Polio vaccines and routine polio immunization in the pre-eradication era

WHO position paper

In accordance with its mandate to provide guidance to Member States on health policy matters, WHO is issuing a series of regularly updated position papers on vaccines and vaccine combinations against diseases that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale immunization programmes; they summarize essential background information on the respective diseases and vaccines and conclude with the current WHO position concerning their use in the global context. The papers have been reviewed by a number of experts within and outside WHO and since 2006 they are reviewed and endorsed by WHO's Strategic Advisory Group of Experts (SAGE) on Vaccines and Immunization. The position papers are designed for use mainly by national public health officials and immunization programme managers. However, they may also be of interest to international funding agencies, the vaccine manufacturing industry, the medical community, the scientific media, and the public.

This paper supersedes the WHO position paper entitled "Introduction of inactivated poliovirus vaccine into oral poliovirus vaccine-using countries" (see No. 28, 2003, pp 241–252). A subsequent position paper will replace the paper entitled "Inactivated poliovirus vaccine following oral poliovirus vaccine cessation. Supplement to the WHO position Paper” (see No. 15, 2006, pp 137–144). The present document deals with routine polio immunization in the pre-eradication era, particularly in developing country settings. Footnotes provide a limited number of core references; their respective abstracts as well as a more comprehensive list of references are found at http://www.who.int/immunization/documents/positionpapers/en/index.html.

Grading tables (The GRADE working group 2004) that assess the quality of scientific evidence for a few key statements are also available at this link and are referenced in the position paper.

Background

Epidemiology

Poliomyelitis (polio) is an acute, communicable disease of humans caused by three poliovirus serotypes (types 1, 2 and 3, respectively). Where sanitation is poor, these viruses are spread mainly by fecal-to-oral transmission, whereas the oral-to-oral mode of transmission probably dominates in settings with a high standard of sanitation. However, in most settings, mixed patterns of transmission are likely to be common. In the pre-vaccine era, virtually all children
were exposed to polioviruses and on average 1: 200 susceptible individuals developed paralytic poliomyelitis.

Progress in polio control (and more recently, polio eradication) is due mainly to widespread use of vaccines. An inactivated poliovirus vaccine (IPV, the Salk vaccine) was licensed in 1955; live attenuated oral poliovirus vaccine (OPV, Sabin vaccine) was licensed as monovalent OPV in 1961 and as trivalent OPV in 1963. In most countries that introduced polio vaccination in those early years, OPV replaced IPV for ease of administration, suitability for mass vaccination campaigns, superior induction of mucosal immunity in the gut, and lower production costs. In 1974, OPV was recommended as part of the Expanded Programme on Immunization (EPI) and OPV was again the vaccine of choice in 1988, when the World Health Assembly resolved to eradicate poliomyelitis globally by the year 2000. Since then, 3 of the 6 WHO Regions have been certified as free of wild-strain polio virus (WPV) and WPV of serotype 2 (WPV2) has not been detected worldwide since 1999. Given this progress towards polio eradication, many industrialized countries have lately switched from using OPV to IPV in routine immunization programs, primarily to eliminate the burden of vaccine-associated paralytic poliomyelitis (VAPP), a rare adverse events associated with OPV.

In 2009, a total of 23 countries reported one or more polio cases due to wild polioviruses. Of these, 4 are ‘polio-endemic’ (Afghanistan, India, Nigeria, and Pakistan) as they have never eliminated WPV indigenous circulation, although transmission of WPV 1 and 3 is now restricted to small geographic areas within these countries. The remaining countries were previously polio-free, but have reported cases and outbreaks due to imported WPV 1 or 3. Angola and Chad have had sustained WPV transmission lasting for >12 months after importation (Resurgence of wild poliovirus, 2009).

Poliovirus and disease

Poliovirus is a human enterovirus of the *Picornaviridae* family. The virus is composed of a single-stranded, positive-sense RNA genome and a protein capsid. The three serotypes of poliovirus carry capsid proteins that differ slightly with regard to cellular receptor specificity and antigenicity.

