World Health Organization
Global Vaccine Safety
Essential Medicines & Health Products
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INFORMATION SHEET
OBSERVED RATE OF VACCINE REACTIONS
POLIO VACCINES

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The Vaccines

Oral poliovirus vaccine (OPV)

Globally many manufacturers produce the trivalent OPV using Sabin vaccine seeds provided by the World Health Organization except for the Pfizer polio Sabin type 3. Most manufacturers grow the viruses in cultures containing monkey kidney cells and continuous cell lines (Vero or diploid cells). POLIO SABIN (oral) vaccine is a magnesium chloride stabilised preparation of live attenuated polio viruses of the Sabin strains type 1 (LS-c, 2ab), type 2 (P712, Ch, 2ab) and type 3 (Leon 12ab). Each dose of OPV contains residual amounts (less than 25 µg) of antibiotics including streptomycin and neomycin. No adjuvants or preservatives are used (Sutter et al., 1999).

Inactivated poliovirus vaccine (IPV)

Like OPV, inactivated poliovirus vaccine contains three poliovirus strains, Mahoney type 1, MEF-1 (Middle East Forces) type 2 and Saukett type 3. The vaccine is administered via the injectable route. The viruses are grown either in Vero cells or human diploid (MRC-5) cells and then concentrated, purified and inactivated with formaldehyde (Plotkin, 1999).

Types of vaccines

Route	Vaccine antigens	Excipients
Oral	Sabin polio strains - type 1, 2 and 3. The vaccine contains $10^{5.9} \pm 0.5$ $TCID_{50}$ type1, $10^{5.0} \pm 0.5$ $TCID_{50}$ type 2 and $10^{5.7} \pm 0.5$ $TCID_{50}$ type 3	Streptomycin and neomycin, $MgCl_2$ No adjuvants or preservatives are used
Parenteral	Polio strains (1, 2 and 3)- Each dose of vaccine contains 40 D antigen units of type 1, eight D antigen units of type 2 and 32 D antigen units of type 3	Trace amounts of antibiotics (neomycin, streptomycin and polymyxin B). Some vaccines contain 2-phenoxyethanol as a preservative. Thiomersal cannot be used for IPV.

Adverse events following Oral Poliovirus Vaccine

Mild adverse events

In general, OPV is well tolerated by vaccine recipients.

Serious adverse events

Despite its many advantages, OPV carries the risk of vaccine-associated paralytic poliomyelitis (VAPP) particularly among infants who receive the vaccine for the first time and their contacts. In addition, when polio vaccine coverage is low in the population, this live attenuated vaccine may revert its virulence and transmissibility and pose additional risk for emergence of vaccine-derived polioviruses (VDPVs), which have been associated with outbreaks. Because of these risks, OPV use will be discontinued worldwide once the goal of eradicating all wild poliovirus (WPV transmission) is achieved.

Vaccine-associated paralytic polio (VAPP)

Reversion of the small number of substitutions conferring small genetic changes to the attenuated phenotype occurs during OPV replication in humans and is the underlying cause of the rare cases of VAPP in OPV recipients and their close contacts.

Sabin strains can replicate in the gut of vaccine recipients and poliovirus maybe excreted for 4 to 6 weeks. During this time, the few attenuating mutations present in the vaccine strains revert rapidly and the virus changes via several mechanisms. These include back mutations, site suppression mutations, recombination and a steady drift in molecular sequence. This reversion of the attenuating mutations during OPV replication in humans is the underlying cause of the rare cases of VAPP observed in OPV recipients and their close contacts.

The case definition for VAPP includes the following:

- A case of acute flaccid paralysis with residual weakness at 60 days after onset of symptoms;
- A negative stool sample for wild-type poliovirus but positive for vaccine virus as examined in a WHO accredited laboratory;
- Evaluation and confirmation of the case by an expert committee (WHO 1998).

The onset of symptoms with VAPP usually occurs 4–30 days following receipt of oral polio vaccine (OPV) or within 4–75 days after contact with a recipient of OPV. In immunodeficient individuals (especially those with low antibody – hypogammaglobulinemia) VAPP may occur outside these windows.

