, 1995; Georgescu *et al.*, 1994). Among the possible supressor mutations, a mutation in the codon of aa 54 of VP1 has been frequently observed in P3/Sabin-derived isolates from VAPP cases (Macadam *et al.*, 1989; Minor *et al.*, 1989). A mutation at nt 143 of the 5'-NCR was also found in several strains isolated from VAPP cases (Driesel *et al.*, 1995). Other mutations have also been detected in the genome of a P3/Sabin-derived strain isolated from VAPP case (Cann *et al.*, 1984). Mutations at nt 472 and aa 91 (VP3) or suppressor mutations have also been observed in strains isolated from the stool of healthy vaccinees (Evans *et al.*, 1985; Minor and Dunn, 1988; Macadam *et al.*, 1989; Dunn *et al.*, 1990; Ogra *et al.*, 1991; Tatem *et al.*, 1991; Contreras *et al.*, 1992; Abraham *et al.*, 1993; Mallet *et al.*, 1997). P3/Sabin-derived strains with a recombinant genome have also been isolated from VAPP cases and healthy vaccinees (Minor *et al.*, 1986; Cammack *et al.*, 1988; Macadam *et al.*, 1989; Tatem *et al.*, 1991; Furione *et al.*, 1993; Georgescu *et al.*, 1994; Driesel *et al.*, 1995). These studies have demonstrated that OPV-derived polioviruses with a genomic modifications and increase in neurovirulence are observed after administration and multiplication of OPV strains in humans.

Possible factors involved in the establishment of poliomyelitis

Although genomic modifications known or suspected to increase neurovirulence have been observed in strains isolated from VAPP cases, the observation of similar genomic modifications in strains isolated from healthy contacts (Friedrich *et al.*, 1995a, 1996b) of VAPP cases and healthy vaccinees (Macadam *et al.*, 1989, 1991, 1993) has supported the view that host factors are also involved in the establishment of poliomyelitis. In certain patients, a particular biochemical characteristic of host factor(s) involved in the replication of the virus in cells could increase the multiplication of the virus. Immune deficiency may also represent a factor involved in the establishment of poliomyelitis (Zuckerman *et al.*, 1994). VAPP has been observed in vaccine recipients and contacts of vaccine-recipients with immune abnormalities (Wyatt, 1973; Wright *et al.*, 1977; Abo *et al.*, 1979; Sakano *et al.*, 1980; Hara *et al.*, 1981; Gonzales and Cordero, 1988; Sutter and Prevots, 1994; Sutter *et al.*, 1997). Although non-paralytic poliovirus infections have been observed in some patients with immunodeficiency (Lopez *et al.*, 1974), vaccine-related poliovirus strains have been isolated from patients with VAPP and immunodeficiency from different organs (materials) such as nasopharyn, throat, stool and CNS (Chang *et al.*, 1966; Feigin *et al.*, 1971; Riker *et al.*, 1971; Saulsbury *et al.*, 1975; Yoneyama *et al.*, 1982; Gaebler *et al.*, 1986; Asindi *et al.*, 1988; Pohl *et al.*, 1992; CDC, 1997). Heritable immunodeficiences, immunodeficiences caused by protein-calorie malnutrition and/or deficiency in vitamin A, medication considered immunosuppressive (e.g., steroid use, chemotherapy of cancer), and HIV infection may be involved in the establishment of poliomyelitis in certain cases (Lederman and Winkelstein, 1985; Mathias and Routley, 1985; Gross *et al.*, 1987; Sutter *et al.*, 1993; Arya, 1994; Sutter and Prevots, 1994; Arya, 1996). The first reported VAPP case with the isolation of a vaccine-related poliovirus strain from an HIV-infected child occurred in Romania (Ion-Nedelcu *et al.*, 1994). It has been suggested that the cumulative effect of HIV and/or nutritional lymphocytic abnormalities could produce a significant rise in VAPP cases in developing countries (Arya, 1994). Intramuscular injections (Wyatt, 1986, 1994; Dalakas *et al.*, 1995; Izurieta *et al.*, 1995; Ross, 1995; Strebel *et al.*, 1995a,b; Weinberg and Rustioni, 1995; Ehrengut, 1997) given shortly after exposure to OPV through vaccine or contact with a recent vaccinee might also represent a risk factor for VAPP cases. However, other host factors and pathological conditions could also be involved.