Most poliovirus infections cause asymptomatic viral replication limited to the alimentary tract. However, following an incubation period in immunocompetent individuals of approximately 7-10 days (range 4-35 days) about 5% of those infected develop clinical signs such as fever, headache and sore throat. Paralytic poliomyelitis, experienced in less than 1% of poliovirus infections, occurs when the virus enters the central nervous system and replicates in anterior horn cells (i.e. motor neurons) of the spinal cord. Depending on the degree and extent of motor neurons affected, temporary or permanent paralysis of the affected muscles may ensue. In rare cases, viral destruction of bulbar cells results in respiratory
The typical neurological manifestation of paralytic poliomyelitis is acute flaccid paralysis (AFP) of limbs, predominantly lower limbs, usually asymmetric and with intact sensation. Persistent paralyses with resulting deformities are common sequelae of polio. The case-fatality rate among paralytic cases varies between 2% and 20%, but is substantially higher with bulbar involvement, especially in adolescents and adults.

Immunocompetent individuals infected by poliovirus develop protective immunity through humoral (i.e. circulating antibody) and mucosal (i.e. secretory IgA) immune responses. Presence of neutralizing antibody against polioviruses is considered a reliable correlate of protection against poliomyelitis. However, immunity induced by one serotype does not provide protection against the other two serotypes. Mucosal immunity decreases the replication and excretion (shedding) of the virus, and thus provides a potential barrier to its transmission. Individuals with B-cell related immune defects are at increased risk for paralytic manifestations of polio.

**Polio vaccines**

**Oral poliovirus vaccine**

OPV is composed of live, attenuated polioviruses that were derived by passage of their parent WPV strains in non-human cells to give the three vaccine strains (Sabin1, Sabin 2, and Sabin 3). The attenuation results in much lower neurovirulence and in reduced transmissibility.

Standard OPV virus titre according to WHO requirements should be not less than $10^6$ infectious units per dose for type 1 virus, $10^{5.0}$ infectious units per dose for type 2, and $10^{5.8}$ infectious units per dose for type 3. In addition to trivalent OPV (tOPV) which is used in many countries for routine or supplemental vaccination, monovalent poliovirus vaccines, solely against type 1 (mOPV1) and against type 3 (mOPV3), have been licensed since 2005 for use in some countries. Monovalent poliovirus vaccines against type 2 (mOPV2) are under licensure for stockpile purposes. Also, in 2009, two bivalent (types 1 and 3) OPV (bOPV) were licensed, while others are under evaluation. The mOPV and bOPV vaccines are used only during mass campaigns to optimize population immunity or to combat a single or dual strain circulation.

No combination products with OPV as one of the components have been licensed. However, both in industrialized and developing countries, OPV is usually administered concurrent with other vaccines such as BCG, DTP, hepatitis B, measles, *Haemophilus influenza* type b, and rotavirus vaccine. No interference between OPV and these vaccines (or between OPV and concurrent vitamin A supplementation) has been observed (*Halsey N et al 1985; Cameron JC et al, 2006*). OPV is highly heat-sensitive and must be kept frozen or, after thawing, at temperatures between 2 and 8°C for a maximum of 6 months. Each vaccine dose consists of 2 drops (~0.1 mL).

For OPV schedules including birth dose, see final chapter on WHO policy recommendations.
Vaccine safety

Although OPV is a very safe vaccine, on rare occasions adverse events may occur. Vaccine-associated paralytic poliomyelitis (VAPP) is the most important of these rare adverse events. Cases of VAPP are clinically indistinguishable from polio caused by WPV (Esteves K 1988), but can be distinguished based on laboratory analyses. The global incidence of VAPP has been estimated at 4 cases per million birth cohort per year, or 375 VAPP cases globally per year, with most cases occurring in the largest OPV-using countries (Risk assessment, 2002). Prior to 1997, when OPV was the only polio vaccine used in the United States, the risk of VAPP in first-dose OPV recipients was estimated at about 1 case per 750,000 children (CDC, 1997). In industrialized countries, the risk of VAPP decreases sharply (>10-fold) with subsequent OPV doses, whereas in developing countries this decline is more gradual, probably as a consequence of lower vaccine effectiveness. VAPP occurs in both OPV recipients and their unimmunized contacts and is most frequently (60% of cases) associated with Sabin 3, followed by Sabin 2 and Sabin 1.

