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Clinical Study Protocol

Protocol Title:	**A Phase 4, Randomized, Open-Label Study to Assess the Induction of Humoral and Intestinal Polio Immunity Following a Three-Dose Trivalent Inactivated Polio Vaccine (IPV) Schedule Relative to Two Sequential Schedules of IPV followed by Bivalent Oral Polio Vaccines (bOPV) Administered During the First Year of Life**
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Sponsor:	**Fundación para Estudios Biomédicos Avanzados (FEBA) de la Facultad de Medicina de la Universidad de Chile (**with grant support from the Bill and Melinda Gates Foundation) Independencia 1027, Santiago, Chile
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
AFP	acute flaccid paralysis
AUC	area under the curve
BMGF	Bill and Melinda Gates Foundation
bOPV	bivalent oral polio vaccine
BW	birth weight
CDC	Centers for Disease Control and Prevention
cVDPV	circulating vaccine-derived poliovirus
CRF	case report form
CRO	Clinical Research Organization
DSMB	Data Safety Monitoring Board
eCRF	electronic case report form
GCP	Good Clinical Practices
GMC	geometric mean concentration
GMT	geometric mean titer
GSK	Glaxo SmithKline
HIV	human immunodeficiency virus
ICF	informed consent form
IEC	Independent Ethics Committee
IM	intramuscular
IME	important medical event
IPV	inactivated polio vaccine
IRB	Institutional Review Board
mOPV2	monovalent oral polio vaccine type 2
NIP	National Immunization Program

OPV	oral polio vaccine
PAHO	Pan American Health Organization
PI	Principal Investigator
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
tOPV	trivalent oral polio vaccine
USA	United States of America
USD	United States dollars
VAPP	vaccine-associated paralytic poliomyelitis
WHA	World Health Assembly
WHO	World Health Organization

1.0 BACKGROUND AND RATIONALE

The global effort to eradicate polio has made significant progress in recent years. From 01 January through 02 October 2012, only 154 cases of wild-type paralytic polio have been reported to the World Health Organization (WHO) and only 3 countries account for wild-type poliovirus transmission —Afghanistan, Pakistan, and Nigeria. (1) No cases have been reported in India since January 2011, suggesting that transmission there has at last been successfully interrupted. It is hoped by 2014 that there will be no more cases of disease caused by wild-type polioviruses anywhere in the world. Nevertheless, success in global eradication is not yet assured, as the global polio eradication program came close to meeting its goal in 2001, reaching a nadir of 483 cases. Regrettably, the exportation of wild-type polioviruses from endemic countries occurred due to political and programmatic issues affecting vaccine coverage. In addition, outbreaks due to vaccine adapted strains occurred.

At its tenth plenary meeting in May 2012, the Executive Board of the World Health Assembly (WHA) declared "the completion of poliovirus eradication a programmatic emergency for global public health." (2) The Assembly also asked the WHO Director General to develop "a comprehensive polio eradication and endgame strategy that exploits new developments in poliovirus diagnostics and vaccines," to address the "…potential timing of a switch from trivalent to bivalent oral poliovirus vaccine for all routine immunization programs," and to promote "…the research, production, and supply of vaccines, in particular inactivated polio vaccines, in order to enhance their affordability, effectiveness, and accessibility."

Despite recent successes, and the recommitment from the global community to finalize global eradication of polioviruses, programs and countries involved in the endgame strategy face several significant challenges:

1. How to ensure the complete elimination of wild-type polioviruses in a diversity of epidemiologic settings.

2. How to optimize immunization strategies for diverse settings using current polio vaccines—oral (OPVs) and inactivated (IPVs)—as well as those in development.

3. How to achieve the elimination of all polioviruses, especially the vaccine-derived polioviruses arising from the use of OPVs, while maintaining population immunity until eradication is certified.

4. How to make IPV available and affordable to most countries to hasten eradication and provide security against re-emergence of polioviruses in the post-eradication era.

1.1 Ensuring Complete Elimination of Wild-Type Polioviruses Using All Vaccines

Achieving polio eradication depends upon achieving not only individual protection through the use of an effective vaccine, but also maintaining enough community protection to prevent poliovirus reintroduction and transmission. The oral polio vaccine developed by Albert Sabin has been in widespread use since the early 1960s and has formed the backbone of the global polio eradication initiative. (3) Largely as a result of routine infant OPV immunization, polio was eliminated from Europe and North America by the 1980s. Most notable for the global program, intense OPV-based vaccination campaigns spearheaded by the Pan-American Health Organization (PAHO) and Latin American Ministries of Health resulted in elimination of polio from Latin America and the Caribbean by 1991, an achievement that demonstrated that polio eradication in the developing world was possible.

Until recently, trivalent OPV (tOPV, incorporating types 1, 2, and 3 polioviruses) has been the preferred vaccine for polio control and eradication. However, a reduced immune response to OPV strains has been recognized, particularly to vaccine virus types 1 and 3 in developing countries compared to industrialized countries. In a review of seroconversion after 3 doses of OPV in developing countries, the rate was 73% (range 36% to 99%) to type 1 and 70% (range 40% to 99%) to type 3, compared to rates typically >97% in industrialized countries for all 3 serotypes. (4) In some developing countries like India and Pakistan, poorer immune responses are observed and more doses of OPV are required. Postulates for this reduced immune response include interference between the 3 poliovirus serotypes contained in OPV, co-infection with other enteroviruses, maternal antibody, diarrheal disease, and tropical enteropathy. (5, 6) In India, which was until 2011 one of the last strongholds for endemic wild-type poliovirus, it was demonstrated that the use of monovalent OPVs (mOPVs) against poliovirus 1 and 3 were far superior to trivalent OPV in achieving seroconversion rates in children using fewer doses. (7)

Furthermore, the last naturally acquired wild-type 2 poliovirus worldwide was detected in 1999, suggesting that this wild type virus has been eradicated for more than a decade now. Thus the only type 2 disease presently encountered is caused by circulating vaccine-derived poliovirus type 2 strains (cVDPV2), which through mutation have acquired some properties of neurovirulence and transmissibility found in wild-type viruses. In fact vaccine-derived type 2 poliovirus (cVDPVs) are now the only cause of type 2 poliovirus circulation. To eliminate the risk of generating more cVDPV2 outbreaks, as well as reduce the impact of type 2 vaccine-associated paralytic poliomyelitis (VAPP), the WHO is promoting to replace OPV with a bivalent OPV (bOPV) formulation (which contains only Sabin types 1 and 3) for use worldwide. Like mOPVs, bOPV provides better immunogenicity and protection against type 1 and 3 compared with OPV, as was clearly demonstrated in a recent case-control study in Afghanistan and Pakistan. (8) However, switching from OPV to bOPV will result in new

birth cohorts without immunity to type 2 poliovirus, and thus potentially susceptible to virulent and transmissible type 2 polioviruses arising from cVDPV type 2 outbreaks, and type 2 wild-type poliovirus if it is somehow reintroduced potentially through a break in laboratory containment or from some long-term excretors. These transition challenges in the use of OPV require research to better define the overall endgame strategies for global polio eradication including differential strategies for different regions. A main issue will be the incremental use of bivalent OPV in a world with an ongoing risk for type 2 cVDPV in which the benefit of IPV needs to be appropriately dimensioned.

1.2 How to Optimize Immunization Strategies for Diverse Settings Using Current Polio Vaccines

As proposed in this study, one approach to improve the immunogenicity and protection afforded by OPV, is to combine the benefits of bOPV with those of IPV. Vaccination regimens employing sequential combinations of IPV and OPV have been utilized in a number of countries, including the United States of America (USA). In developed countries where elimination of polio was achieved, VAPP was seen as a major public health problem with more paralysis being caused by the vaccine then the wild type viruses. Although somewhat more costly, giving IPV before OPV prevented most VAPP and provided the benefits of both vaccines in a combined schedule. The initial IPV immunization promoted priming and humoral immunity and the subsequent OPV vaccination was expected to induce higher levels of both humoral and intestinal immunity required to maintain population-level protection, while decreasing the risk of VAPP.

Estimates of VAPP reduction from sequential IPV/OPV schedules range from 50% to 75%. (9) Furthermore, the sequential schedule of IPV followed by OPV in the USA achieved high seroconversion rates, with optimal effect in one study obtained during 2 doses of IPV followed by 2 doses of OPV, a regimen that also produced intestinal immunity comparable to 3 doses of OPV. (10) The efficacy of this strategy has also been studied in the developing world: a trial of IPV followed by OPV in Guatemalan infants demonstrated robust development of both humoral and intestinal immunity even after only 2 doses of IPV. (11)

The potential benefits of using IPV in the context of the Polio eradication endgame include achieving protection against type 2 cVDPVs following the transition from OPV to bOPV, eventual protection from cVDPVs for all 3 serotypes during the process of OPV cessation, and prevention of VAPP — particularly after wild-type paralytic polio is eliminated. However, research regarding the optimal strategy (especially relating to timing and number of IPV doses) for utilization of IPV in the polio eradication endgame is incomplete. Such research can also provide important information for an eventual transition to inclusion of IPV in pediatric combination vaccines for use in the developing world.

1.3 Achieving Elimination of All Polioviruses While Maintaining Population Immunity

Since man is the sole reservoir, poliovirus eradication can be achieved, but the last challenge will be to sustain eradication by eliminating oral poliovirus immunizations. As long as OPV is used, there will be a risk of VAPP and a risk of reversion to cVDPVs with outbreaks of vaccine-derived polio, which may threaten the success of the eradication endgame. Outbreaks of cVDPV were first documented in 2000 to 2001 in the Island of Hispaniola, and subsequent epidemics have occurred in more countries that had been free of paralytic polio, including China, the Philippines, Indonesia, Cambodia, and Madagascar, as well as countries with circulating wild-type polioviruses. (12) The major risk factor for emergence of cVDPVs appears to be low vaccine coverage for the serotype that emerges. The most significant and persistent cVDPV outbreak, caused by a type 2 vaccine strain, occurred in Nigeria and so far has affected more than 300 children over an 8-year period between 2005 and 2012, and still appears to be continuing, spreading to neighboring DR Congo. (13) Almost all recent outbreaks of cVDPV have been caused by serotype 2, coincident with shifts in vaccination programs toward bOPV or mOPV1 and 3, resulting in reduced population immunity to type 2 viruses.

In addition to the potential for cVDPV transmission, OPV uncommonly causes VAPP in vaccine recipients or their close contacts, especially after the first doses when immunity has not yet developed. The WHO estimates approximately 250 to 500 cases of VAPP will continue to occur throughout the world annually if OPV use continues indefinitely. (14) For these reasons, the WHO has published a framework that addresses the rationale, risks, and timing of a globally coordinated complete OPV cessation. One of the major concerns during this last phase of the global polio eradication is the risk of wild-type and vaccine derived transmission in communities. As most poliovirus infections are asymptomatic (paralysis occurs in 1 of every 100 to 1000 infected), silent transmission can occur for long periods of time before paralytic cases become manifest.

The transmission of polioviruses occurs via oral-oral or fecal-oral routes, and the vast majority of polio infections causes no symptoms and is not clinically detectable. It is believed that fecal-oral transmission is more important in developing countries with poor hygiene and sanitation, though this is not known with certainty. Because it replicates in the intestinal tract, OPV is a good inducer of intestinal immunity that can decrease fecal-oral transmission of wild-type polioviruses in a community, a phenomenon thought to have played a major role in addition to the herd protection in terminating polio transmission. After the transition from OPV to bOPV and following OPV cessation, however, community level immunity to residual cVDPVs and re-emergent wild-type polioviruses will decrease rapidly unless IPV induced immunity can be secured.

First developed in the 1950s by Jonas Salk, IPV contains killed strains to all 3 poliovirus types, and the methods of manufacture have evolved to enhance antigenic potency. It is the safest polio vaccine and does not cause VAPP or cVDPVs, and has not been associated with severe adverse reactions. IPV also appears to provide protection against pharyngeal acquisition and shedding of polioviruses that is equivalent to OPV, and can therefore interrupt oral-oral transmission of poliovirus, which is believed to be the primary route of spread in industrialized countries with better hygiene. (15, 16) Consequently, IPV alone was used to eliminate wild-type poliovirus in a number of industrialized Northern European countries including Norway, Sweden, Finland, and the Netherlands. In contrast to OPV, however, IPV does not seem to induce robust intestinal immunity, nor does it provide secondary immunization of contacts, and thus the impact of IPV on reducing transmission in developing countries setting where fecal-oral transmission is thought to dominate, is not known. (17) IPV is currently more costly, requires injection, fails to induce secondary immunizations, and induces less intestinal immunity or reduction in fecal shedding which is a measure of ability to reduce transmission in the community by fecal oral route.

A recent meta-analysis of fecal polio shedding in IPV and OPV vaccinated subjects concluded that IPV had no significant impact on fecal shedding, either when given exclusively or as a supplement to OPV, measured by the proportion of subjects who shed poliovirus in stools following a challenge. (17) In fact, persons vaccinated with IPV alone were as likely to shed polioviruses post-challenge with OPV as naïve persons receiving OPV for the first time. Some studies have shown a correlation between high serum neutralizing titer and fecal excretion, but there is controversy regarding this purported relationship. (18) A caveat to the above statement is that the majority of studies examining fecal excretion have not used explicitly quantifiable methods; the most quantifiable measure of fecal poliovirus excretion is an index that measures viral excretion over a period of time after an OPV challenge. Studies that assessed the impact of IPV on viral excretion after OPV challenge using quantitative measures do suggest that IPV could lower the duration of shedding and titer of poliovirus in stools compared to unvaccinated children with a range between studies of 63% to 91% reduction in the total amount of virus shed. (17) A review by Sutter et al., using a shedding index based on proportion and duration of shedding, and the average titer shed, suggested that IPV reduced this index by 95% compared to unvaccinated persons whereas OPV reduced it by 99% (19).

Whether the inferiority of IPV relative to OPV in reducing fecal viral shedding accurately reflects their relative ability to reduce fecal-oral transmission of wild-type or vaccine-derived poliovirus in developing country settings with poor hygiene, sanitation, and crowding, is unclear. If IPV provides only individual protection in these settings, the eradication program could be put in jeopardy in that a substantially greater proportion of infections will become subclinical—IPV preventing overt disease, but not transmission. Thus, by the time a case of polio-caused acute flaccid paralysis (AFP) is detected, a cVDPV could be widespread and

containment difficult. On the other hand, if IPV induces intestinal immunity and retards transmission, then containment of a cVDPV outbreak would be substantially easier. Thus, assessing whether IPV can reduce fecal shedding as measured by the shedding index following OPV challenge provides important information regarding the potential benefits and risks of including IPV in routine immunization programs in developing countries.

1.4 Making IPV Available and Affordable to the World

In addition to the potential for emergence of a virulent cVDPV, other potential threats to eradication include the undetected reintroduction and transmission of wild-type virus, from immunecompromised individuals who can become long-term shedders, or the accidental "escape" of virus from a research or vaccine production facility, or even the use of poliovirus as an agent of bioterrorism. (20, 21) These are risks for populations with inadequate polio vaccine coverage, which will require a prolonged and concerted global vaccination strategy (polio vaccine endgame). Ultimately IPV will play an important role as part of sequential and/or combination vaccine regimens in order to maintain population immunity for the endgame. IPV is licensed in over 80 countries, and is now used as the sole polio vaccine in many industrialized nations. A typical IPV-only schedule includes 3 primary doses in the first year, with 1 or 2 boosting doses in early childhood. Given in this manner, IPV is effective at promoting humoral immunity which provides individual protection against paralytic disease (22).