The precise rate of VAPP varies with the study and the methodology used to measure it. The rate of VAPP is higher for the first dose of OPV than for subsequent doses, ranging from one case per 700,000 to one case per 3.4 million first doses. The risk of VAPP among first dose recipients was estimated as 1 case per 2.8 million children in India compared with first dose recipient risk of 1 case per 1.4 million children in the United States. A 1969 WHO Collaborative study found a VAPP rate of one in every 5.9 million doses administered for vaccine recipients and one in every 6.7 million doses administered for contacts. Studies have found no significant differences in VAPP rates between developing and industrialized countries. In countries where wild poliovirus transmission has been extensive until recently, VAPP occurs more commonly in children and vaccine recipients than in adults and contacts. WHO estimates VAPP risk at 2-4 cases per million birth cohort. VAPP is more common in individuals who are immunocompromised. No study has demonstrated transmission from a VAPP case resulting in another VAPP case. (Varughese, 1989, Joce, 1991, Maass, 1987, Novello, 1987, Andrus, 1995, CDC, 1996, Esteves, 1988).

VDPVs

Vaccine-derived poliovirus (VDPV)

On very rare occasions, the live, attenuated vaccine-virus can - over time and prolonged replication - genetically change. A vaccine-derived poliovirus (VDPV) is a live, attenuated strain of the virus contained in OPV, which has changed and reverted to a form that may be able to cause paralysis in humans and may develop the capacity for sustained circulation. VDPVs differ from the parental (original) Sabin strains found in the vaccine by 1 to 15% of VP1 nucleotides. This is a measurement of genetic change that is used to monitor the circulation of viruses. On rare occasions, in areas where populations are under-immunized, VDPVs can regain the ability to circulate in populations, and can occasionally cause paralysis. Most circulating VDPV are type 2 (between 2000 and 2011, there were 492 type 2, 79 type 1 and 9 type 3 VDPV reported). Oral polio vaccine protects against VDPVs and is used to contain outbreaks. Hence, the problem is not with the vaccine itself, but low vaccination coverage. If a population is fully immunized, they will be protected against both vaccine-derived and wild polioviruses.

Aseptic meningitis/encephalitis

On rare occasions, particularly in immunodeficient infants, aseptic meningitis and encephalitis have been reported after OPV (Andronikou et al., 1998; Yeung et al., 1997; Rantala et al., 1989).

Other vaccine safety concerns

Guillain–Barré syndrome (GBS)

Current data do not indicate an increased risk of GBS following receipt of OPV (CDC, 1996). Research conducted in Finland during the 1980s had suggested an increased incidence of GBS following mass OPV vaccination (Kinnunen et al., 1989; CDC, 1997; Uhari et al., 1989). Since the findings which led the US Institute of Medicine to conclude that there was an association between OPV and GBS (Stratton et al., 1994), the Finland results have been reanalysed and other factors have been identified as having contributed to the increase in the incidence of GBS. These factors include an influenza epidemic and widespread circulation of wild type-3 poliovirus (Kinnunen et al., 1998). During this time period, another observational study was also completed in the United Stateswhich did not support a causal relationship between OPV and GBS (Rantala et al., 1994; CDC, 1996; Kinnunen et al., 1998).

Transverse myelitis (TM)

There are case reports of transverse myelitis reported after OPV, but occurred following the administration of multiple vaccines. TM was not observed in the clinical trials that occurred prior to licensure of the polio vaccine and no other controlled studies have been conducted. Therefore, the data is inadequate to determine whether a causal relationship exists between OPV and TM (Stratton et al., 1994, Heath K 2006).

Simultaneous administration

OPV can be administered with other vaccines, with no evidence of increased rates of adverse events nor reduced immunogenicity. OPV is frequently administered simultaneously with diphtheria–tetanus–pertussis (DPT) vaccines and therefore side effects from the latter may often be falsely attributed to OPV. Rotavirus vaccines when administered simultaneously have not affected immune responses to OPV. However in general, the immune responses (i.e., antibody levels) to rotavirus vaccination were lower when rotavirus vaccines were co-administered with OPV. This is particularly greater after the first dose of OPV (M. Patel et al. 2012).

Provocation poliomyelitis

In persons incubating wild poliovirus infection, intramuscular injections (e.g. DTP) may provoke paralysis in the injected limb (Sutter et al.1992; Strebel, 1995).

Simian papovavirus SV40
From 1954 to 1962, both the inactivated and live attenuated forms of polio vaccine were prepared in primary cultures of rhesus monkey kidney cells, some of which were derived from monkeys that were naturally infected with SV40. This is a live simian papovavirus 40 (SV-40) which may cause neural tumour in animals, and viruses from the same papovavirus family may cause neural tumours in human beings. Some studies tried to investigate possible causation between the receipt of polio vaccine and the development of tumours (Dittmann, 1992). Long-term follow-up studies do not support such an association (Butel & Lednicky, 1999). A meeting convened at the National Institute of Health in 1997 concluded, "No measurable increase in neoplastic diseases has occurred in humans exposed to SV40 contaminated polio vaccines" (Plotkin et al., 1999). All currently produced oral polio vaccine is now tested for SV40 and none has been found positive.