Sabin viruses can replicate in populations with low OPV coverage, acquire the neurovirulence and transmissibility characteristics of WPV, and cause circulating vaccine-derived poliovirus (cVDPV) cases and outbreaks (Kew Olen M et al 2005). Since 2000, 10 outbreaks of cVDPVs have been reported from three continents, and one large outbreak due to cVDPV type 2 is currently ongoing in Nigeria (Vaccine-derived polioviruses. WER 2009). In each of these incidents, immunity gaps were identified and OPV was used for controlling the outbreak. These cVDPV events demonstrate the importance of achieving and maintaining very high polio immunization rates.

Although very rare, in a small fraction of individuals B-cell immune deficiencies (i.e., not the immune deficiencies associated with HIV/AIDS), Sabin viruses can continue to replicate for prolonged periods, resulting in vaccine-derived poliovirus in immune deficient individuals (iVDPVs).

No additional adverse events have been associated with concurrent administration of OPV and other childhood vaccines including rotavirus vaccine (Cameron JC et al, 2006)

Immunogenicity and field efficacy/effectiveness

Several lines of evidence demonstrate the effectiveness of OPV in controlling polio and eliminating the circulation of polioviruses, including the sharp decline in polio cases following introduction of polio vaccines in both industrialized and developing countries. OPV has been the vaccine-of-choice for the global eradication initiative; it has eradicated WPV2, eliminated polio types 1 and 3 in 3 of the 6 WHO Regions, and dramatically (>99%) decreased the number of polio cases in the remaining 3 regions.
During the first 1-3 weeks following vaccination, the majority of non-immune vaccinees disseminate the viruses of the OPV through nasopharyngeal secretions and faeces. In unprotected populations, these vaccine viruses are easily transmitted within and outside the household resulting in inadvertent protection of non-immune individuals (herd immunity), or in boosting of existing immunity in others. Although inadvertent dissemination extends the public health impact of OPV and hence, is an important advantage of the vaccine, uncontrolled exposure to this vaccine is a confounder for example when evaluating vaccine schedules (for OPV as well as IPV) or the duration of protection following primary immunization. Besides, cVDPVs may also be disseminated in this way (see above: Vaccine safety).

The level of protective efficacy of tOPV has been evaluated in different epidemiological settings. For example, large case-control studies from Taiwan (Kim-Farley RJ et al 1984) and Oman (Sutter RW et al 1991) estimated the 3-dose field efficacy of tOPV at >90%. Induction of herd immunity explains the nearly 100% reduction in the incidence of polio that was achieved through a pulse immunization campaign involving 62% of children aged 0-4 years in a highly endemic Indian town of 160 000 inhabitants (John TJ, 1983).

Case-control studies comparing the field efficacy of mOPV1 and tOPV against WPV1 showed that in Uttar Pradesh, the per-dose efficacy of tOPV was significantly lower than that observed in the rest of India, which in turn was lower than in industrialized countries (Grassly NC et al 2007). Also, in Uttar Pradesh, the estimated per-dose efficacy of mOPV1 was considerably higher than the one-dose efficacy of tOPV (i.e. 30% vs. 11%). A case-control study in Nigeria found that the per-dose efficacy of mOPV1 was more than four times higher than estimates for tOPV (i.e., 67% vs. 16%) (Jenkins HE et al 2008). Seroconversion trials have confirmed that compared with tOPV, the monovalent OPV (and bOPV) are significantly more immunogenic (El-Sayed N et al, 2007; ref on bOPV to follow). (Reference to Grading Table I. Conclusion: High scientific evidence that OPV protects against clinical poliomyelitis).