The efficacy of IPV alone in maintaining population immunity depends on a number of factors including rates of vaccine coverage, and the general hygiene and sanitation (which can dictate whether the principal route of transmission is fecal-oral or oral-oral). In many areas of the developed world, IPV has been highly effective at protecting populations from re-introduction of polio. In an outbreak of wild-type poliovirus in the Netherlands in 1992, where a 6-dose IPV vaccination schedule was utilized, 71 cases of paralytic polio cases occurred exclusively in an un-immunized subset of the population. (23) In a subsequent analysis of students in a single school at the heart of this outbreak, the rate of overall polio infection (diagnosed by seroconversion and/or stool culture) was 13% in IPV vaccinated children and 57% in unvaccinated children, suggesting a herd immunity impact on transmission. (24)

IPV will clearly play a central role in the final stages of global polio eradication, and this has begun in some developing countries, including in Central and South America. However, significant barriers to widespread use of IPV throughout the developing world remain. Foremost among these barriers is cost and need for injection (at present approximately 3 United States dollars [USD] per dose on the UNICEF contract) and current manufacturing capacity, estimated at only 40% of likely need.

1.5 Interference between Oral Polio and Rotavirus Vaccines

Rotavirus vaccine trials performed in South Africa (Rotarix™) (25, 26), Bangladesh (Rotarix™) (27), and Latin America (Rotarix™ and RotaTeq™) (28, 29) have shown that concomitant rotavirus vaccine administration does not affect the immune responses to OPV as measured by seroconversion rates after the third dose. The immune response to rotavirus, as measured by antirotavirus IgA seroconversion rates and geometric mean concentrations (GMCs) achieved, were lower when both vaccines were co-administered, compared with groups receiving IPV or groups in which the oral vaccines were staggered by 15 days. In the South African studies, a seroconversion rate reduction was observed after the first dose, more strikingly in infants receiving this dose at 6 weeks of age. After the second dose, seroconversion rates tended to level. In the Bangladesh study, seroconversion rates after the second dose were 15% lower and GMCs 38% lower in the group receiving concomitant vs. staggered rotavirus-OPV vaccines. Rotavirus vaccine shedding was also lower (43% overall). In the Latin American studies, for Rotarix™ a comparison of GMCs from 2 different studies reported a 32% reduction in GMCs and 18% reduction in seroconversion rates among children participating in the study receiving concomitant vaccines compared to the study in which vaccines were staggered (30). Nevertheless, vaccine efficacy observed in both studies was 82% and 85% respectively. For RotaTeq™ a reduction in 47% and 5% was observed for GMCs and seroconversion rates in the co-administration group.

It is feasible that a schedule based on IPV at 8 weeks, time of the first rotavirus vaccine dose in our current proposal, followed by an IPV (Groups 2 and 3) or bOPV (Group 1) at 16 weeks together with the second rotavirus vaccine dose, may provide different antirotavirus IgA seroconversion rates and GMCs. This information is important for policy makers when deciding on the benefits of 1 versus 2 doses of IPV in the primary polio vaccination series.

1.6 Study Rationale

The rationale for this study (**IPV 002ABMG**) and its companion clinical trial (**IPV 001ABMG**) being conducted elsewhere in Latin America are to evaluate the sequential use of both IPV and bOPV vaccines in various sequences administered to young infants. The overarching goal of both studies is to provide evidence for better immunization policy making in regions of the world that must switch to use of bOPV in the 2014-2015 time frame using or not using IPV as a supplement. Many options for a sequential use of bOPV and IPV are possible, that might optimize humoral immune responses, intestinal immunity and thereby prevent community transmission as well as prevent VAPP. It is the intent of these 2 studies to evaluate selected immunization options and their potential advantages, which have relevance in Latin America and elsewhere globally.

The primary objective of this trial is to compare 2 sequential schedules of IPV followed by bOPV (1 dose of IPV followed by 2 doses of bOPV, or 2 doses of IPV followed by 1 dose of

bOPV) relative to a 3-dose regimen of IPV alone, to assess the non-inferiority of each of the sequential regimens. Specifically, the study seeks to show that both of the sequential regimens are equivalent (not-inferior) to the 3-dose IPV regimen in the seroconversion rates to both type 1 and type 3 poliovirus such that not more than 10% of subjects fall below the 95% confidence interval observed for the 3-dose IPV alone regimen and the geometric mean titers (GMTs) are no more than 2/3 logs less than those for the 3-dose IPV regimen. In addition, the study will evaluate by a novel method (poliovirus shedding index), the adequacy of IPV vaccines in inducing intestinal immunity, specifically by reducing the shedding of poliovirus type 2 after an OPV challenge.

This study employs 3 different polio vaccination groups: 1) a 3-dose IPV regimen; 2) 2 doses of IPV followed by 1 dose of bOPV, and 3) 1 dose of IPV followed by 2 doses of bOPV. The hypotheses of the study are:

- A 3-dose IPV/bOPV sequential schedule including 1 or 2 doses of bOPV is non-inferior in terms of types 1 and 3 seroconversion rates and GMTs to a 3-dose IPV schedule.
- Two and possibly 1 IPV dose(s) provides significant seroconversion rates and GMTs to type 2 poliovirus and sufficient priming to induce a rapid immune response in the context of an oral challenge at 7 months of age.
- Three, 2, and possibly 1 dose of IPV will induce intestinal immunity to poliovirus type 2 as measured by a combination of quantity of virus in stools and duration of shedding (shedding index).

In addition to these 3 hypotheses, the study will explore the following hypothesis:

- Co-administration of bOPV and rotavirus at 16 weeks of age (the second rotavirus dose) provides similar antirotavirus IgA seroconversion rates and GMCs compared to subjects receiving rotavirus vaccine together with IPV.

The answers to these hypotheses will help to determine the safety and potential benefits of a sequential IPV/bOPV schedule while constraining cost.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

1. To assess the non-inferiority of the humoral immune response following 2 doses of IPV and 1 dose of bOPV compared to 3 doses of IPV as measured at 1 month after the final (third) dose by seroconversion and GMTs to polio types 1 and 3.

2. To assess the non-inferiority of the humoral immune response following 1 dose of IPV and 2 doses of bOPV compared to 3 doses of IPV as measured at 1 month after the final (third) dose by seroconversion and GMTs to polio types 1 and 3.

2.2 Secondary Objectives

1. To compare the humoral immune response to 1 dose of IPV followed by 2 doses of bOPV compared to 3 doses of IPV as measured at 1 month after the final (third) dose by seroconversion and GMTs to polio type 2.

2. To compare the humoral immune response to 2 doses of IPV followed by 1 dose of bOPV compared to 3 doses of IPV as measured at 1 month after the final (third) dose by seroconversion and GMTs to polio type 2.

3. To compare the humoral immune response to polio type 2 as measured by seroconversion and GMTs achieved within seven day of an mOPV type 2 challenge in children receiving 1, 2, or 3 doses of IPV in the primary series.

4. To determine the safety of the different vaccine schedules.

5. To describe and compare the shedding of type 2 polio virus post mOPV2 challenge as expressed by a 28-day shedding index in infants who have received 1, 2, or 3 doses of IPV.

2.3 Exploratory Objective

1. To compare antirotavirus IgA seroconversion rates and GMCs of Group 1 infants receiving bOPV together with the second dose of Rotarix^{TM} at 16 weeks of age with Group 2 and 3 infants receiving this second Rotarix^{TM} dose together with IPV.

3.0 STUDY DESIGN

This is a multicenter, randomized, unblinded study. Healthy infants attending the well-child care at outpatient clinics and due for their first dose of polio vaccines will be eligible for the study. Infants 8 wks ± 7 days of age will be randomized and allocated to the treatment groups shown in Table 1.

Table 1 Summary of Vaccine Group Assignments, Vaccine Administrations, and Specimen Collections (subject age in weeks)

Study Groups	Vaccines Administered*		Oral Vaccine Challenge	Specimens Collected/ Outcomes Assessed**	
	Sanofi IPV	Sanofi bOPV	GSK mOPV2	Antibody (blood)	Shedding (stool)
	(weeks)	(weeks)	(weeks)	(weeks)	(weeks)
Group 1 (N=190)	8[#]	16[#], 24[@]	28	8[¶], 16, 28, 29	28, 29, 30, 31, 32
Group 2 (N=190)	8[#], 16[#]	24[@]	28	8, 24, 28, 29	28, 29, 30, 31, 32
Group 3 (N=190)	8[#], 16[#], 24[@]	None	28	8, 24, 28, 29	28, 29, 30, 31, 32

* Vaccine administered: ±7 days for each time point.
** Outcomes: Safety will be assessed during each visit. Stool samples will be collected and stored for later testing.
[#] Routine vaccine DTPwHib/HepB and *S pneumoniae*; oral rotavirus vaccine (if accepted).
[@] Routine vaccine DTPwHib/HepB and *S pneumoniae*.
¶ This sample can also be obtained at 7 weeks of age if parents preference.

4.0 STUDY POPULATION

The study will be conducted in up to 7 "vacunatorios" in Chile. Parents or legal guardians of healthy infants, who are receiving well-child care at designated outpatient clinics, will be approached to participate in the study. The inclusion and exclusion criteria to be eligible for the study are as follows:

4.1 Inclusion Criteria

Subjects who meet the following criteria will be included in the study:

1. Age: 8 weeks (-7 to +7 days).
2. Healthy infants of all ethnicities and both genders without obvious medical conditions that preclude the subject to be in the study as established by the medical history and physical examination.
3. Written informed consent obtained from 1 parent or legal guardian who, in the opinion of the investigator, is capable of understanding and complying with the protocol requirements.

4.2 Exclusion Criteria

Subjects who meet the following criteria will be excluded from the study:

1. Previous vaccination against poliovirus.
2. Low birth weight (BW <2,500 grams).
3. Twins or multiple pregnancy infants.
4. Another family or household member who has received OPV within the past 6 months or is going to receive OPV within the following 6 months.
5. Any confirmed or suspected immunosuppressive or immunedeficient condition including human immunodeficiency virus (HIV) infection.
6. Family history of congenital or hereditary immunodeficiency.
7. Major congenital defects or serious chronic illness (neurologic, pulmonary, gastrointestinal, hepatic, renal, or endocrine).
8. Known allergy to any component of the study vaccines.

9. Uncontrolled coagulopathy or blood disorder contraindicating intramuscular injections.

10. Administration of immunoglobulins and/or any blood products since birth or planned administration during the study period.

11. Subject who, in the opinion of the Investigator, is unlikely to comply with the protocol or is inappropriate to be included in the study for the safety or the benefit-risk ratio of the subject.

4.3 Contraindications to Subsequent Vaccination

The following adverse events (AEs) constitute absolute contraindications to further administration of the study vaccines:

- Serious adverse event (SAE; see Section 8.2) or important medical event (IME; see Section 8.2) after vaccination.
- Known hypersensitivity to any component of the vaccine or severe reaction following previous administration of the vaccine.
- Any intercurrent medical condition that in the judgment of the study physician will interfere with scheduled vaccinations and/or possibly impair the immune response to polio vaccination including those listed in Section 4.2.

If any of these AEs occur during the study, the subject will not receive additional doses of vaccine but may continue other study procedures at the discretion of the Investigator. The subject will be followed until resolution of the event and until end of the follow up period.

4.4 Subject Withdrawal and/or Termination

Study participants may be withdrawn from the study at any point for any reason. Withdrawal will not affect in any way the treatment of the infant by the health care system. If the child is withdrawn, investigators will ensure that the child will complete his vaccination schedule according to the Chilean National Immunization Program (NIP) schedule. The data collected for withdrawn subjects, in addition to case report form (CRF) data, will include the reason for withdrawal. Subjects will not be replaced. Subjects who have withdrawn from the study will be asked to accept follow up for determination of the safety endpoints, especially those who have an ongoing SAE.

In addition, the following are conditions that will exclude the participating subject from continuation in the study protocol:

- Administration of poliovirus vaccines outside the study protocol or administration of OPV to another child within the household.
- Poor compliance with the study protocol.
- Any contraindication to the study vaccines that arises during the study period.

If any of these conditions for exclusion develop during the study, the subject will be followed for safety purposes until the end of the study period.

Handling Data from Subjects Who Have Withdrawn

- Safety data for subjects withdrawn will be included in the per-protocol analysis if they have received at least 1 dose of study vaccines.
- Immunogenicity data will be included in an intention to treat analysis if they have received at least 1 dose of study vaccines.
- Immunogenicity data for children who received additional polio vaccine outside of the study protocol will only be included up to the time of this protocol violation.
- Subjects will be followed up to the termination of the study for any safety outcomes of interest as defined in the protocol.

5.0 TREATMENT OF SUBJECTS

5.1 Vaccines

The vaccines to be used in this study include bOPV, mOPV2, and IPV (see Section 14.2 for package inserts).

5.1.1 Bivalent Oral Polio Vaccine (bOPV)

Produced by Sanofi Pasteur, Lyon, France, bivalent OPV vaccine contains types 1 and 3 polioviruses and it is indicated for supplementary immunization activities in children from 0 to 5 years of age to prevent or contain outbreaks caused by these 2 serotypes. The vaccine contains at least 6.0 log $CCID_{50}$ of LS c2ab live attenuated polio virus type 1; and at least 5.8 log $CCID_{50}$ Leon I2aIb strain of polio virus type 3. The vaccine dose is 2 drops (0.1 mL) using a multi-dose dropper vial, given directly into the mouth. The vaccine should be stored in a freezer at -20°C, and after thawing it can be stored up to 6 months at refrigerated temperatures of +2 to +8°C.

5.1.2 Monovalent Oral Polio Vaccine Type 2 (mOPV2)

Monovalent OPV type 2 live attenuated poliomyelitis virus vaccine (mOPV2) is produced by Glaxo SmithKline, Rixensart, Belgium, as a sterile suspension of poliovirus serotype 2 for oral administration. Each dose (0.1 mL) contains not less than $10^{5.0}$ $CCID_{50}$ of the Sabin strain type 2 (P 712, Ch, 2ab). This will be the challenge OPV strain used to assess intestinal shedding and immunity. The vaccine should be stored in a freezer at -20°C, and after thawing it can be stored up to 6 months at refrigerated temperatures of +2 to +8°C.

5.1.3 Inactivated Polio Vaccine (IPV)

Inactivated poliovirus vaccine is produced by Sanofi-Pasteur as a sterile suspension of 3 types of poliovirus. Each dose of vaccine (0.5 mL) contains 40 D antigen units of Mahoney strain (Type 1); 8 D antigen units of MEF-1 strain (Type 2); and 32 D antigen units of Saukett strain (Type 3). It also contains 0.5% of 2-phenoxyethanol and a maximum of 0.02% of formaldehyde as preservatives. It may also contain 5 ng of neomycin, 200 ng of streptomycin, and 25 ng of polymixin B as residuals of the vaccine production. The vaccine does not contain Thimerosal. The vaccine should be kept refrigerated at +2 to +8°C, and should never be frozen. The dose of IPV vaccine should be 0.5 mL administered intramuscularly in the anterolateral aspect of the thigh.

5.2 Vaccine Intervals and Administration

All polio vaccine doses should be administered at least 4 weeks or more apart. For IPV, the administration site is restricted to the anterolateral aspect of the left thigh.