Other neurological complications associated with OPV

OPV has also rarely been associated with other neurological complications. The reported cases include: headache, vomiting and fever (Rantala *et al.*, 1989), convulsions (Ehrengut and Ehrengut-Lange, 1979; Ehrengut 1980, 1981, 1990), meningitis (Pohle *et al.*, 1971; Gutierrez and Abzug, 1990), encephalitis (Pohle *et al.*, 1971; Yeung *et al.*, 1997), multiple organ dysfunction (Rasch *et al.*, 1986), near miss sudden infant death syndrome (Chonmaitree and Lucia, 1986), facial paralysis (Friedrich *et al.*, 1995b,c), transient paralysis (Friedrich *et al.*, 1995a,c), transverse myelitis (Friedrich *et al.*, 1995b,d), Gulillain-Barré syndrome (Wutzler *et al.*, 1984; Uhari *et al.*, 1989; Friedrich *et al.*, 1995b,c, 1996c; Ehrengut, 1996), chronic progressive neurologic disease (Davis *et al.*, 1977),

and fetal damage after maternal poliovirus vaccination (Burton *et al.,* 1984). In many of these cases, poliovirus strains were isolated from the patients. In the reported case of a healthy girl that became ill with long-lasting headache, vomiting and fever but not paralysis after OPV administration (Rantala *et al.,* 1989), a poliovirus type 3 was isolated from the CSF and characterized by nucleotide sequencing as vaccine-derived. In a study (Pohle *et al.,* 1971), in which most of the 14 patients presented meningoencephalitis after immunization campaigns with OPV, type 2 or 3 polioviruses were isolated from the CSF and feces of 11 patients, while in the remaining cases only from feaces or pharyngeal secretions. In two cases of aseptic meningitis associated with OPV administration reported in another study (Gutierez and Abzug, 1990), polioviruses were isolated from the nasopharynx and CSF in one case, and from the rectal swab and CSF in the second case; intratypic characterization of the poliovirus isolated from CSF of the second case classified the virus as vaccine-related. Recently, poliovirus type 1 was also isolated from the nasopharynx, stool and brain of a case of encephalitis associated with OPV (Yeung *et al.,* 1997); intratypic characterization by molecular hybridization and PCR of the poliovirus isolate from the brain confirmed its vaccine origin. Poliovirus type 2 was also isolated from the stool, lung biopsy and CSF of a patient with multiple organ dysfunction associated with OPV (Rasch *et al.,* 1986); oligonucleotide mapping of all the three isolates classified them as vaccine-related. In a case of near miss sudden infant death syndrome (Chonmaitree *et al.,* 1986), 24 hours after the receipt of OPV, poliovirus type 2 was isolated from the rectal swab and CSF; the oligonucleotide fingerprinting characterized the CSF isolate as vaccine-related. In another study, poliovirus type 2 was isolated from the throat and blood of a patient with convulsions after OPV administration (Ehrengut, 1981).

Poliovirus strains have been also isolated from stool samples from several cases of facial paralysis (Friedrich *et al.,* 1995b,c), transient paralysis (Friedrich *et al.,* 1995a,c), transverse myelitis (Friedrich *et al.,* 1995b,d), and Guillain-Barré syndrome (Friedrich *et al.,* 1995c, 1996c). Intratypic characterization using molecular hybridization, PCR and nucleotide sequencing confirmed the vaccine origin of these isolates (Friedrich *et al.,* 1995a,b,c,d, 1996c). The partial nucleotide sequencing of some of these strains also demonstrated mutations known to increase the neurovirulence of the vaccine strains (Friedrich *et al.,* 1995a,b,c). In another reported case, vaccine-related poliovirus type 3 was isolated from the brain of a child with Guillain-Barré syndrome after OPV administration (Ehrengut, 1996). Thus, these studies demonstrated that, on rare occasions, also other neurological complications are associated with the use of the attenuated OPV strains.

Conclusions

The OPV has been effectively used in the control and reduction of poliomyelitis cases associated with wild poliovirus strains. Despite the advantages of using this vaccine in the poliomyelitis eradication program, rare paralytic poliomyelitis cases have been associated with the vaccine strains. Other rare adverse effects have also been associated with the use of OPV. These effects include fever, vomiting, headache, meningitis, encephalitis, convulsions, facial paralysis, transient paralysis, Guillain-Barré syndrome, transverse myelitis, and fetal damage after maternal OPV administration. The study of the adverse effects associated with the OPV strains might contribute to a better knowledge of the possible diseases caused by polioviruses and the mechanisms by which diseases are triggered, which might help to eliminate or reduce these rare adverse effects associated with OPV.

Vaccine-derived poliovirus strains have been isolated from different organs/materials of patients with OPV-associated neurological complications. Molecular biology studies of poliovirus strains isolated from paralytic poliomyelitis cases and more recently from cases of Guillain-Barré syndrome, transverse myelitis, facial paralysis and transient paralysis associated with OPV have confirmed their vaccine origin and have also demonstrated genomic modification of these isolates. Genomic modifications, such as mutation and/or recombination known or suspected to increase neurovirulence, have been observed in strains isolated from VAPP cases, healthy contacts and healthy vaccinees. These findings indicated that host factors are also involved in the establishment of poliomyelitis. As the attenuated OPV strains multiplicate in humans, and vaccine-derived polioviruses with genomic modifications known to increase the neurovirulence are excreted from them, it is important to consider the possibility of persistent infections and transmission and circulation of OPV-derived neurovirulent polioviruses in a non-immune population after the end of the OPV campaign. These studies demonstrated that poliovirus surveillance of both wild and vaccine-derived strains would be important in the final step of the eradication of poliovirus from the planet.

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