**Factors influencing seroconversion rates**

Whereas the rates of seroconversion following administration of 3 doses of tOPV may approach 100% in industrialized countries (McBean et al 1988), similar immunization induce detectable antibody to poliovirus types 1 and 3, respectively, in only 73% (range, 36%-99%) and 70% (range, 40%-99%) of children in developing countries (Patriarca PA et al 1991). Suboptimal responses to OPV in developing countries are determined by a complex array of factors related to the vaccine, host, and environment. Available data suggest that type 2 vaccine virus often interferes with responses to types 1 and 3 vaccine viruses. Other enteric pathogens may interfere with the response to all the 3 vaccine viruses. Viral interferences may be overcome by modifying the absolute and relative dosage of the three Sabin types. Increasing the interval between doses beyond 30 days may also be important, in view of the prolonged excretion of vaccine virus and the potential for interference with responses to subsequent doses. Other factors that have been shown to negatively influence the response to
OPV particularly in developing countries include high levels of maternal antibody, vaccination during the rainy season, diarrhea at the time of vaccination, household exposure to other OPV recipients, and breast-feeding (Patriarca PA et al 1991; WHO Collaboratory Group, 1995; John T, 1993). Factors influencing seroconversion rates should be taken into consideration when deciding on national vaccination schedules.

**OPV administered at birth**

A birth dose administered at, or as soon as possible after birth can significantly improve the seroconversion rates of subsequent doses and induce mucosal protection before enteric pathogens may interfere with the immune response (Bhaskaram P et al 1997). Also, provision of the first OPV dose at a time when the infant is still protected by maternally-derived antibodies may, at least theoretically, also prevent VAPP. Although the data on birth dose seroconversion rates show great variability, from low rates in India (~10%), median rates in Egypt (32%) and Oman, to high seroconversion rates in Indonesia (53%), data from China (Dong DX, 1984), India (Khare S et al, 1993; Jain PK et al, 1997), Ghana (Osei-Kwasi M et al 1995), and Brazil (Wekx LY et al 1992) demonstrate that in general, the birth dose increases the immunogenicity of the other doses in a vaccination schedule (Reference to Grading Table II. Conclusion: High scientific evidence that OPV schedules starting with a birth dose are at least as immunogenic as otherwise comparable OPV schedules starting at 6-8 weeks of age.

**Duration of protection**

The data on duration of vaccine-induced antibody persistence are limited, especially for developing countries. In developed countries, antibody concentrations decline over time, sometimes to levels below detectable, but immunity against paralytic disease appears to be life-long. In the United States, young army recruits who had received polio vaccination (mainly OPV) 15-25 years earlier showed seronegativity rates for poliovirus types 1, 2, and 3 as low as 2.3%, 0.6%, and 14.6%, respectively, with no significant differences by age, sex, and ethnicity (Kelley PW et al, 1991). In the Gambia, following routine EPI vaccination, slightly declining antibody concentrations against poliovirus type 1 were found in children 8-9 years of age as compared to children aged 3-4 years, but the two age groups showed almost identical percentages (88% and 89%) of detectable antibody levels. Fewer children aged 8-9 years than aged 3-4 years had antibodies against poliovirus type 3 (78% vs. 89% P < 0.001). (Viviani S et al, 2004). Also, among 67 children who had received only two doses of the vaccine more than 80% retained neutralizing antibodies when tested after 5 years (Nishio O et al, 1984), (Reference to Grading Table III. Conclusion: Low scientific evidence for ≥80% long-term (>5-10 years) protection following ≥3-4 doses of OPV).

**Inactivated poliovirus vaccine**

IPV is usually made from the selected WPV strains Mahoney (Salk serotype 1), MEF-1 (Salk serotype 2) and Saukett (Salk serotype 3) that are grown in Vero cell culture or in human
diploid cells. Harvested viral components are inactivated with formaldehyde. The final vaccine mixture is formulated to contain at least 40, 8, and 32 D-antigen units of serotypes 1, 2 and 3, respectively. (D-antigen, which is expressed only on intact poliovirus particles, is used to adjust the concentration of the individual viruses included in the trivalent IPV). All current versions of IPV show higher antigenicity than the first generation vaccine products and are sometimes referred to as IPVs of enhanced potency. IPV may contain trace amounts of formaldehyde, streptomycin, neomycin or polymyxin B, some IPV versions contain the preservative phenoxyethanol (0.5%), but neither thiomersol (incompatible with IPV antigenicity) nor adjuvants.