- All other intramuscular (IM) EPI routine vaccines will be administered to the anterolateral aspect of the right thigh (or the arm at 16 weeks when 3 vaccines are to be administered including IPV, pentavalent combination vaccine, and *S. pneumoniae*). These vaccines should not be injected in the gluteal area or areas where there may be a major nerve damage.
- IPV will be administered IM at Week 8 (Group 1), Weeks 8 and 16 (Group 2), or Weeks 8, 16, and 24 (Group 3).
- Bivalent OPV will be administered as oral drops (2 drops for each vaccination) at Weeks 16 and 24 (Group 1) or Week 24 (Group 2).
- An oral challenge dose (2 drops) of mOPV2 will be administered at Week 28.

Prior to an injection of any vaccine, all known precautions should be taken to prevent adverse reactions. This includes a review of the potential participant's history with respect to possible allergic reactions to the vaccine or similar vaccines. Epinephrine Injection (1:1000) and other appropriate agents should be available to control immediate allergic reactions. Health-care providers should obtain the previous immunization history of the subject, and inquire about the current health status of the subject.

Infants participating in the study will be provided the recommended vaccines aside from polio vaccine as per the National Immunization Schedule of Chile (DTPw/HBV/Hib, *S. pneumoniae* vaccine).

In addition, a 2-dose (Rotarix^{TM}) oral rotavirus vaccine will be offered during the study at 8 weeks and 16 weeks of age.

Serology Testing

Rational for each blood sample: After thorough discussions on the minimum number of serum samples required to obtain valid answers to our hypothesis, the research group has arrived to the following:

1. Baseline serum sample at 7-8 weeks to determine antibody titers to polioviruses (and rotavirus) before any vaccination, required as a basis to detect seroconversion rates.
2. Post IPV dose 1 at 16 weeks (Group 1) or IPV 2 at 24 weeks (Groups 2 and 3) to determine IPV/bOPV dose-dependent seroconversions for poliovirus 2 with the shortest possible latency after vaccination to avoid the potential confounder associated with exposure to circulating poliovirus 2 vaccine viruses.

3. Post 3 doses to measure the primary objective, seroconversion and GMTs to types 1 and 3 after the different schedules. This serum will also be used for antirotavirus antibody determinations in order to calculate seroconversion rates and GMCs achieved.

4. One week post-type 2 live poliovirus vaccine challenge at 28 weeks to determine if infants who have not seroconverted to type 2 poliovirus after completing the series of 3 immunizations at 8, 16, and 24 weeks in each of the 3 groups, do so rapidly within 1 week after the challenge. Seroconversion within 1 week strongly suggests that although the individual had not seroconverted prior to the mOPV2 challenge, that they would do so rapidly should they encounter cVDPV2 in the environment; this in turn suggests that although they might become infected by cVDPV2, their risk of developing neuroparalytic disease as a consequence would nonetheless be substantially reduced.

A total of 4 blood samples will be collected for each study subject. A maximum of 3 mL will be obtained by heel stick or venipuncture methods. Each blood sample will be transported within 24 hours in appropriate cold chain conditions to the "Central Study Laboratory" at the Microbiology and Mycology Program, Institute of Biomedical Sciences, Faculty of Medicine, University of Chile. Sera will be obtained and 2 aliquots will be placed into cryovials, labeled with linked coding, and stored in a -20°C freezer. One aliquot will be shipped in appropriate cold chain conditions to the Polio and Picornavirus Laboratory Branch, Center for Disease Control and Prevention. The second aliquot will be left on repository storage at the study center.

Sera will be processed following a standard protocol (see Section 14.1). Neutralizing antibodies against polioviruses 1, 2, and 3 will be determined using a sero-neutralization assay. The laboratory will be blinded with regard to the vaccination status of individuals contributing particular specimens, ensuring the integrity of the study. After successful completion of testing, duplicate specimens will be destroyed. Authorized specimens assays are only for antibody levels to valences included in the study vaccines. Should the case arise, the use of these specimens for any other assay will require the approval of the study Sponsor and the Principal Investigator, as well as Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approval, as per applicable rules and regulations.

Baseline sera and sera obtained at 28 weeks will be processed for antirotavirus IgA concentration as previously described at Glaxo SmithKline laboratories (26).

5.3 Stool Samples for Poliovirus "Shedding Index" determination

Stool samples (5 to 10 grams) will be collected at 5 times for each subject, using WHO approved protocols and kits, and transported and stored following the WHO procedures for detection of polioviruses. Fresh stools will be collected unmixed with urine in a screw-top

container, placed in a cold box with frozen ice packs, and transported to the designated laboratory for storage in a freezer at -20°C. A log book of collected and stored samples will be kept by the study personnel. Stool samples will be used later to determine the excretion of polioviruses as per protocol (Section 14.1). Samples will be sent in batches to the reference laboratory for poliovirus culture.

5.4 Medications/Treatments Permitted (including rescue medication) and not Permitted Before and/or During the Trial

There will be no restrictions in using medications/treatments except for the following conditions: primary immune deficiency or immune deficiency subsequent to treatment, leukemia, lymphoma or advanced malignancy in the subject to be vaccinated or his/her close contact. Only medications to treat SAEs or IMEs will be documented in eCRF. All other medications will be captured and recorded in the source document at the investigators discretion at the investigational site.

5.5 Subject Compliance

Subjects are required to abide by scheduled visits and the vaccine schedule.

6.0 STUDY PROCEDURES

6.1 Enrolment and Study Allocation

Between the birth of the infant and 9 weeks of age parents or caretakers will be advised about the trial. Those who are willing to allow the infant in their care to participate in the study will be asked to provide written informed consent. Parent/Infant pairs interested to participate in the study will be reviewed for eligibility using the inclusion/exclusion criteria; medical history will be taken and a physical examination will be performed.

Eligible subjects will be randomized into 1 of the 3 groups of the study using computer-generated randomization and block sizes of 12; separate numbers and blocks will be set up for each of the study sites. The allocations will be provided to the study Investigator by a central location after informed consent has been obtained. The randomization list will be maintained concealed from the Sponsor, Investigators, study auditor, or Data Safety Monitoring Board (DSMB) unless ruled otherwise by the DSMB or the stopping rules of the study.

6.2 Measures Taken to Minimize/Avoid Bias

This will be a vaccinator-open but immunogenicity assessor-blind study, given that participating infants will be assigned to 3 different groups with different vaccine schedules and vaccines administered. All laboratory personnel processing the serology and stool samples will be blinded to the vaccine group allocation of subjects, which should minimize observer bias.

6.3 Visit Schedule

Overall, subjects will attend up to 8 scheduled visits during the study. Every infant participating in the study will be on the study from 8 weeks (± 7 days) until 8 months of age (± 4 weeks). In addition to the visits every 8 weeks (± 14 days) for the administration of vaccines (at 8, 16, and 24 weeks of age), follow-up visits will occur 4 weeks after the third visit and before mOPV2 challenge dose to measure immunogenicity. Subjects will provide a weekly stool sample (not requiring a visit) up to 28 days post-challenge for virus shedding.

The Schedule of Visits and Study Events is presented in Table 2.

Table 2 Schedule of Visits and Study Events*

Age of Subjects (weeks) **Visit** **Visit intervals in weeks (± 14 days except for first visit 1, 5-8: ± 7 days)**	**8 W** **Visit 1** **0**	**16 W** **Visit 2** **V1 + 8**	**24 W** **Visit 3** **V2 + 8**	**28 W** **Visit 4** **V3 + 4**	**29 W** **Visit 5** **V4 + 1**	**30 W** **Visit 6** **V5 + 1**	**31 W** **Visit 7** **V6 + 1**	**32 W** **Visit 8** **V7 + 1**
Informed consent	X							
Inclusion/exclusion criteria	X							
Medical history	X	X	X	X				
Physical examination	X	X	X	X				
Randomization	X							
Check if contraindications /precautions if will be vaccinated	X	X	X	X				
Stool sampling for all subjects				X	X	X	X	X
EPI: DTPwHib/HepB	X	X	X					
EPI: *S. pneumonia*	X	X						
Optional: Oral rotavirus	X	X						
Study vaccines Group 1	IPV	bOPV	bOPV	mOPV2				
Blood sampling Group 1 (to be done prior to vaccination)	X**	X		X	X			
Study vaccines Group 2	IPV	IPV	bOPV	mOPV2				
Blood sampling Group 2 (to be done prior to vaccination)	X**		X	X	X			
Study vaccines Group 3	IPV	IPV	IPV	mOPV2				
Blood sampling Group 3 (to be done prior to vaccination)	X**		X	X	X			
Post-dose immediate surveillance (30 min) if vaccinated	X	X	X	X				
Recording into CRF of IME	X	X	X	X				X

Serious adverse event	*To be reported at any time during the trial.*							
Protocol termination								X

*Differences in study vaccine and blood sample visits among study groups are accounted for in the table.

**A separate visit at 7 weeks of age (one week before vaccination) may be used for this blood draw in order to avoid 4 needle sticks during one visit.

6.4 Description of "Halting Rules" or "Discontinuation Criteria"

The DSMB will be informed of any SAEs, such as death, non-elective hospitalization, or anaphylaxis within 24 hours of notification. Clusters (3 similar events within 1 week) of IMEs will be reported to the DSMB for evaluation. The DSMB will define the halting rules before the start of the study, as well as any special considerations for modification of the study based on the benefit and safety of the study participants.

6.5 Accountability Procedures for the Investigational Product, Including the Comparator

Comprehensive training of all study staff will ensure that study protocol requirements are being followed. Vaccine will be stored according to cold chain requirements, and detailed inventory logs will be maintained.

6.6 Maintenance of Treatment Randomization Codes and Procedures for Breaking Codes

An independent biostatistician will make the random allocation number. No specific procedures are anticipated for breaking the code, however, as per Good Clinical Practice (GCP), the Sponsor will hire an independent study monitor. We do not anticipate situations when the code would need to be broken, but if such a situation arises, the monitor with Principal Investigator (PI) approval could authorize the breaking of the code if the safety of the subjects is compromised.

6.7 Identification of Any Data to be Recorded Directly on the CRFs (i.e., no prior written or electronic record of data)

A study source document will be generated which will serve as the primary data collection instrument, and will serve as the source data for this study. Medications used to treat SAEs or IMEs will be recorded. Investigators will also ensure that vaccination cards required by the NIP of Chile are completed according to requirements. In the case of SAE to be reported, records and documents used by the hospitals or national vital statistics registry will be part of the source documentation in case of hospitalization, death, or any life-threatening event.

6.8 Potential Risk to the Study Subjects

IPV is safe and effective. As with all licensed vaccines allergic reactions of various severity can occur within a few minutes to a few hours after vaccination to components or excipients present in the vaccine product. As with all injectable vaccines, local injection site reactions of various severities may occur. OPV is safe and effective; in extremely rare cases, the live-attenuated virus in OPV can cause VAPP. While most cases of VAPP occur in persons with normal immune systems, persons with immune deficiency, particularly involving the

humoral immune system are at a much higher risk of VAPP than the general population. The risk for study participants is not increased compared to their risk of OPV administration as part of the routine EPI vaccination.

Subjects will be monitored at the study center after vaccinations and SAEs or IMEs observed will be recorded in the subject's CRF. Furthermore, SAEs and IMEs will be followed during the whole study period.

6.9 Potential Benefits

6.9.1 Benefits to the Study Subjects

All children will receive 4 doses of different polio vaccines (IPV and mOPV 2, or IPV, bOPV, and mOPV 2) by the completion of the study. Oral rotavirus vaccine which is licensed but not part of the NIP in Chile will be provided as an additional child benefit. All children will be carefully monitored for milestones of normal health, growth, and development.

6.9.2 Benefits to the Community

The outcome of this trial will provide the population of the participating countries as well as the Latin American Region with information on vaccination policy development for the OPV cessation era. At least 4 countries in Latin America (Mexico, Costa Rica, Brazil, and Uruguay) have included IPV as the mainstay or in a sequential schedule of their NIP policy against polio. Given the imminent shortfall in the availability of OPV for immunization programs around the world, and the recommendation of WHA for the likely switch to bOPV in the final stage of the polio endgame, the research into ways to safely introduce bOPV in polio-free countries and to maintain protection against type 2 virus will help middle- and low-income countries to determine the best way to sustain polio eradication with IPV and to address the possibility that tOPV may not be readily available to PAHO countries following a WHO recommended shift from tOPV to bOPV usage.

7.0 STUDY ENDPOINTS

7.1 Primary Endpoints

Two primary endpoints will be used as the basis for evaluation of the IPV/OPVb sequential regimens compared to three doses of IPV:

- Seroconversion to type 1 (type-specific titers ≥1:8 and > 4-fold over expected levels of maternally-derived antibody) and GMTs achieved at 28 weeks.
- Seroconversion to type 3 (type-specific titers ≥1:8 and > 4-fold over expected levels of maternally-derived antibody) and GMTs achieved at 28 weeks.

7.2 Secondary Endpoints

- Seroconversion to type 2 (type-specific titers ≥1:8 and > 4-fold over expected levels of maternally-derived antibody) and GMTs achieved after 1 dose of IPV at 16 weeks, after 2 doses at 24 weeks, after 3 doses at 28 weeks, and after the mOPV type 2 challenge dose at 29 weeks.
- Viral shedding index for type 2 virus following mOPV2 challenge (28-day area under the curve [AUC] of quantitative virus shedding at Days 7, 14, and 21 post-mOPV2 challenge).

  The shedding index endpoint will be computed for each study subject as a simple average of log10 viral titer measured from stool samples collected at Days 7, 14, and 21 post-challenge with mOPV2. Values of log10 viral titer for measurements below the assay limit of detection will be assigned the value of zero in computing the shedding index endpoint.
- Safety Endpoints: SAEs as defined in the protocol throughout the study period and IMEs as defined in the protocol up to 28 days post-vaccination.

7.3 Exploratory Endpoints

- Antirotavirus IgA seroconversion (> 20 units/mL) and GMCs after the second dose of Rotarix™ at 16 weeks of age.

8.0 SAFETY ASSESSMENTS

8.1 Specification of the Safety Parameters

Safety will be assessed using the following parameters:

- SAEs as defined in the protocol throughout the study period.
- IMEs as defined in the protocol up to 28 days post-vaccination.

8.2 Adverse Events

The Investigator is responsible for recording all SAEs and IMEs as described in Section 8.1.

An SAE, experience or reaction, is any untoward medical occurrence (whether considered to be related to study drug or not) that at any dose:

- Results in death.
- Is life-threatening (the subject is at a risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization: Hospital admissions and/or surgical operations planned before or during a study are not considered SAEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.
- Results in persistent or significant disability/incapacity.
- Is a congenital abnormality/birth defect detected only after study inclusion.

Important medical events (IMEs) are other medically significant events that do not meet any of the SAE criteria above, but may require medical or surgical consultation or intervention to prevent one of the other serious outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias (e.g., neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization.

8.2.1 Procedures for Eliciting Reports of and for Recording Adverse Events and Intercurrent Illnesses

For intercurrent illnesses, parents will be encouraged to use the study institution for medical services or report the use of other medical facilities when retuning for the next scheduled visit. Serious events in any study participants will be reported according to regulatory requirements in Chile, to the PI, and to the DSMB within 24 hours of notification.

8.2.2 Type, Report, and Duration of Follow-Up of Subjects after Serious Adverse Events

In the case that an SAE (death, hospitalization, or anaphylactic reaction) or IME occurs, referral and medical care will be provided by the health care system.