Adverse events following Inactivated Poliovirus Vaccine

Mild adverse events

Localized reactions are common with IPV and this includes injection site erythema (0.5-1%), induration (3-11%) and tenderness (14-29%) (WER 2003). These reactions are generally mild and transient. In most cases, they spontaneously resolve within two to three days and further medical attention is not required. Mild systemic reactions may also occur.

Serious adverse events

Some formulations of IPV contain small amounts of streptomycin, polymyxin B and neomycin, which can theoretically cause reactions in persons allergic to these antibiotics – but no confirmation of such reactions has been found in post-marketing surveillance (Plotkin et al., 1999; CDC, 1997). No reports of anaphylaxis, thrombocytopenia or transverse myelitis (Stratton et al., 1994) after IPV have been published.

Other safety issues

Simultaneous administration

IPV is frequently administered simultaneously with diphtheria–tetanus–pertussis (DTP) vaccines. The combination of IPV with other vaccines, including DPT and Hib, does not appear to increase adverse reactions (Murdin et al., 1996; Vidor et al., 1994).

Summary of mild and severe adverse events

Vaccine	Description	Rate/doses
Oral	**Serious** **Vaccine-associated paralytic polio**	**Overall rate of** **Recipient VAPP – 1 per 6.4 million doses** **Total VAPP - 1 per 2.9 per million doses**
	Aseptic meningitis/encephalitis	**Case reports only**
Inactivated	**Mild- Injection site reactions** **Injection site erythema** **Induration** **Tenderness** **Serious**	**0.5-1.5 per 100** **3-11 per 100** **14-29 per 100** **None**

References

Andronikou S, Siamopoulou-Mavridou A, Pontikake M, et al. (1998). Poliovirus vaccination in an infant with hypogammaglobulinaemia. *Lancet*, 351(9103):674.

Andrus JK, Strebel PM, de Quadros CA, et al. (1995). Risk of vaccine-associated paralytic poliomyelitis in Latin America, 1989–91. *Bulletin of the World Health Organization*, 73(1):33–40.

Begg NT, Chamberlain R, Roebuck M (1987). Paralytic poliomyelitis in England and Wales 1970–84. *Epidemic Infelligence*, 99:97–106.

Butel J, Lednicky JA (1999). Cell and molecular biology of Simian Virus 40: Implications for human infections and disease. *Journal of the National Cancer Institute*, 91:119–34.

CDC (1996). Centers for Diseases Control and Prevention. Paralytic poliomyelitis 1980–94*. MMWR: Morbidity and Mortality Weekly Report*, 46:79–83.

CDC (1997). Centers for Diseases Control and Prevention. Poliomyelitis prevention in the United States: introduction of a sequential vaccination schedule of inactivated poliovirus vaccine followed by oral poliovirus vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR: Morbidity and Mortality Weekly Report*, 46(RR-3):1-25.

CDC (1996). Centers for Diseases Control and Prevention. Update: Vaccine side effects, adverse reactions, contraindications, and precautions. Recommendations of the Advisory Committee on Immunization Practices. *MMWR: Morbidity and Mortality Weekly Report*, 45(RR-12):1–35.

Centers for Disease Control and Prevention (CDC). Update on vaccine-derived polioviruses--worldwide, July 2009-March 2011.MMWR Morb Mortal Wkly Rep. 2011 Jul 1;60(25):846-50.

Dittmann S (1992). Immunological preparations. MNG Dukes, ed. *Meyer's side effect of drugs*, 12th Ed. Elsevier Science Publishers, 1992:791–840.

Esteves K (1988). Safety of oral poliomyelitis vaccine: results of a WHO enquiry. *Bulletin of the World Health Organization*, 66:739–46.

Galazka AM, Lauer BA, Henderson RH, Keja J (1984). Indications and contraindications for vaccines used in the Expanded Programme on Immunization. *Bulletin of the World Health Organization*, 62:357–66.

Global polio eradication initiative. Circulating VDPV data accessed on 10 December 2012 http://www.polioeradication.org/Dataandmonitoring/Poliothisweek/Circulatingvaccinederivedpoliovirus.aspx.

Joce R, Wood D, Brown D, Begg NT (1992). Paralytic poliomyelitis in England and Wales, 1985–1991. *British Medical Journal*, 305:79–82.

Kelly H. Evidence for a causal association between oral polio vaccine and transverse myelitis: A case history and review of the Literature J Paediatr Child Health. 2006 Apr;42(4):155-9.