IPV is administered by intramuscular (preferred) or subcutaneous injection. The vaccine is quite stable (see package insert for individual manufacturer's recommendation). Freezing should be avoided since it could diminish the vaccine potency. IPV is available either as a stand-alone product, or in combination with one or more of other vaccine antigens including diphtheria, tetanus, whole-cell or acellular pertussis, hepatitis B, and/or *Haemophilus influenzae* type b. In the combination vaccines, the alum and/or pertussis vaccine have an adjuvant effect.

For IPV schedules, see final chapter on WHO policy and recommendations.

**Vaccine safety**

IPV is one of the safest vaccines used for routine immunization, alone or in combinations, with no proven causal relationship to adverse events except minor local erythema (0.5–1%), induration (3–11%), and tenderness (14–29%) (Phua KB et al. 2008).

**IPV immunogenicity and field efficacy/effectiveness**

The original field trial of IPV in the United States (*Francis et al 1954*) established the efficacy of the first generation IPV against polio in industrialized countries. Since then, a case control study of vaccinated infants in a developing country (i.e., Senegal) (*Robertson S, et al 1988*) reported 89% efficacy following 2 doses of enhanced potency IPV given approximately 6 months apart, and 36% efficacy following 1 dose of IPV, in preventing paralysis. In terms of immunogenicity, studies conducted in Puerto Rico (*Dayan GH et al 2007*) and Cuba (*The Cuba IPV Study 2007*) demonstrated that IPV given at 6, 10, and 14 weeks of age resulted in lower seroconversion rates compared with IPV given at 2, 4, and 6 months of age, probably due to interaction between remaining maternally-derived antibody and seroconversion (*Simoes EA et al, 1986*). (Reference to Grading Table IV. Conclusion: High scientific evidence that IPV protects against clinical poliomyelitis).

The rationale for the recent introduction of IPV in several countries has been mainly the need to prevent VAPP, but in some settings also to close existing immunity gaps, or as a means to optimize the administration of other antigens. Introduction of IPV has been possible because of the decreased risk of importation of wild PV due to progress in global eradication. In the
United States, following the shift from routine use of OPV to a combined IPV/OPV schedule in 1997, and to a IPV-only schedule in 2000, VAPP cases rapidly disappeared (Prevots DR et al, 2000; CDC, MMWR, 2005).

There is limited experience with IPV used in routine immunization schedules in developing countries. Where IPV has- or is being used (e.g. Egypt, Gulf Cooperation Council states, Malaysia, South Africa), it is usually administered in a sequential schedule with OPV. As IPV administered to infants at 6, 10, and 14 weeks results in suboptimal seroconversion, this schedule requires a supplementary dose either at the time of measles vaccination or in the second year of life.

*Duration of protection*

Circulating antibody persist for decades (possibly life-long), but antibody titers decrease over time so that some adults may lack detectable antibody, typically first losing antibody to type 3 poliovirus. Persisting neutralizing antibodies against polio viruses are usually found in all vaccinees 5 years after the primary immunization series (Schwarz TA et al 1990; Carlsson RM et al, 1986; Langue J et al, 2002). Also, neutralizing antibodies were found in all of the 250 Swedish children studied who had received 3 doses of IPV approximately 18 years earlier (Bøttiger M et al, 1990). (Reference to Grading Table III. Conclusion: Low scientific evidence for ≥80% long-term (>5-10 years) protection following ≥3-4 doses of IPV).