Investigators will be notified by the Contract Research Organization (CRO) of all SAEs that require prompt submission to their IRB or IEC. Investigators should provide written documentation of IRB/IEC notification for each report to the CRO. The CRO will ensure that all SAEs are reported to the appropriate regulatory authorities.

Any SAEs or IMEs observed from screening/randomization up to the end of the study will be followed up to resolution. Resolution means that the subject has returned to a baseline state of health or the Investigator does not expect any further improvement or worsening of the AE.

9.0 STATISTICAL ANALYSIS

9.1 Primary Objectives

The primary statistical analyses of this study are comprised of comparisons of sequential IPV/bOPV regimens relative to the 3-dose regimen of IPV alone to assess any potential non-inferiority of the sequential regimens (1 dose of IPV followed by 2 doses of bOPV; 2 doses of IPV followed by 1 dose of bOPV). The determination of non-inferiority will be based on humoral antibody responses to type 1 and type 3 polioviruses. Specifically, the sequential regimens will be considered non-inferior if the rates of seroconversion to type 1 and type 3 polioviruses over the entire 3-dose regimen are no more than 10% less than those for the 3-dose IPV regimen and if the GMTs are no more than 2/3 logs less than those for the 3-dose IPV regimen. For each sequential regimen, the overall comparison with IPV will be performed to control the Type I error rate at 0.05 (1-sided). The evaluations of each sequential regimen relative to the common 3-dose IPV comparison group will be considered as independent and no adjustment for multiplicity of comparisons across these evaluations will be made.

Two primary endpoints will be used as the basis for the evaluation of each of the IPV/bOPV sequential regimens and the IPV only regimen: 1) type 1 and type 3 seroconversion (type-specific titers $\geq$1:8 and > 4-fold over expected levels of maternally-derived antibody computed cumulatively across the 3 injections) and 2) geometric mean titers (GMTs). Clopper Pearson "exact" confidence intervals for the difference in binomial proportions will be computed for each of the 2 type-specific seroconversion rates, and confidence intervals for the difference in GMTs will be computed based on Wilcoxon rank statistics. Each of the 2 seroconversion outcomes will be tested for non-inferiority of the sequential regimen relative to the non-sequential IPV regimen with a non-inferiority margin of 10%. The GMT outcomes will be tested for non-inferiority of the sequential regimen relative to the non-sequential IPV regimen with a non-inferiority margin of 2/3 logs. Nominal 1-sided alpha levels of 0.05 will be used for these tests. The sequential regimen will be considered non-inferior overall if a non-inferiority outcome is obtained for each of the 3 endpoints. The Type 1 error for this overall conclusion of non-inferiority is guaranteed to be less than 0.05. If an overall non-inferiority result is obtained then a second set of tests for superiority for both the type 1 and type 3 seroconversion outcomes and for the GMT outcome will be performed. Because of the sequential nature of this testing strategy, the overall Type 1 error rate will be preserved without any further adjustment for the multiplicity of comparisons. Superiority of the sequential regimens will be concluded if at least 1 of the 3 outcomes (2 seroconversion, 1 GMT) is found to be statistically superior. To supplement these formal statistical tests, plots of the point and interval estimates for differences between groups in the

type-specific outcomes will be produced on which lines indicating the non-inferiority margins and superiority thresholds will be drawn.

In order to give a more comprehensive view of the immune responses relative to the sequential and non-boosted regimens, the aforementioned statistical tests for analyses of the primary trial objectives will be supplemented with descriptive analyses including tabulated type-specific rates of seroconversion following each injection, type-specific rates of seroprotection (neutralizing antibody titers > 1:8), and plots of the type-specific reverse cumulative distribution of antibody titers following administration of each component in the vaccine regimen.

9.2 Secondary Objectives

Analyses associated with each of the 2 primary objectives will be supplemented with more detailed descriptive and comparative analyses in 2 analogous secondary objectives. Specifically, the 2 type-specific antibody titers before and after each dose in the 3-dose regimen will be evaluated and compared across the sequential and all-IPV regimens. Rates of seroconversion at each dose will be computed by strata defined by pre-dose level and by levels of responses to prior doses. Rates of seroprotection will be evaluated and compared across regimens following each dose. Marginal and stratified analyses of the quantitative antibody titers will also be performed. Particular attention will be paid to comparison of the responses to the first bOPV dose in the 2 sequential regimens and to the final IPV dose across the sequential non-sequential regimens.

Secondary analyses will include comparisons based on humoral responses to type 2 poliovirus of sequential IPV/bOPV regimens relative to the 3-dose regimen of IPV alone to assess any potential non-inferiority of the sequential regimens (1 dose of IPV followed by 2 doses of bOPV; 2 doses of IPV followed by 1 dose of bOPV). Specifically, the sequential regimens will be considered non-inferior if the rates of seroconversion to type 2 polioviruses over the entire 3-dose regimen are no more than 10% less than those for the 3-dose IPV regimen. The statistical approach and methods used for this analysis will be the same as those described above for the primary analyses of antibody responses to type 1 and type 3 poliovirus including the tiered testing of type 2 responses for superiority and detailed comparisons of the distribution of antibody titers (e.g., GMTs).

Secondary analyses of safety data will consist of tabulation by study arm and testing for differences between groups in rates of SAEs and IMEs.

A shedding index endpoint will be computed for each study subject as a simple average of $\log_{10}$ viral titer measured from stool samples collected at Days 7, 14, and 21 post-challenge with mOPV2. Values of $\log_{10}$ viral titer for measurements below the assay limit of detection will be assigned the value of zero in computing the shedding index endpoint. The median

shedding index will be computed for each of the groups and formally compared using a Wilcoxon test. Reverse cumulative distribution curves for the shedding index endpoint will also be compared graphically to informally identify differences in the upper and lower extremes of these distributions. Additional comparative analyses will be performed on the subcohort of subjects without serologic evidence of environmental exposure to mOPV2 prior to challenge on week 28 and who have been primed to type 2 by immunization (based on serologic response 1 week post-mOPV2 challenge).

9.3 Exploratory Objective

Rates of antirotavirus IgA seroconversion and GMCs for Group 1 infants receiving bOPV together with the second dose of Rotarix™ at 16 weeks of age will be compared with those from Group 2 and 3 infants receiving this second Rotarix™ dose together with IPV. More specifically, Clopper Pearson "exact" confidence intervals for the difference in binomial proportions will be computed for comparing seroconversion rates for each of the groups (2 and 3) receiving Rotarix concomitantly with IPV to that for Group 1 receiving Rotarix concomitantly with bOPV. Each of the 2 comparisons will be first performed as a test for non-inferiority with a non-inferiority margin of 10%. Nominal 1-sided alpha levels of 0.05 will be used for these tests. If the initial test demonstrates non-inferiority of responses to Rotarix for the groups with concomitant administration of Rotarix with IPV then a second test will be performed to test for superiority of response. These formal tests will be supplemented with informal comparison of the reverse cumulative distribution curves of rotavirus IgA antibody titers.

9.4 Criteria for Termination of the Trial

The trial will be terminated once the study is fully enrolled and all study subjects have completed the study requirements. The study may also be terminated if the DSMB identifies a safety signal that meets the requirements for termination as defined in the DSMB halting criteria.

9.5 Procedures for Accounting for Missing, Unused, and Spurious Data

In spite of best efforts to collect complete data for all study subjects, some data will be missing at the end of the trial. The reasons for missing data will be ascertained and appropriate statistical methods will be used to accommodate these absences in the analyses of trial data that minimize potential biases and maximize efficiency conditional on the causes for data being missing. Data values that are identified by quality control procedures to be spurious will not be used in final analyses of trial data.

9.6 Procedures for Reporting Any Deviation from the Original Statistical Analysis Plan

The Statistical Analysis Plan (SAP) may be amended at any time during conduct of the trial but will be finalized and frozen prior to the first examination of unblinded data. All versions of the SAP up to and including the finalized SAP will be archived in the study records. All of the analyses described in the finalized SAP will be performed as specified. Other analyses that are not included in the SAP may be specified subsequent to its finalization. Such analyses will be described in an addendum to the finalized SAP and will be performed if agreed among the participating institutions.

9.7 The Selection of Subjects to be Included in the Analyses

The Sponsor will attempt to maximize the use of available data for analyses.

9.8 Sample Size

A maximum of 570 subjects will be enrolled.

For sample size calculations, we assume that the rates of seroconversion for the 3-dose IPV regimen are at least 90% for types 1 and 3. For evaluable group sizes of 152, there is a power of 0.80-0.86 (depending on degree of correlation among the type-specific tests) to declare overall non-inferiority when the rates of seroconversion for type 1 and type 3 are at least 90% and are equal for sequential and IPV only regimens and GMTs are equal for sequential and IPV only regimens. The power to declare superiority of a sequential regimen over the IPV only regimen for type 1 or type 3 seroconversion endpoints is >0.90 if the IPV only IPV seroconversion rate is 0.90 and that for the sequential regimen is 0.98. If type 1 and 3 seroconversion rates for the IPV only IPV regimen are greater than 0.90 then the power to assess superiority is considerably reduced simply because there is so little scope for improvement by bOPV boosting. The power to declare superiority of GMTs is 90% for types 1 and 3 if the true difference in type-specific GMTs is 0.33 logs or greater. The power to declare superiority of GMTs is 90% for type 2 if the true difference in type 2 GMTs is 0.55 logs or greater. Thus, assuming 80% of enrolled subjects will be evaluable for the 3 serology-based endpoints, the size of each of the 3 groups will be 190. Thus, this trial will enroll a total of a 570 subjects.

10.0 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

10.1 Study Monitoring and Source Data Verification

After appropriate ethical approval by an IRB/IEC and regulatory approval by authorities are obtained (and the final protocol has been amended as required by IRB/IEC and or regulatory authorities), an initiation site visit will be conducted before the first subject is enrolled in the study. The subjects cannot be enrolled until occurrence of such a visit and its documentation. During this site visit, the requirements of GCP, protocol procedures, and all logistical issues will be discussed at length. The training of study Investigators will also be documented.

After the study is initiated, the study monitor will be in regular contact with the sites to obtain information on the performance of the study. These contacts will be scheduled to take place at regular intervals. Subsequent to start of recruitment, routine-monitoring visits would occur after prior appointment with the Investigators.

The Investigator and his/her staff will be obliged to devote a suitable amount of time and an appropriate place for the monitoring visits. During each visit, the monitor will review the CRF of each subject in the study with regard to completeness, thoroughness, and compliance with the protocol. In addition, at a minimum, the original subject data (e.g., entry cards, index cards, original findings) will be reviewed to ensure that:

- Subject informed consent is signed and incorporated.
- Inclusion/exclusion criteria are properly followed.
- The CRF data are consistent with the physician's original records, which also have to clearly indicate that the subject is included in a clinical study.
- All relevant clinical and laboratory findings and concomitant medication are documented in the CRFs.
- Quantity and dosing schedule of concomitant medication and vaccines is documented in the CRFs.
- Quantity and dosing schedule of the Investigational/Comparator Product is in accordance with the protocol.
- All relevant information (e.g., any SAE or IME) has been recorded in the appropriate place in the CRFs including compliance with the NIPs.
- The Investigational/Comparator Product is being stored correctly, and its supply is being properly accounted for.

- Incorrect or illegible entries in the CRFs would be submitted to the Investigator for correction.

The monitor will retrieve completed CRFs during the regularly held monitoring visits.

During the study trial period, the PI will be available to answer questions with regard to the performance of the study.

10.2 Auditing

In addition to the above-outlined monitoring visits, the participating institutions may be audited. This audit may be carried out by an external independent auditor appointed by the sponsor or by the responsible regulatory authority(ies). Such an audit would be done to review whether the data have been properly recorded in the interim or final report and whether the performance of the study is in accordance with the protocol, the standard operating procedures (SOPs) developed for the study, and other relevant guidelines. Subject confidentiality will be maintained at all times.

The Investigator will inform the study Sponsor immediately if an audit has been requested by a regulatory authority.

11.0 ETHICS

The study will be conducted according to GCP, the principles of the Declaration of Helsinki, and the codes and regulations of Chile.

The study will be submitted for unconditioned approval to the Ethical Review Boards and as locally required to the regulatory authorities of each participating center. The Ethical Review Boards are to be constituted according to international guidelines. Each participating center has to ensure they obtain any other approval legally required for the corresponding country.

Written informed consent has to be obtained from the parents or legal guardians of the participating infants. Whether one or both parents have to provide consent will be determined by local legal requirements.

All subjects will be insured for participation in this study. The insurance policy is available at the investigational sites. Parents or guardians are made aware of this and of procedures to follow in case of a claim

Expenses of parents or guardians will be reimbursed as a lump sum, which has been agreed upon by the Ethical Review Boards. There will be no financial incentives for parents to enroll their children.

Any public advertising of the study will be submitted to the Ethical Review Boards for information or approval according to local regulations

11.1 Subject Information and Informed Consent

The informed consent form (ICF) will be used to explain the risks and benefits of study participation to the parent(s) or guardian(s) of the subject in simple terms before the subject will be entered into the study. The ICF contains a statement that the consent is freely given by the parent(s) or guardian(s) of the subject, that the parent(s) or guardian(s) of the subject is (are) aware of the risks and benefits of entering the study, and that the parent(s) or guardian(s) of the subject is (are) free to withdraw the subject from the study at any time. Written consent must be given by the parent(s) or guardian(s) of the subject, after the receipt of detailed information on the study.

The Investigator is responsible for ensuring that informed consent is obtained for each subject by the parent(s) or guardian(s) and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study vaccines. The Investigator will provide the parent(s) or guardian(s) of each subject with a copy of the signed and dated consent form.

12.0 STUDY ADMINISTRATION

12.1 Direct Access to Source Data/Documents

The Investigator/institutions will permit (by way of written agreement) trial-related monitoring, audits, IRB/IEC review, and regulatory inspection, providing direct access to source data/documents.

12.2 Data Handling and Record Keeping

The source document data will be entered into an electronic data file (eCRF); the laboratory data will be incorporated into a laboratory source document and then entered into the eCRF. The source documents will be stored at the main study site.

12.3 Protection of Data Privacy

The names and identity of the parents or guardians and their children will be kept private by the Investigators and staff of the study sites. They will not be given outside of the study sites without the parent's or guardian's permission, except as required by law. Other information without names and identities will be shared with the Sponsor, the DSMB, and the Bill and Melinda Gates Foundation (BMGF).

12.4 Financing and Insurance

Financing will be arranged by the Sponsor. Insurance will be provided to the study participants by the Sponsor.

12.5 Publication Policy

All data from this trial with respect to study objectives will be submitted for publication. All publications emanating from this trial will be reviewed by the participating institutions and Investigators. Authors will be determined based on actual input into the publications, as per existing guidelines.