Kinnunen E, Farkkila M, Hovi T, et al. (1989). Incidence of Guillain–Barré syndrome during a nationwide oral poliovirus vaccine campaign. *Neurology*, 39:1036–6.

Kinnunen E, Junttila O, Haukka J, et al. (1998). Nationwide oral poliovirus vaccination campaign and the incidence of Guillain–Barré syndrome. *American Journal of Epidemiology*, 147: 69–73.

Manish Patel, A. Duncan Steele, Umesh D. Parashar (2011) Influence of oral polio vaccines on performance of the monovalent and pentavalent rotavirus vaccines_Vaccine 30S (2012) A30– A35.

Maass G, Ouast U (1987). Acute spinal paralysis after the administration of oral poliomyelitis vaccine in the Federal Republic of Germany (1963–1984). The International Association of Biological Standardization, 15:185–191.

Murdin A, Barreto A, Vidor E (1996). Inactivated Polio Vaccine: past and present experience. *Vaccine*, 14:735–46.

Novello F, Lombardi F, Amato C, Santoro R, Fiore I, Grandolfo ME, Pasquini P (1987). Paralytic poliomyelitis in Italy, 1981–1985. *European Journal of Epidemiology* I, 3:54–60.

Olen M. Kew, RolandW. Sutter,Esther M. de Gourville, Walter R. Dowdle,and Mark A. Pallansch Vaccine-Derived Polioviruses and the Endgame Strategy for Global Polio Eradication∗ Annu. Rev. Microbiol. 2005. 59:587–635.

Plotkin SA, Murdin A, Vidor E (1999). Inactivated Polio Vaccines. In Plotkin S, Orenstein W, eds. *Vaccines*. Philadelphia, PA, WB Saunders Company, 1999:345–363.

Rantala H, Cherry JD, Shields WD, et al. (1994). Epidemiology of Guillain–Barré syndrome in children: relationship of oral polio vaccine administration to occurrence. *Journal of Pediatrics*, 124:220–3.

Roland W. Sutter, Olen M Kew, Stephen l. Cochi. Polio Vaccine – Live. In Plotkin S, Orenstein W, Paul A Offit 5th Edition 2008. *Vaccines*. Saunders Elsevier Company: 605 – 685.

Roure C, Rebiere I, Aymard M, Dubrou S (1991). Surveillance de la poliomyélite en France. *Bulletin Epidemiologique Hebdomadaire* 15: 59–61.

Stratton KR, Howe CJ, Johnston RB, Jr., eds. (1994*). Adverse events associated with childhood vaccines. Evidence bearing on causality*. Washington, DC, National Academy Press.

Strebel PM, Sutter RW, Cochi SL, et al. (1991). Epidemiology of poliomyelitis in the United States one decade after the last reported case of indigenous wild virus-associated disease. *Clinical Infectious Diseases*, 14:568–79.

Sutter RW, Cochi SL, Melnick JL (1999). Live attenuated Poliovirus Vaccines in Plotkin SA, Orenstein WA, eds. *Vaccines*. Philadelphia, PA, WB Saunders Company, 1999:364–408.

Sutter RW, Patriaca PA, Suleman AJM, Brogan S, Cochi SL, El-Bualy MS (1992). Attributable risk of DTP injection in provoking paralytic poliomyelitis during a large outbreak in Oman. *Journal of Infectious Diseases*, 165, 444–449.

Strebel PM, Ion-Nedelcu N, Baughman AL, Sutter RW, Cochi SL (1995). Intramuscular injections within 30 days of immunization with oral poliovirus vaccine – a risk factor for vaccine-associated paralytic poliomyelitis. *New England Journal of Medicine*, 332: 500–6.

Uhari M, Rantala H, Niemelä M (1989). Cluster of childhood Guillain–Barré cases after an oral poliovaccine campaign. *Lancet*, 2:440–1.

Varughese P, Caner A, Acres S, Furesz J (1989). Eradication of indigenous poliomyelitis in Canada: impact of immunization strategy. *Canadian Public Health Journal,* 80:363–8.

Vidor E, Caudrelier P, Plotkin S (1994). The place of DPT/eIPV vaccine in routine paediatric vaccination. *Reviews in Medical Virology*, 4:261–277.

Yeung WL et al. (1997). An infant with encephalitis. *Lancet*, 350:1594.

WER. Introduction of inactivated poliovirus into oral poliovirus using country. 2003: 28: 241-252.

WHO Global Eradication of Poliomyelitis. Report of the second meeting of the Global Technical Consultative Group. WHO/EPI/GEN/98.04

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