**Sequential administration of IPV and OPV**

Over the past decade, a number of countries in Central and Eastern Europe, the Middle East, the Far East and Southern Africa have adopted sequential schedules of 1-2 doses of IPV followed by 2 or more doses of OPV. IPV/OPV schedules appear to reduce or prevent VAPP while maintaining the high levels of gut immunity conferred by OPV. In addition, such schedules economize on limited resources through reducing the number of IPV doses, and may optimize both the humoral and mucosal immunogenicity of polio vaccination. The effectiveness of this approach in preventing WPV-polio as well as VAPP has been documented by two large country experiences: Denmark (von Magnus H 1984) used a schedule of 3 doses of IPV followed by 3 doses of OPV; Hungary (Dömök I 1982) used a schedule of 1 dose of IPV followed by 3 doses of OPV. In a randomized, controlled study in the US (Modlin J et al 1997) 2 doses of IPV followed by 2 doses of OPV resulted in excellent seroconversion: 3 months after the final dose, 96%-99%, 99%-100%, and 81%-100% of infants had antibodies to poliovirus types 1, 2, and 3, respectively. Subjects with two or more prior OPV doses were significantly less likely than those with none or one dose to excrete virus in feces after an OPV challenge. From 1997 to 2000 the United States changed from reliance on OPV to options for a sequential schedule of IPV followed by OPV. Thirteen cases paralytic poliomyelitis occurred during the 1997-1999 transitional policy period and were associated with the all-OPV schedule; none occurred with the IPV-OPV schedule (Alexander LN et al 2004). (Reference to Grading Table V. Conclusion: Moderate level of scientific evidence
that sequential immunization schedules starting by two or more doses of IPV and followed by two or more doses of OPV induce protective immune responses to all three poliovirus serotypes in \( \geq 90\% \) of vaccinees.

Simultaneous administration of IPV and OPV

A large randomized trial in The Gambia, Oman, and Thailand compared the immunogenicity of 4 doses of OPV, 3 doses of IPV, and 4 doses of OPV plus 3 doses of IPV. In both The Gambia and Oman, the simultaneous schedule had the highest level of seropositivity to all three polio virus types. Only in Thailand was 4 doses of OPV equivalent to the simultaneous schedule (WHO Collaborative Study Group, 1996). Studies in Pakistan comparing the serological responses to various OPV and / or IPV schedules confirm the favorable immunological response to combined IPV/OPV vaccination (du Chatelet IP et al, 2003). Combined OPV/IPV schedules could correct the lower immunogenicity of OPV in developing countries.

The clinical impact of combined IPV-OPV was demonstrated in Gaza, where the incidence of paralytic polio had remained high (\( \geq 10 \) per 100,000 inhabitants) in spite of 90% OPV coverage. Following the change from OPV only to OPV plus IPV (pentavalent combination vaccine) the annual incidence of paralytic polio dropped from 10 to 2.2 per 100,000 inhabitants during the first 3 years, and in the following 5 years (1981-1985) to 0.16 per 100,000 inhabitants (Lasch EE et al 1986). However, mainly for reasons of increased cost combined schedules are unlikely to gain acceptance in settings where low immunogenicity of OPV only is of particular concern.

Cost-effectiveness of routine polio vaccination

The literature on economic evaluation of routine OPV immunization is very limited. Cost-saving estimates of routine polio vaccination have been generated for various points in time during the past 50 years in the USA (Thompson KM et al 2006). Since the introduction of routine vaccination in the US, approximately 1.1 million cases of paralytic polio, and over 160,000 deaths have been prevented at a vaccination cost of approximately USD 1.7 billion. Due to treatment cost savings, polio vaccination generated a net benefit of approximately USD 180 billion.

Country-specific analyses of the incremental cost-effectiveness of switching from OPV to IPV (USA, South Africa, Australia) concluded that changing from OPV to IPV is not cost-effective at current IPV prices. A recent analysis for South Africa estimated a minimum cost per VAPP case averted (based on 2 doses of IPV) of approximately USD 740,000 (2005 USD) (Griffiths UK et al 2006). In 1996, the results of an incremental cost-effectiveness analysis for the US projected a cost approximately USD 3 million (1995 USD) per VAPP case averted (Miller MA et al 1996), while a later US study using the actual costs found the incremental cost-effectiveness ratio to be approximately 14 million (2002 USD) per VAPP case averted (Thompson KM et al 1996). Finally, a recent Australian study provided an
estimate of AUSD 17 million (1999 AUSD, with 1 AUSD = approximately 1.7 USD in 1999) per VAPP case averted based on an incremental cost-effectiveness analysis of a change to a sequential IPV/OPV schedule (Tucker AW et al 2001). While cost-effectiveness analysis does not support the switch from OPV to IPV based on expected economic benefits, all of these countries introduced IPV either in a sequential IPV/OPV schedule or as an IPV-only schedule, because of the overriding need to reduce or eliminate VAPP and the belief that a switch would help maintain public confidence for vaccination in general.