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14.0 APPENDICES

1. Neutralization Assays and stool poliovirus quantification assay Description
2. Package Inserts for all IPVs and OPVs.

14.1 Appendix 1: Neutralization Assays and Stool Culture and Viral Quantification Description

The following documents are included in this appendix:

- Poliovirus Serology - Microneutralization Test for Polio Antibodies
- Isolation and identification of polioviruses (WHO. Isolation and identification of polioviruses. In: Polio Laboratory Manual, 4th edn. Document WHO/IVB/04.10. Geneva, Switzerland: World Health Organization. www.who.int/vaccines/en/poliolab/WHO-Polio-Manual-9.pdf. 2004:87-91.)
- Poliovirus Titration

Poliovirus Serology

Microneutralization Test for Polio Antibodies

Prepared by	Date Adopted	Supersedes Procedure
William Weldon		

Review Date	Revision Date	Lab Supervisor	CDC CLIA Director

Table of Contents

Introduction

The polio serology assay measures neutralizing antibody titers to poliovirus types 1, 2, and 3 using a modified microneutralization assay. The principle of the test is that the presence of anti-poliovirus antibodies in a serum sample will bind to the virus and block infection of susceptible cells. Because poliovirus is cytopathic, virus that is not bound by antibody infects and lyses cells. The amount of neutralizing antibody is quantitated as a 50% endpoint titer, or the last dilution of serum that protects susceptible cells from poliovirus infection and cytopathic effect

The test takes approximately 7 days to complete, from the dilution of sera to staining and reading plates. Each test serum is run in triplicate and diluted from 1/8 to 1/1024; a single 96-well plate contains 4 test sera (Figure 1). This test may be performed manually, automated, or a combination of the two approaches (Figure 2).

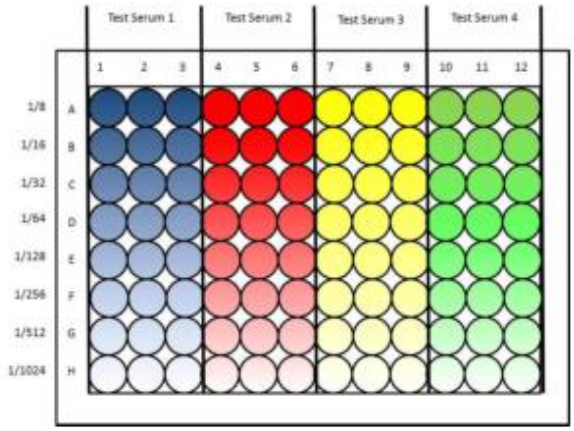


Figure 1. 96-well plate setup for Polio Serology

For a single run, up to 96 sera, which fit on 72 plates (24 plates per serotype), can be tested. Control plates are generated for each run and consist of 3 back titration plates (1 for each Sabin virus) and a cell control plate. At the end of each run, control plates are checked for accurate dilution of each Sabin poliovirus (back titration plates) or cell monolayer confluency (cell control plate).

If more than seven (7) sera are being tested, the samples must be randomized using a balanced block randomization scheme with integrated controls.Included in each run is a control serum designated In-House Reference Serum (IHRS), which is pooled from serum samples with high neutralizing antibody titers to each Sabin poliovirus.

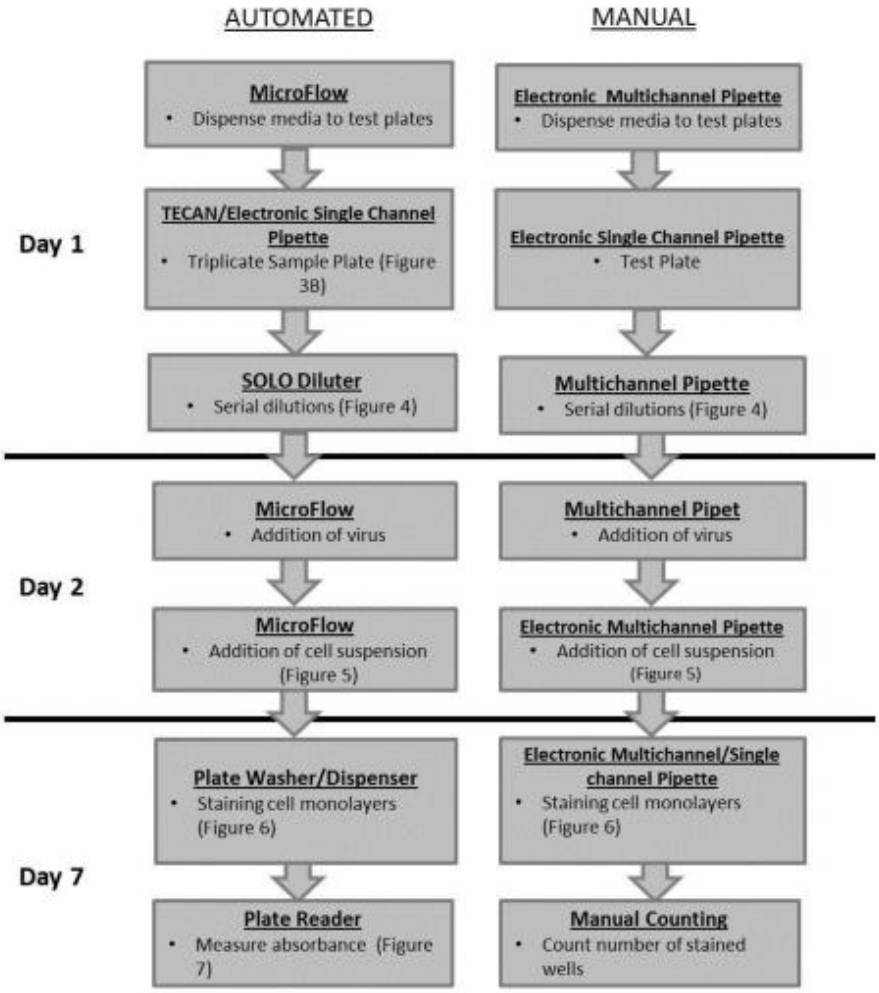


Figure 2. Workflow for automated poliovirus microneutralization assay

3

Materials and Equipment

- Hep-2C cells (ATCC # CCL23, DSR Product ID: HEPC)
- T-150 tissue culture flasks (Corning, #430823)
- 96-well tissue culture, clear, sterile plates (Corning, #3997)
- Low evaporation lids (Corning, #3931)
- 96-well tissue culture, clear, sterile, without lid plates (Corning, custom order)
- Plastic wrap (Saran Wrap)
- Deep Well 96-well microtiter plate, 2.2ml capacity. (USA Scientific, #7553-9600)
- Sterile pipettes; 10 ml, 25ml (Falcon, #357551, #357325)
- Single-channel pipettes:
  - Manual: LTS 20, 200, 1000 (Rainin)
  - Electronic: 10-300, 50-1000 (Biohit)
- 12-channel pipettes
  - Electronic: 10-300, 50-1200 (Biohit)
- Pipette tips
  - Rainin: RT-L200F, RT-L1000F, RT-L10F
  - Biohit: 350 µL, 1000 µL, 1200 µL
- Pipette tips for SOLO (Hudson Robotics, # 800-331-S)
- Cell culture media
  - Eagle's Minimum Essential Media (EMEM)(Gibco, #11095-072; SRP Cat.# CP0047)
  - Penicillin/streptomycin (Gibco, #15140)
  - Fetal Bovine Serum - Optima (Atlanta Biologicals, #S12450)
  - 0.05% Trypsin-EDTA (Gibco, #25300)
- 500 mL, 0.20 µm filter (Nalgene, #450-0020)
- In House Reference Sera (CDC)
- Sabin virus stocks grown in Hep2C cells (NIBSC)
- CO_2 water-jacket incubator (ThermoFisher)
- Crystal violet stain (0.05% crystal violet, 0.5% Tween-20, 50% ethanol, in H_2O)

  To prepare crystal violet stock solution:

2 g	crystal violet (Sigma, C-3386)
1000 ml	95% ethanol

  Mix together, until dissolved overnight (may be stored up to one year)

  To prepare working dilution crystal violet solution:

250 ml	crystal violet stock solution
5 ml	Tween-20 (Fisher Scientific, #BP337-100)
750 ml	deionized H_20

Automation Equipment

- SOLO Multichannel Diluter (Hudson Robotics)
- ELISA plate washer (BioTek)
- Twister Plate Handler (Zymark)
- MicroFlow reagent dispenser (BioTek)
- Tecan Genesis RSP 100, automated liquid handling system
- Automatic Cell Counter (BioRad)
- ELISA plate reader (Tecan) or equivalent

Protocol

In the week or two preceding the test runs:

1. Assign sera randomly to each run using a balanced block randomization scheme (see randomization attachment).
2. Use the list generated by the randomization to label plates (See Randomization Procedure). Each test serum is run in triplicate, so 4 sera may be put on each plate (Figure 1). Each plate is duplicated two more times for the other 2 poliovirus serotypes. There will be a back-titration plate for each serotype, and one cell control plate.

RUN[a]	PV1 Plate[b]	PV2 Plate[b]	PV3 Plate[b]	Position[c]	DASH #[d]
420	5	28	53	1	2011709611
420	5	28	53	2	2011709629
420	5	28	53	3	2010714898
420	5	28	53	4	2011710079
420	6	29	54	1	2010715212
420	6	29	54	2	2010714911
420	6	29	54	3	2010714944
420	6	29	54	4	2010715178
420	7	30	55	1	2011709587
420	7	30	55	2	IHRS
420	7	30	55	3	2011709701
420	7	30	55	4	2011709912

[a] each run of 1-96 sera
[b] PV1,polio type 1; PV2, polio type 2; PV3, polio type 3
[c] see Figure 1
[d] unique specimen ID

Table 1. Example of randomized sample list for poliovirus microneutralization assay.

3. In this example of a randomized sample list, serum sample number 2011709611 will be in run number 420, position 4 on plates 5 (PV1), 29 (PV2), and 53 (PV3). The in house reference serum (IHRS) is in position 2 on plates 7 (PV1), 30 (PV2), and 55 (PV3)
4. For each run, the IHRS is tested an average of 4-6 times, depending on the number of samples being randomized.
5. Prepare MEM + 2% FBS and MEM +10% FBS:
    a. Serum must be inactivated at 56°C for 30 minutes and filtered with a Nalgene filter
    b. Add 1 mL of streptomycin/penicillin to 1000 mL of EMEM (1%)
    c. Add 20 ml (2%) or 100 mL (10%) of fetal bovine serum to 1000 ml bottle of EMEM

Tuesday prior to each test run:

1. Seed T-150 flasks with 30 ml of Hep2-C cells at $5x10^5$ cells/ml.
    a. Seed enough flasks to have ~3 or 4 flasks for one run of 96 sera
2. Incubate at 37°C, 5% CO_2, humidified incubator for 24 to 72 hours.

One day before test run:

1. Manually aliquot 100 µl test sera into deep well polypropylene microplate, sealed with a rubber cover, and heat inactivated at 56°C in a waterbath for 30 minutes
2. Store at 4°C
3. Prepare IHRS by diluting to a 1:16 dilution.
    a. IHRS has been previously inactivated at 56°C for 30 minutes and is stored at -70°C
    b. 100 µL IHRS + 300 µL MEM (1:4 dilution)
    c. 400 µL 1:4 dilution + 1200 µL MEM (1:16 dilution)
    d. The 1:16 dilution is used as the initial dilution for IHRS
4. Use a multichannel pipette to add 300 µl MEM 2% FBS to 100 µl heat inactivated test sera aliquots (for a final dilution of 1:4)
5. For a full run (i.e. 96 sera), prepare two stacks of 12 microplates for each serotype.
    a. Use a lidded microplate for the top of each stack with the low evaporation lid (#3997 and #3931)
    b. The 11 remaining microplates are all lidless
    c. Cell control and back titration plates can be setup on lidded plates

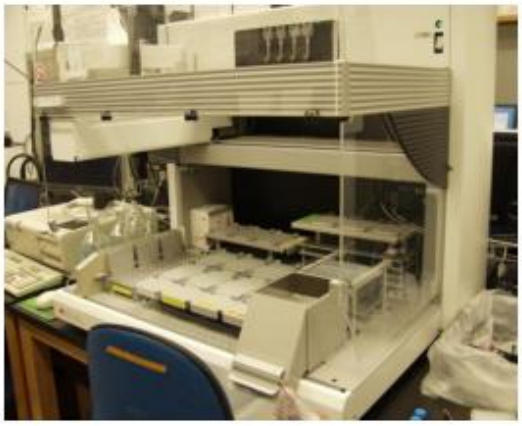
AUTOMATED

6. Use the MicroFlow reagent dispenser program "MEDIA 25UL" to add 25 µl MEM 2% FBS to the test plates.
    a. Add 25 µl MEM 2% FBS to the back titration plates (S1 ,S2 and S3)
    b. Add 50 µl MEM 2% FBS to the cell control plate
7. Use the TECAN programs "1 or 2 plate triplicate transfer" to make triplicate sample plates (see Figure 3A,B).
    a. This step transfers 100 µL of test serum (from Step 3) to test plate in triplicate.
8. Using electronic single-channel pipette, transfer 25 µL of test serum from triplicate sample plate (Step 6) to three different test plates (one for each serotype)(Figure 3C).
9. Make serial 2-fold dilutions with SOLO diluter from row A to row H (serum dilutions will range from 1:8 to 1:1024) (Figure 4).
    a. This step generates the test plates for addition of virus and cells.
    b. See Appendix I, II for instructions on operation of SOLO diluter

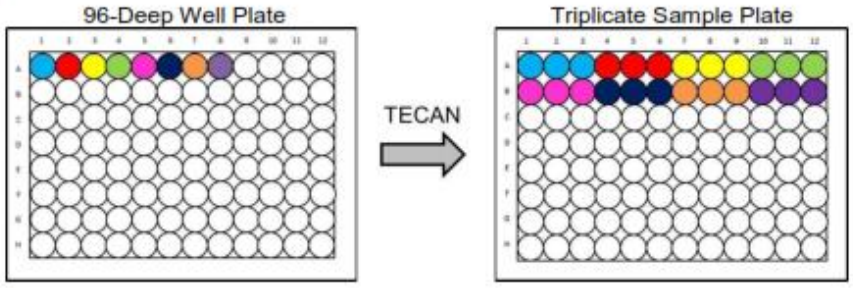
MANUAL

5. Use electronic multichannel pipette to dispense 25 µL MEM 2% FBS to the test plates
    a. Add 25 µl MEM 2% FBS to the back titration plates (PV1 ,PV2 and PV3)
    b. Add 50 µl MEM 2% FBS to the cell control plate
6. Use an electronic multichannel pipette to transfer 25 µL of each test serum (from Step 3) to each test plate in triplicate.
7. Using a multichannel pipette, make serial 2-fold dilutions from row A to row H (serum dilution will range from 1:8 to 1:1024)(see Figure 4B for plate layout).
    a. Discard 25 µL from row H to make final volume for all wells 25 µL
8. Cover the top plate of each stack of plates and wrap in plastic wrap.
9. Store overnight at 4°C.

A



B



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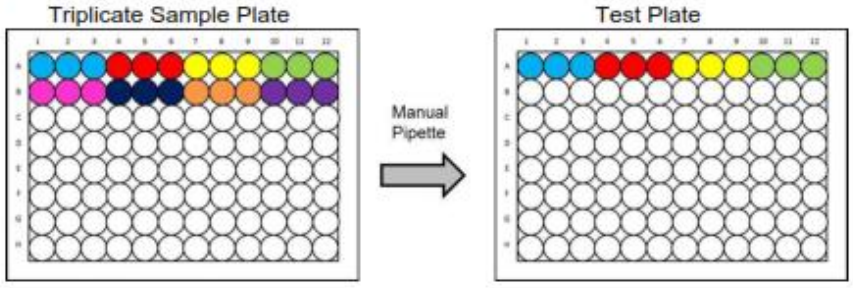
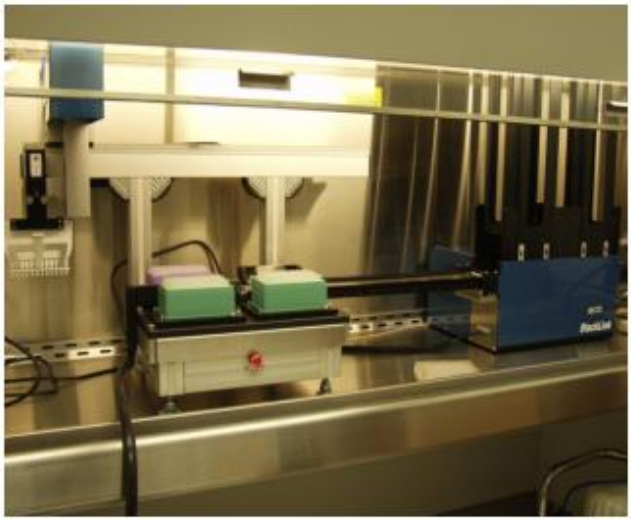


Figure 3. TECAN system (**A**). For each run, 100 ul of sample is transferred from sample plate to dilution plates in triplicate (enough for starting 3, 25 ul sample dilutions) (**B**). The TECAN configuration will allow for triplicates in consecutive order. This step can transfer 96 samples from one 96-deep well plate to a 96-well triplicate sample plate in 22 min.

A



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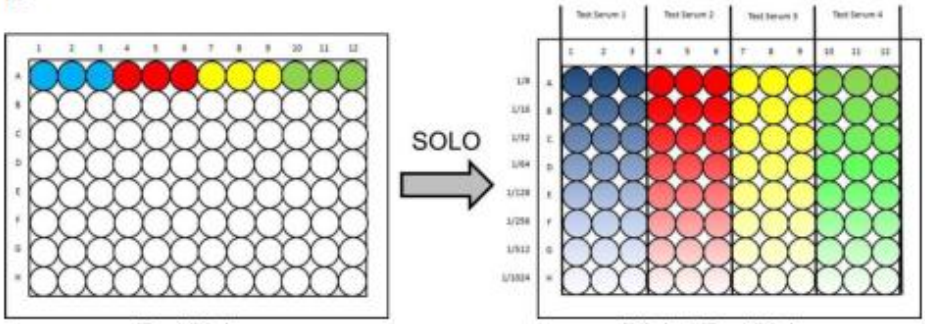


Figure 4. SOLO diluter system (**A**). Each test serum is serially diluted (2-fold) from 1/8 to 1/1024 in triplicate (**B**). This is repeated for each test plate designated for poliovirus serotypes 1, 2, or 3.

Day of run:

1. Dilute each poliovirus serotype in MEM +2% FBS to contain 100 $CCID_{50}$ according to Table 1 (page 11).
   a. Prepare sufficient virus challenge suspension for the number of sera to be tested; each plate requires approximately 2.5 ml of diluted challenge virus.
   b. See "*Poliovirus Titration for Serology Assay*" document for virus titration and $CCID_{50}$ calculation protocol
2. Prepare the back titrations of each poliovirus serotype in MEM +2% FBS. Titrate each virus from 100 $TCID_{50}$ a further three 10-fold steps (Table 1).

AUTOMATED

3. Use the MicroFlow program VIRUS 25UL to add 25 µl of 100 $CCID_{50}$ of relevant poliovirus antigen to all wells in the diluted test plates. Use a different dispensing cartridge for each virus (Figure 5).

MANUAL

3. Use an electronic, multichannel pipette to add 25 µL of 100 $CCID_{50}$ of relevant poliovirus antigen to all wells in the diluted test plates.

4. Prepare back titration plate (Figure 6) for each Sabin strain using dilutions prepared in step 2 (Table 1).
   a. Add 25 µl of 100 $TCID_{50}$ of virus to rows A and B (*i.e.*, 24 wells/dilution)
   b. Add 25 µl of the next three 10-fold dilutions to rows C and D, E and F, and G and H, respectively (See Table 2 for dilutions).
   c. Change pipette tips between each dilution
5. Wrap all plates in plastic wrap and incubate for 3 hours at 35°C and 5% CO_2
6. During incubation, wash Hep2-C monolayer cell cultures, trypsinize, count cells using automatic cell counter (BioRad) or a hemocytometer.
7. Prepare a cell suspension in MEM +10% FBS to contain approximately 3 x 10^5 cells/ml. Prepare a sufficient volume of cells; each plate requires approximately 2.5 ml of cell suspension, and every run requires 3-4 confluent T150 flasks. Store cells in glass bottle at 4°C until ready to use.

AUTOMATED

8. Use MicroFlow program "CELL 25UL" to add 25 µl of prepared cell suspension to each well of every plate (Figure 5).

MANUAL

8. Use a repeating, multichannel pipette to add 25 µL of prepared cell suspension to each well of every plate (Figure 5).

9. Wrap all plates in plastic wrap. ***Avoid abrupt handling of plates***
10. Carefully transfer plates to incubator for 5 days incubation at 35°C and 5% CO_2

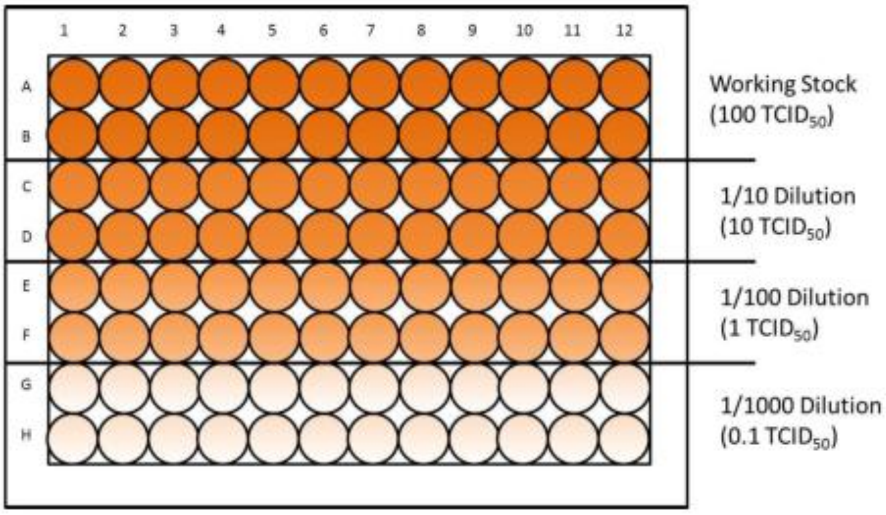
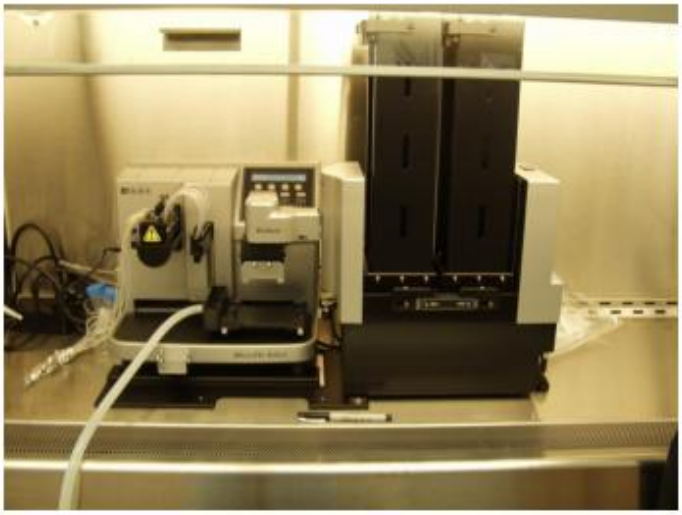


Figure 6. Layout for back titration plate. A back titration plate is made for each virus tested in microneutralization assay.

Sabin 1 (NIBSC 01/528) 100 $TCID_{50} = 10^{-5.28}$						**100 $TCID_{60}$**	**10 $TCID_{60}$**	**1 $TCID_{60}$**	**0.1 $TCID_{60}$**
Virus	100 µL	100 µL	100 µL	100 µL	800 µL	7 mL	100 µL	100 µL	100 µL
Medium	38 µL	900 µL	900 µL	900 µL	7.2 mL	63 mL	900 µL	900 µL	900 µL
Sabin 2 (NIBSC 01/530) 100 $TCID_{50} = 10^{-5.2}$									
Virus	100 µL	100 µL	100 µL	100 µL	800 µL	7 mL	100 µL	100 µL	100 µL
Medium	82 µL	900 µL	900 µL	900 µL	7.2 mL	63 mL	900 µL	900 µL	900 µL
Sabin 3 (NIBSC 01/532) 100 $TCID_{50} = 10^{-4.68}$									
Virus	100 µL	100 µL	100 µL		800 µL	7 mL	100 µL	100 µL	100 µL
Medium	82 µL	900 µL	900 µL		7.2 mL	63 mL	900 µL	900 µL	900 µL
						Working Stock	Back Titration Plate		

Table 1. Virus Dilution for 100 $TCID_{50}$ and Back Titration Plate for Sabin type 1, 2, and 3

A



B

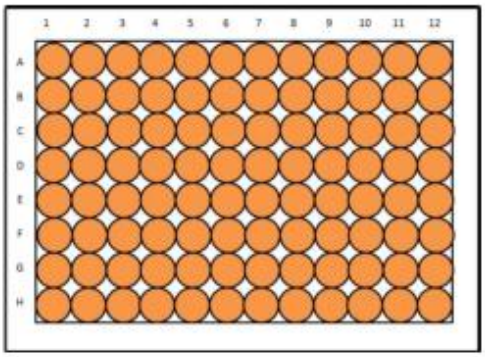


Figure 5. BioTek MicroFlow system (**A**). Adds 25 µL of 100 $TCID_{50}$ of virus or 25 µL of 3 $x10^5$ Hep2c cells to all wells in test serum plate for each respective Sabin strain (**B**).

After 5 day Incubation

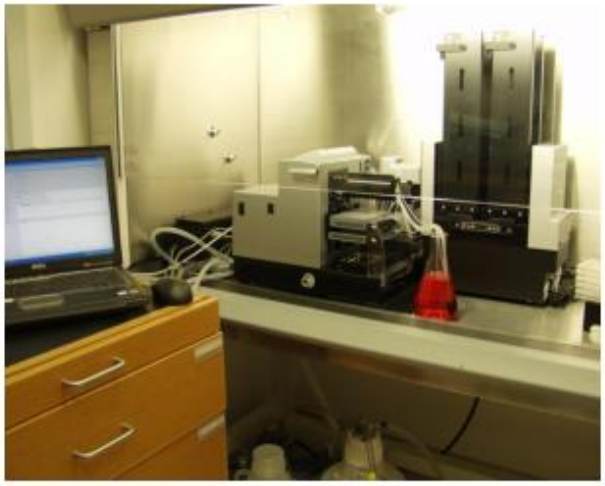


Figure 7. Plate Washer / Dispenser system.

AUTOMATED

1. After 5 days incubation, wash and stain plates with crystal violet solution (Figure 7)(See Appendix III for operation instructions).
2. This will aspirate wells and dispense 50 µL of crystal violet stain (0.05%) to all wells.
3. Incubate for a minimum of 40 minutes at room temperature.
4. Run wash program (See Appendix III for operation instructions).

MANUAL

1. After 5 days incubation, aspirate/discard media with multichannel pipette into hypochlorite solution.
2. Using a repeating, multichannel pipette, add 50 µL crystal violet stain (0.05%) to all plates.
3. Incubate for a minimum of 40 minutes at room temperature.
4. Aspirate/discard stain with multichannel pipette, fill each well with tap water (approximately 250-300 µL), and discard.
   a. Repeat washing step 2 more times.

Figure 8. TECAN Spectrafluor Plus system.

5. Allow plates to dry at room temperature for approximately 30 minutes.
6. Plates should be kept at room temperature until results are calculated and results are reported.

AUTOMATED

7. Read plates with ELISA reader at 570 nm wavelength (Figure 8) (See Appendix IV for operation instructions).

MANUAL

7. For each triplicate test serum, count the total number of wells positive for neutralization (i.e. purple). Follow same counting protocol as outline in Step 8.

   a. To calculate titer:

   Formula 1

   Titer = (# positive wells / # replicates) + 2.5

   b. To calculate reciprocal titer:

   Formula 2

   Reciprocal titer = 2^{titer}

8. Due to technical errors or natural variations in the assay, each plate is cross checked to verify correct order of plates and compare plate staining pattern to electronic data file to verify titer (Figure 9).

Example 1

a. For Test Serum 1, the reader software will automatically read this as a titer of 7.83 (1:227)
b. By crosschecking the plate, we will count D1 as positive for neutralization because the 1:128 and 1:256 dilutions are positive for neutralization (i.e. purple)
c. Using Formula 1, the titer is adjusted to 8.17 (1:288)

Example 2

d. For Test Serum 2, the reader software will automatically read this as a titer of 6.83 (1:114)
e. By crosschecking the plate, we will count F5 as negative for neutralization because the 1:512 (G5) and 1:1024 (H5) dilutions are negative for viral growth
f. Using Formula 1, the titer is adjusted to 6.5 (1:91)

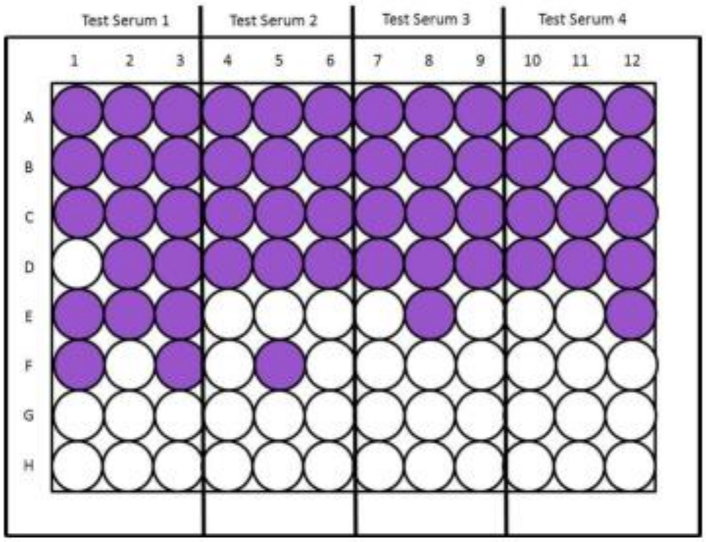


Figure 9. Example of cross-checking a crystal violet stained 96-well plate for poliovirus serology assay.

Appendix

I. Instructions for SOLO Serial Diluter with Stackers

1. Turn on power to hood.
2. Allow compressor to reach appropriate pressure (around 100 PSI).
3. Load tips on SOLO deck and sample plates in input stack.
4. Login to computer.
5. Open SoloSoft: login
6. Go to File>Open>Serial Dilution Plates 1-8.
7. On left menu, click on Get Tips
8. Click on Refill Tip box
9. File>Save or Close and when prompted to save file say Yes.
10. File>Close
11. Repeat steps for: Serial Dilution Plates 9-16 & Serial Dilution Plates 17-24.
12. Go to File>Exit to exit SoloSoft.
13. Open SoftLinx V
14. Click on Manage Instruments
15. Make sure that the Instrument Type Status is "Initialized". If status is "Configured", highlight each one, then click Initialize Instrument.
16. Close menu by clicking small red x in top right corner.
17. Go to Open Protocol
18. Choose program to run (i.e. 24 Plate Serial Dilution).
19. Click green start arrow to start run.