Although the cost-effectiveness of IPV may change with on-going efforts to lower its costs, OPV is currently the most cost-effective polio vaccine. Following the eradication of WPV, OPV cessation will be required to eliminate all remaining cases of paralytic poliomyelitis (i.e. those from VAPP and VDPV), which means that OPV for routine vaccination may become unavailable in the future.

Choice of polio vaccines

Although global eradication through vaccination remains the priority of the WHO policy on poliomyelitis, some policy decisions for the pre-eradication era can be made independent of future, post-eradication polio vaccination choices. The current paper covers the pre-eradication period only. Due to the great heterogeneity between countries in terms of polio control achievements, the main objective of this position paper is to present the underlying principles, in order for countries to make their own informed policy decisions.

The national choice of vaccines and vaccination schedules during the pre-eradication period must include either OPV, IPV, or a combination of both, to achieve and maintain high levels of population immunity, and should be based on assessments of the probabilities and consequences of WPV importation.

As long as WPV transmission has not been interrupted everywhere, all polio-free countries and areas remain at risk of re-importation of WPV, particularly from the remaining polio-endemic countries. From 2003 to 2009, WHO has recorded 133 WPV importation events in 29 previously polio-free countries (i.e. the WPV detected was genetically determined to have originated in another country), leading to 60 outbreaks (defined as 2 or more genetically related cases) with a total burden of 2,193 polio cases in 25 countries (Resurgence of WPV1, 2006; Resurgence of WPV1, 2009).

At this time, 109 importation events (83%) have been controlled and the affected countries have returned to polio-free status (i.e. > 6 months have passed without detection of a genetically related case). However, outbreaks following 24 importation events in 13 countries are still active. (Resurgence of WPV1, 2009). The risk of importations with subsequent spread was highest in countries immediately bordering endemic countries and was also higher in countries with low routine immunization coverage.
The force-of-infection of poliovirus infection is primarily determined by the hygiene and sanitation standards of a given country. In general the force-of-infection is much higher in tropical developing countries compared to industrialized countries. In addition, other factors such as the population density, the contact rates, and mode of transmission (fecal-to-oral, or oral-to-oral) determine the ease and speed of transmission of virus in a given setting (Fine P et al, 1999).

OPV alone has been the vaccine of choice for controlling endemic and epidemic poliomyelitis in most parts of the world, because it is substantially superior to IPV in inducing gut immunity to decrease wild virus spread, provides long term immunity, can boost immunity and indirectly immunize others through spread of vaccine viruses, is easy to administer, and is substantially cheaper than IPV. The mainly pharyngeal mucosal immunity induced by IPV may be comparable to that of OPV, but IPV has a much lower impact than OPV on replication and excretion of poliovirus in the lower intestinal tract (Ogra PL et al. 1968, Onorato IM et al, 1991). Nonetheless, IPV has been used successfully to eliminate polio in 2 to 3 countries with very high IPV coverage rates (>95%) in their national polio immunization programmes and predominantly oral-to-oral mode of transmission (Bottiger M, 1993).

**Prevention of vaccine-derived polioviruses**

In addition to the risk of WPV importation into polio-free areas, there is a risk of importation and/or spread of VDPVs. AFP surveillance increasingly identifies VDPVs associated with paralysis, particularly following outbreaks of cVDPVs (Risk assessment, 2002). Most industrialized countries have already decided that, in their specific settings (i.e. geographical distance from endemic countries, very high immunization coverage, temperate climates, and high sanitation and hygiene) the risks of cVDPVs and of VAPP due to continued use of OPV are greater than those due to wild poliovirus importations. Consequently, some of these countries have adopted routine vaccination schedules that rely either exclusively on IPV or on a sequential IPV/OPV schedule (Prevot DR et al, 2000). So far, such countries have had no documented importation of WPVs or spread after importation of VDPVs.

**WHO policy recommendations**

All children world-wide should be immunized against polio and every country should seek to achieve and maintain high levels of coverage with polio vaccine.