II. Recompression Instructions for SOLO Serial Diluter with Stackers

If the SOLO stops during a run due to the compressor recycling (grippers will release the plate), do the following steps:

1. Minimize the SoftLinx window to expose the SoloSoft window.
2. Wait about 5 min for the pressure to build up to 100 PSI, the grippers will reengage the plate (this may happen a couple of times).
3. In the Solo Pipettor Error menu, click Ignore.
4. When prompted to Home, select Yes. The pipettor will travel to the Home position, reinitialize, then continue at the position it where it stopped.

III. Setting up the Plate Washer/Dispenser

Plate Washing\Staining Instructions:

1. Turn on power to hood.
2. Allow Biostack and Plate Washer to perform self-test.
3. Open Liquid Handling Control software.

4. On the day of the assay, run the Auto Clean sequence. Go to File>Open>EL406>Maintenance Protocols>W-CLEAN-w-BUFFER>Press Run.This will take 1 hour. You can run this program at the end of the day if you prefer.
5. Load stack of plates in Input stack.
6. Fill Wash B with stain: Go To File>Open>Serology Prime Stain>Press Run.
7. Go To File>Open>Serology Aspirate Fill>Press Run.
8. Press Run to run additional stacks of plates.
9. Allow plates to incubate for 40 min.
10. Go To File>Open>Serology Prime Water>Press Run.
11. Load stack of plates
12. Go To File>Open>Serology Wash>Press Run.
13. At the end of the day, run a shutdown protocol.
14. Go to File>Open>EL406>Maintenance Protocols>W-RINSE-&-SOAK>Press Run.
15. Turn off power to hood.

Plate Reagent Dispensing Instructions:

1. Repeat steps 1-3 above.
2. Go To File>Open>Serology Prime Reagent>Press Run.
3. Go To File>Open>run any of the following protocols:
4. Serology Cell 25ul Dispense>Press Run.
5. Serology Media 25ul Dispense>Press Run.
6. Serology Media 50ul Dispense>Press Run.
7. To purge a reagent: Go To File>Open>Serology Purge Reagent>Press Run.
8. At the end of the day, flush with EtOH/Water.
9. Go To File>Open>Serology Flush Peristalic Pump>Press Run.

IV. Using the Tecan Spectrafluor

Setting up the Tecan Spectrafluor

1. Turn on power to the Tecan SPECTRA Fluor Plus spectrophotometer (Figure 8) and to the computer in room 17/6066
2. Turn on the power to the TWISTER (CLOVER).
3. Press Ctrl + Alt + Delete to login
4. Type in the password to log into computer (see Eric).
5. Load plates into stackers 2,3,4&5(max 19 plate capacity).
6. Open Overlord 2.
7. Click on orange circle in upper left corner to select procedure.
8. Click on open and select procedure “serology 75 plate run”.
9. Press start arrow to run procedure.

Saving Data File

1. Go to My Documents\Serology folder on desktop.
2. Open testresults file which contains the most recent run results.
3. Save this file as Run # _.xls
4. Drag testresults file to trash.
5. Prepare for next run by changing name of copy of testresults file to testresults.

Save Run# file to network folder

1. Place a floppy disk in drive A or thumb drive on computer port.
2. Copy run# file on to disk. Remove disk.
3. Log off then log on using entero password.
4. Insert floppy disk\thumbdrive.
5. Open serology network folder and copy Run# into appropriate folder.
6. Run serology macro to calculate titers.

7. Isolation and identification of polioviruses

7.1 Recommended cell lines for the isolation of polioviruses

Polioviruses grow readily in a wide variety of continuous human and primate cell lines. All specimens suspected of containing polioviruses should be inoculated into the following two cell lines:

- L20B cells, a mouse cell line (L-cells), genetically engineered to express the human poliovirus receptor. (N.B. Some laboratories may need to declare L20B cells as genetically modified materials to local authorities in order to comply with national regulations.)

- RD cells, derived from a human rhabdomyosarcoma.

The selection of only two cell lines for the laboratory diagnosis of poliomyelitis permits the standardization of techniques and the comparability of results among various virus laboratories.
Susceptibility of these cell lines to enteroviruses is as follows:

- L20B: susceptible to polioviruses, which produce a characteristic enterovirus cytopathic effect (CPE). These cells are highly selective for polioviruses. Some non-polioviruses that are capable of producing CPE in L cells (e.g. adenoviruses and reoviruses) are also likely to produce CPE in L20B cells, but their CPE is usually noticeably different from polio-virus induced CPE. A small number of non-polio enteroviruses (e.g. Coxsackie A viruses) may also grow in L20B cells (occasionally only after prior growth in another cell line) and they can produce characteristic enterovirus CPE.

- RD: highly susceptible to polioviruses, many ECHO viruses and some other enteroviruses, all of which produce a characteristic enterovirus CPE.

This combination of cell lines provides great sensitivity and specificity in detecting polioviruses while maintaining the ability to detect some enteroviruses as an assurance of good technique.

A third cell line, HEp-2 (Cincinnati), was formerly recommended for routine use in the network, but has now been replaced by L20B. Polio and coxsackie B viruses grow on HEp-2 (C) producing CPE. Omission of this cell line may result in a decrease in the rate of isolation of non-polio enteroviruses, especially when coxsackie B viruses are circulating in the community. However this disadvantage must be offset against the advantages of greater efficiency of detecting polioviruses when using a combination of L20B and RD, especially from samples containing mixtures of other enteroviruses.

Good laboratory practice

It is important to monitor the sensitivity of the RD and L20B cell lines to polioviruses by periodically titrating reference vaccine poliovirus strains. Care must also be taken to keep cell lines free from Mycoplasma contamination by discarding cells found to be contaminated, and by replacing working cells every 15 passages or three months with new material from the laboratory working cell bank stored in liquid nitrogen.

7.2 Isolation of polio and other enteroviruses

Have available the following items:

- tube cultures of L20B and RD cells;
- maintenance medium;
- 1 ml and 5 ml plastic disposable pipettes.

Do the following:

- Microscopically examine recently monolayered cultures to be sure that the cells are healthy. A suitable monolayer would be one formed within 2–3 days of seeding.
- Remove the growth medium and replace with 1 ml maintenance medium.
- Label two tubes of RD and two of L20B for each specimen to be inoculated (specimen number, date, passage number).
- Label one tube of each cell type as a negative control.

Note: Both cell lines must be inoculated at the same time.

- Inoculate each tube with 0.2 ml of specimen extract and incubate in the stationary sloped (5°) position at 36°C. L20B cells will not survive being rotated and it is unnecessary for poliovirus isolation.
- Examine cultures daily, using a standard or inverted microscope, for the appearance of CPE.
- Record all observations of inoculated and control cultures for at least one week, recording CPE (1+ to 4+) to indicate the percentage of cells affected (1+ to up to 25%; 2+ to 25 to 50%; 3+ to 50 to 5% and 4+ to 75 to 100%), toxicity[1], degeneration or contamination[2].
- If characteristic enterovirus CPE appears, i.e. rounded, refractile cells detaching from the surface of the tube, record, allow to develop until at least 75% of the cells are affected (3+ CPE), then store at –20°C for a second passage in a tube containing 2 ml of medium. Second passage material can be pooled for typing and ITD.
- If no CPE appears after seven days, perform a blind passage[3] and continue examination for a further seven days. (NB. Contents of replicate cell cultures from an individual case should not be pooled for passage, i.e. individual cell cultures should be passaged separately).
- Negative cultures should be examined for a total of at least 14 days before being discarded (see Figure 7.1).
- Any culture positive in RD cells but negative after 14 days in L20B cells should be re-passaged in L20B cells[4] and examined for seven days to exclude the possibility that they are polioviruses (see Figure 7.1).
- Some stool samples contain viruses other than enteroviruses that may be able to produce CPE in L20B cells (some reoviruses and adenoviruses for example). In many cases the CPE produced is clearly distinctive from enterovirus-characteristic CPE. The presence of non-enterovirus CPE causing agents in the samples must be recorded as such. Some non-polio enteroviruses may also produce CPE in L cells and therefore produce CPE in L20B cells. Poliovirus typing should still be attempted on these isolates to exclude the possibility that they contain poliovirus. If indeterminate or non-interpretable results are obtained on typing, the isolate must be sent to the Regional Reference Laboratory (RRL) for analysis.

Good laboratory practice

The utmost care should be taken to avoid viral cross-contamination of cultures during inoculation, passage procedures. Medium should never be decanted from inoculated tubes; medium should be removed with a pipette, and pipettes changed between each procedure. **DO NOT** use micropipettors except if they are used with aerosol resistant tips (ARTs). Care should be taken to avoid aerosols created by vigorous pipetting, and spilled droplets must be immediately cleaned with disinfectant.

Footnotes

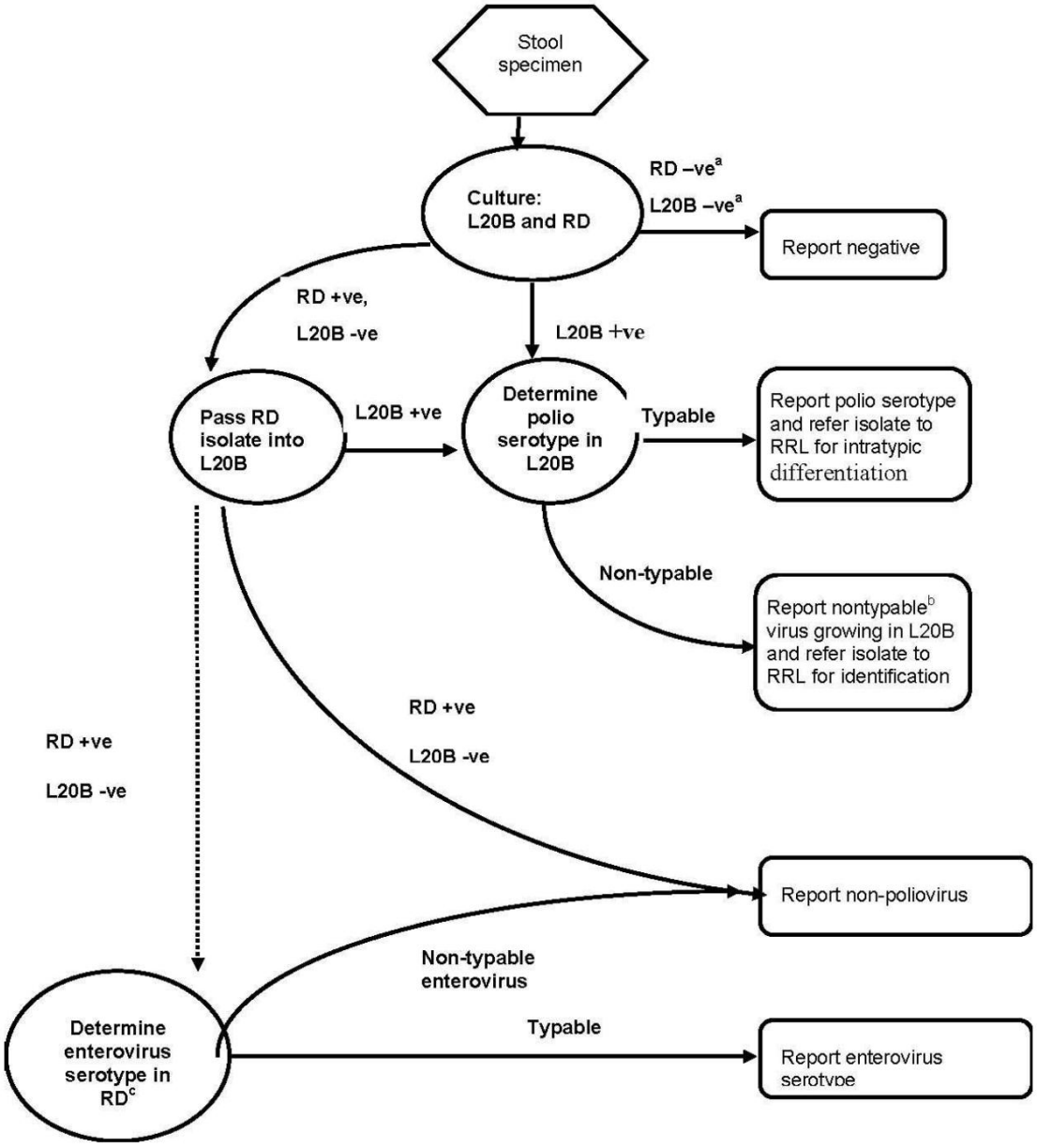
[1] Toxicity: If cell cultures show rapid degeneration within one or two days of inoculation this may be due to non-specific toxicity of the specimen. These tubes should be frozen at –20°C, thawed, and 0.2 ml volumes passaged (i.e. now second passage) in cultures of the same cell type. If toxic appearances recur, return to the original specimen extract and dilute this in PBS at 1/10 and re-inoculate cultures as described above. This should be considered as the first passage.

[2] Microbial contamination: Contamination of the medium and cell death resulting from bacterial contamination makes detection of viral CPE uncertain or impossible. Return to the original specimen extract, re-treat with chloroform and inoculate fresh cell cultures as described above.

[3] Blind passage: As sometimes happens with continuous cell lines, at the end of one week “ageing” or degeneration of cultures becomes evident also in the inoculated control cultures. Freeze the tubes at –20°C, thaw and passage 0.2 ml of culture fluid to tubes containing fresh monolayers of the same cell type and examine daily for a further 7–10 days. If cultures show no CPE by this stage, the result is regarded as negative.

[4] Re-passage in L20B cells: It is now known that a small percentage of poliovirus isolates do not to grow well in L20B cells on first passage, and may not produce recognizable CPE. They do, however, grow in RD cells, and on passage in L20B cells these isolates produce recognizable CPE. It is important, therefore, that in order not to miss any poliovirus all cultures positive in RD cells but negative in L20B cells should be passaged in L20B cells by inoculating 0.2 ml of RD or RD2 passage isolate in L20B cells (see Figure 7.1).

Figure 7.1 Flowchart for poliovirus isolation in RD and L20B cells



[a] Passaged two times for a minimum of 14 days in total.

[b] Inform regional laboratory coordinator and national programme if nontypable solate obtained in L20B cells from samples from non-endemic or recently endemic country.

[c] Type non-polio enteroviruses only at request of EPI programme.

7.2.1 Supplementary tests for poliovirus isolation

In the final stages of the programme, when polio has become a focal or sporadic disease, concern may increase about possibly missing wild polioviruses in specimens from acute flaccid paralysis (AFP) cases. Specimens from cases of high concern may be subjected to additional testing using one or more of the following methods.

Additional passage: As described above, material from an inoculated culture is transferred to a tube of freshly monolayered cells after freezing and thawing to release any virus present. The use of young, healthy cells may permit the development of recognizable CPE not apparent in the original culture, particularly in case toxicity and contamination were present. No more than one additional passage (three passages in all) should be done, since each manipulation increases the risk of viral cross contamination and the finding of false positives.