**Choice of vaccine**

As outlined in the schematic below, the potential for WPV importation (nowhere less than moderate) and transmission are crucial factors to be considered when defining the national policy on polio immunization.
OPV alone, including a birth dose (zero dose), is recommended in all polio-endemic countries and those at high risk for importation and subsequent spread. The birth dose should be administered at, or as soon as possible after birth to increase the seroconversion rates of subsequent doses and to induce mucosal protection before enteric pathogens may interfere with the immune response. Also, administration of the first OPV dose at a time when infants are still protected by maternally-derived antibodies may, at least theoretically, prevent VAPP. Even in cases of perinatal HIV infection, an early OPV vaccination seems to be well tolerated and so far, no additional risk of VAPP has been documented in such cases.

OPV alone, preferably with a birth dose, is recommended also in all countries with medium or high WPV transmission potential, as determined mainly by the level of immunization coverage, sanitation, and overall socio-economic status. A birth dose of OPV is not considered necessary in countries where the risk of polio virus transmission is low, even if the potential for importation is high/very high.

Where the risk of WPV importation is high/very high, the transmission potential should be low before alternatives to OPV alone may be considered. Using routine immunization coverage with 3 doses of polio vaccine as a main determinant of transmission potential, WHO, based on expert opinion, suggests that in countries with very high risk of WPV importation, a sequential IPV/OPV schedule should not be introduced unless immunization coverage is approximately 95%, or, with lower importation risk, approximately 90%. Where a sequential IPV/OPV schedule is used, it is recommended that the initial administration of one or two doses of IPV be followed by at least two doses of OPV to ensure sufficient levels of protection in the intestinal mucosa while decreasing the burden of VAPP at the same time.
IPV alone can be considered as an alternative to OPV alone (or an IPV/OPV sequential schedule) only in countries with the lowest risk of both WPV importation and WPV transmission. Switching from OPV to IPV for routine vaccination during the pre-eradication era is not cost-effective based on the existing economic analyses and current IPV costs.

**Schedules**

Apart from a potential birth dose, the primary series of 3 OPV vaccinations should be administered according to the respective national immunization programmes, for example at 6, 10, and 14 weeks or 2, 4 and 6 months of age. Intervals between doses must be at least 4 weeks.

IPV is given intramuscularly (preferably) or subcutaneously, and may be offered as a component of fixed vaccine combinations. A primary series of 3 or 4 doses should be administered at ages 2, 4, and 6 months (3-dose schedule), or alternatively at 6, 10, and 14 weeks followed by a booster dose with an interval of at least 6 months (4-dose schedule).

Where sequential IPV/OPV is used, WHO recommends that IPV be administered at 2 months of age (or at 2 and 4 months with two initial IPV doses), and that the subsequent two OPV doses be administered at 6-18 months and 4-6 years of age. For persons of any age, the first three doses should be separated by at least 4 weeks, although an interval of 6–8 weeks is preferred. Both IPV and OPV can be administered simultaneously with other vaccines of the national childhood immunization programme.

**Vaccination of travelers**

Travelers to polio-endemic countries/areas who have previously received three or more doses of OPV or IPV should be offered another dose of polio vaccine as a once-only dose before departure. Non-immunized individuals intending to travel to polio-endemic destinations should complete a primary schedule of polio vaccines, using either IPV or OPV. For frequent travelers to polio-endemic areas staying for brief periods of time, a one-time-only additional dose of a polio vaccine after the primary series should be sufficient to prevent disease.

To reduce the risk of international spread of WPV, those living in polio-endemic countries should have completed a full course of vaccination against polio, preferably with OPV, before travelling abroad. Such travelers should receive an additional dose of OPV between 1 and 12 months prior to each international travel. In case of urgent travel, a minimum of one dose of OPV should be given, ideally 4 weeks before departure. Some polio-free countries (e.g. Saudi Arabia) may require travelers from polio-endemic countries to be immunized against polio in order to obtain an entry visa and/or to receive an additional dose on arrival in the country.
Selected references

(NB references will occur chronologically as footnotes in the text as X (first author only)


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