Adsorption of specimen onto a monolayer: Instead of transferring the treated specimen extract directly into cultures containing maintenance medium, the cell growth medium is first removed, the cell layer rinsed with sterile PBS and 0.2 ml of specimen extract allowed to adsorb to the cell layer for one hour at room temperature with gentle rocking or occasional rolling of the tubes to distribute the inoculum and prevent drying of peripheral cells. One ml of maintenance medium is then added to each tube. Use of this method may result in the detection of marginal concentrations of virus, reduces the effect of toxic specimens, and has been shown to speed the appearance of CPE by at least one day. Against this benefit must be weighed the possibility of viral (and possibly bacterial) cross-contamination of tubes due to the extra opening/closing of cell cultures during this procedure. **Due to the high risk of cross-contamination when using high titred samples, this method must not be used for passaging or inoculation of isolates.**

Poliovirus Titration

Prepared by	Date Adopted	Supersedes Procedure
Eric Rhoden		

Review Date	Revision Date	Lab Supervisor	CDC CLIA Director

Materials & Equipment

- HeLa cells
- 96-well tissue culture plates
- plastic wrap
- pipettes; 10 ml, 25ml
- pipettors: p10-200,p50-1200, 12-channel p50-1200, p5-200(Biohit)
- pipette tips (Biohit)
- pipette tips for TECAN and SOLO robotic systems
- EMEM (SRP Cat.# CP0047)
- Hyclone FBS (SRP Cat.# CP0039)
- Sabin virus stocks grown in Hep2C cells(REVB/EVS freezer #60)
- 37°C incubator
- Bio-Rad Automatic Cell Counter
- BioTek ELISA plate washer
- Perkin-Elmer Victor V plate reader
- BioTek MicroFlow reagent dispenser
- TECAN robotic system
- Hudson SOLO system
- Crystal violet stain

  Mix together and let sit until dissolved (may be stored up to one year):

2 g	crystal violet
1000 ml	95% ethanol

  For Use:

500 ml	crystal violet/ethanol mixture
10 ml	Tween-20
1500 ml	deionized H_20

Protocol

I. Cell propagation and plate preparation

A. Obtain HeLa cells from CDC Cell Culture Branch, SRP (available every Monday.

B. For cell plate preparation on Monday, use the Bio-Rad automatic Cell Counter to count cells and to determine the cell suspension dilution. Use the **MicroFlow** program "CELL 200UL" to seed into 96-well, flat-bottom, polystyrene tissue-culture plates (Costar Cat. No. 3598 or equivalent) at a density of $2x10^5$ cells/mL in 200 μL MEM-10% FBS medium. Wrap the plates in plastic wrap and incubate for 24 hours at 37°C in a humidified 5% CO_2 incubator prior to their use in the drug sensitivity assay.

II. Virus dilution plate preparation

A. One virus dilution plate is enough to inoculate one cell plate

B. Place an aliquot of the virus sample in a 37°C warm air incubator until just thawed. Remove to a wet ice bucket.

C. Use MicroFlow program " VIRUS 171UL" to fill 96-well, flat-bottom polypropylene plates with MEM-2% FBS medium, delivering 171 μL of complete medium to all wells in columns 3-12.

D. Manually add 250 μL of well vortexed diluted virus to all wells of columns 1 and 2 of the plate.The virus panel dilutions (Figure 1) were determined based upon previous dilution experiments.

E. Use the **Biomek** programs "new vir dil 1-4 & new vir dil 5-8" to perform a staggered $0.5Log_{10}$ dilution of the virus dilution by transferring 79 μL from column 1 to 3, 3 to 5, 5 to 7, and 7 to 9. Repeat with column 2 to 4, 4 to 6, 6 to 8, and 8 to 10. **Columns 11 and 12 do not receive virus (Figure 1).** This plate layout facilitates use of **Biomek** to transfer compound to the cell plates.

III. Virus infection of cell plates

A. Using Biomek program "Virus Infection 4 pl", transfer 150 μL of virus from the virus dilution plate to the cell plate. If you move from most dilute to most concentrated, you can use the same tips for an entire cell plate (i.e. one virus).

B. Wrap completed plates in plastic wrap and incubate in a humidified 37°C, 5% CO_2 incubator for 3 days.

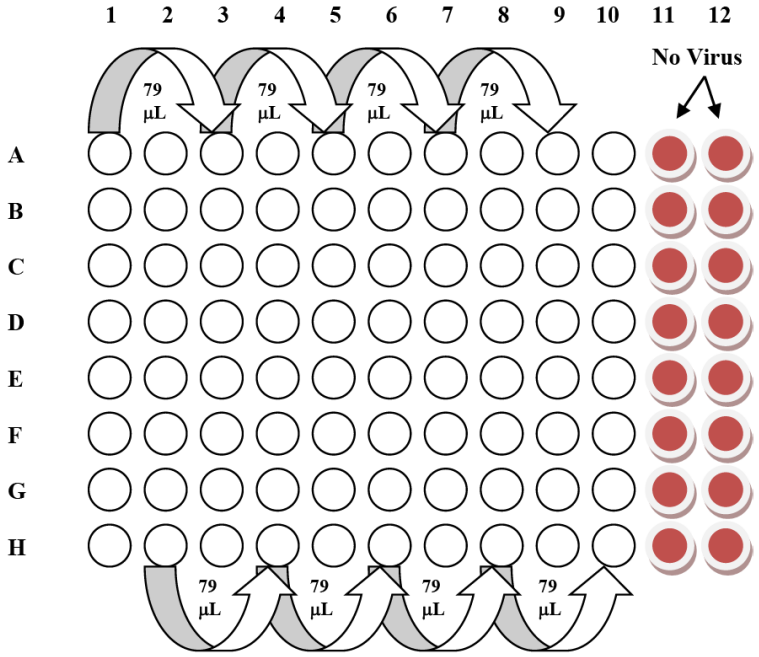
IV. Plate staining

A. After 3 days incubation, stain plates with crystal violet solution. To prepare crystal violet solution, combine 500 mL 0.2% crystal violet in 95% ethanol with 10 ml Tween-20 and 1500 mL deionized water.

V. Plate reading

1. Turn on power to the Perkin-Elmer Victor V plate reader and to the computer in room 17/6066
2. Open the Victor V software and load plates into stackers.
3. Run program “absorbance @ 595 nm 0.1s”.
4. Export plate results in Excel for analysis.

Figure 1. Dilution of virus plate. Dilute in 0.5 $\log_{10}$ steps across the plate, with no virus in columns 11-12. Virus dilutions are prepared in duplicate (i.e. two columns of each dilution)



14.2 Appendix 2: Package Inserts for All IPVs

The following package inserts are included in this appendix:

- Oral Bivalent Types 1 and 3 Poliomyelitis Vaccine (Sanofi bOPV)
- Polio Sabin™ Mono Two (GSK mOPV2)
- Imovax Polio – Poliomyelitis Vaccine (Sanofi Imovax Polio)
- Poliovirus Vaccine Inactivated IOPL® (Sanofi IPOL)

456 960151

VACCIN POLIOMYELITIQUE ORAL BIVALENT TYPES 1 et 3

Suspension buvable en récipient multidose

Veuillez lire attentivement cette notice avant d'utiliser ce médicament. Elle contient des informations importantes pour votre traitement.
- Si vous avez d'autres questions, si vous avez un doute, demandez plus d'informations à votre médecin ou à votre pharmacien.
- Gardez cette notice, vous pourriez avoir besoin de la relire.
- Si vous avez besoin de plus d'informations et de conseils, adressez-vous à votre pharmacien.

Dans cette notice :

1. QU'EST-CE QUE VACCIN POLIOMYELITIQUE ORAL BIVALENT TYPES 1 ET 3, ET DANS QUELS CAS EST-IL UTILISE ?

Le Vaccin Poliomyélitique Oral Bivalent Types 1 et 3 est indiqué dans les Activités Supplémentaires de Vaccinations (SIAs) contre la poliomyélite chez l'enfant de 0 à 5 ans, afin d'interrompre la transmission des virus poliomyélitiques de types 1 et 3 dans les zones encore endémiques. Le programme de vaccination poliomyélitique de routine doit continuer à utiliser les vaccins trivalents conformément aux recommandations nationales.

2. QUELLES SONT LES INFORMATIONS A CONNAITRE AVANT DE PRENDRE VACCIN POLIOMYELITIQUE ORAL BIVALENT TYPES 1 ET 3 ?

Ne prenez jamais VACCIN POLIOMYELITIQUE ORAL BIVALENT TYPES 1 et 3 en cas :
- d'hypersensibilité connue à l'un des composants du vaccin, à la néomycine, la streptomycine et à la polymyxine B, ou de réactions sévères à la suite d'une administration antérieure d'un vaccin poliomyélitique oral.
- de déficit immunitaire primaire ou secondaire à un traitement, une leucémie, un lymphome ou une maladie maligne avancée chez le sujet qui va être vacciné ou son entourage..

Faites attention avec VACCIN POLIOMYELITIQUE ORAL BIVALENT TYPES 1 et 3 :
- En cas de vomissements ou de diarrhée après l'administration, ou immédiatement après, une deuxième dose peut être administrée après disparition des symptômes.
- Il peut être préconisé de différer la vaccination en cas de fièvre ou de maladie aiguë en fonction des recommandations nationales.
- Les virus contenus dans le vaccin peuvent être excrétés par les personnes vaccinées et atteindre des personnes de leur entourage, y compris des femmes enceintes ou qui allaitent. La tolérance du Vaccin Poliomyélitique Oral Bivalent Types 1 et 3 chez les femmes enceintes ou qui allaitent n'est pas connue. En clinique, les études épidémiologiques n'ont pas mis en évidence d'effet malformatif ou foetotoxique associé à l'exposition de femmes enceintes au Vaccin Poliomyélitique Oral Bivalent Types 1 et 3.
- Ce vaccin ne doit pas être utilisé en vaccination de routine.
- Ce vaccin ne doit pas être injecté.

Prise d'autres médicaments

Si vous prenez ou avez pris récemment un autre médicament, y compris un médicament obtenu sans ordonnance, parlez-en à votre médecin ou à votre pharmacien.

Grossesse et allaitement

Vaccin à usage pédiatrique uniquement.

Demandez conseil à votre médecin ou à votre pharmacien avant de prendre tout médicament.

3. COMMENT PRENDRE VACCIN POLIOMYELITIQUE ORAL BIVALENT TYPES 1 ET 3 ?

Le flacon devra d'abord être agité doucement, afin d'éviter la formation de mousse, mais suffisamment pour obtenir un mélange homogène du contenu.

L'obtention d'une ou de plusieurs doses de vaccin à partir d'un flacon multidose dépend essentiellement du soin apporté à la manipulation.

Posologie

La dose vaccinale est de 2 gouttes (0,1 ml) mesurée à l'aide du compte-gouttes fourni avec le vaccin et administrée directement dans la bouche. Prendre bien soin de ne pas contaminer le compte-gouttes multidose avec la salive de la personne vaccinée.

Mode d'administration

Le vaccin doit être administré exclusivement par voie orale.

4. QUELS SONT LES EFFETS INDESIRABLES EVENTUELS ?

Comme tous les médicaments, Vaccin Poliomyélitique Oral Bivalent Types 1 et 3 est susceptible d'avoir des effets indésirables, bien que tout le monde n'y soit pas sujet.

Le Vaccin Poliomyélitique Oral Bivalent Types 1 et 3 contient deux des trois composants du vaccin poliomyélitique oral trivalent. Il devrait présenter le même profil de tolérance que le vaccin poliomyélitique oral trivalent.
- Réactions générales : fièvre, frissons, asthénie (fatigue), myalgies (douleurs musculaires), et arthralgies (douleurs articulaires).
- Rares cas d'atteinte neurologique, paresthésie (sensation de picotements, fourmillements), parésie (paralysie légère), névrite (inflammation d'un nerf) et myélite (inflammation de la moelle épinière).
- Exceptionnellement, syndrome de Guillain Barré.
- Une paralysie post-vaccinale due à la réversion de la neurovirulence du virus vaccinal peut exceptionnellement se produire. Ces cas surviennent entre 4 et 8 semaines suivant la vaccination.

D'après les données cliniques historiques concernant l'OPV trivalent, le risque de poliomyélite paralytique associée au vaccin (PPAV) est estimé à 0,42 par million de personnes vaccinées.

Chez les nourrissons nés grands prématurés (à 28 semaines de grossesse ou moins) des pauses respiratoires peuvent survenir pendant 2 à 3 jours après la vaccination.

Si vous remarquez des effets indésirables non mentionnés dans cette notice, ou si certains effets indésirables deviennent graves, veuillez en informer votre médecin ou votre pharmacien.

5. COMMENT CONSERVER VACCIN POLIOMYELITIQUE ORAL BIVALENT TYPES 1 ET 3 ?

Tenir hors de la portée et de la vue des enfants.

Ne pas utiliser Vaccin Poliomyélitique Oral Bivalent Types 1 et 3 après la date de péremption mentionnée sur la boîte.

La date d'expiration fait référence au dernier jour du mois.

A conserver au congélateur (-20°C).

Une fois décongelé, le produit peut se conserver 6 mois au réfrigérateur (entre +2°C et +8°C).

Pastilles de Contrôle du Vaccin (PCV)

Les Pastilles de Contrôle du Vaccins (PCV) figurent sur l'étiquette du Vaccin Poliomyélitique Oral Bivalent Types 1 et 3 fourni par l'OMS.

Le cercle de couleur qui figure sur l'étiquette du flacon est une PCV. Il s'agit d'un cercle sensible à la combinaison temps-température qui indique l'accumulation de chaleur à laquelle le flacon a été exposé. Il met en garde l'utilisateur final quand l'exposition à la chaleur est susceptible d'avoir dégradé le vaccin au-delà du seuil acceptable.

Le carré central est plus clair que le cercle.
Si la date de péremption n'est pas dépassée, UTILISER le vaccin.

Point de destruction du vaccin :
Le carré central est de même couleur que le cercle.
NE PAS UTILISER le vaccin.

Point au-delà duquel il faut détruire le vaccin :
Le carré central est plus foncé que le cercle.
NE PAS UTILISER le vaccin.

L'interprétation de la PCV est simple : fixer le carré central. Sa couleur change progressivement. Tant que la couleur de ce carré est plus claire que celle du cercle, le vaccin peut être utilisé. Dès que la couleur du carré central est identique à celle du cercle ou plus foncée, le flacon doit être détruit.

6. INFORMATIONS SUPPLEMENTAIRES

Que contient VACCIN POLIOMYELITIQUE ORAL BIVALENT TYPES 1 et 3 ?

La substance active est :

Virus de la poliomyélite type 1*, souche LS- c2ab (vivant, atténué) au moins 6.0 log† $DICC_{50}$‡

Virus de la poliomyélite type 3*, souche Léon-12a1b (vivant, atténué) au moins 5.8 log† $DICC_{50}$‡

Pour chaque dose de 0,1 ml (2 gouttes)

* Produit sur cellules Vero

† Précédemment exprimé en "au moins 10^x $DICC_{50}$"

‡ $DICC_{50}$: Dose infectante pour 50 % des cultures cellulaires (unités virales infectieuses).

Les autres composants sont :

Albumine humaine, solution de Tampon HEPES, solution de chlorure de magnésium (contenant du polysorbate 80 et du rouge de phénol).

Le vaccin est conforme aux normes de l'OMS.

Qu'est ce que VACCIN POLIOMYELITIQUE ORAL BIVALENT TYPES 1 et 3, et contenu de l'emballage extérieur ?

Ce vaccin est une suspension buvable en flacon multidose (20 doses (2 ml) – Boîte de 10)

Titulaire de l'autorisation de mise sur le marché

SANOFI PASTEUR

2 AVENUE PONT PASTEUR - 69007 LYON - FRANCE

Fabricant

SANOFI PASTEUR

PARC INDUSTRIEL D'INCARVILLE - 27100 VAL-DE-REUIL - FRANCE

La dernière date à laquelle cette notice a été approuvée est le 02/2011.

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ORAL BIVALENT TYPES 1 and 3 POLIOMYELITIS VACCINE

Oral suspension in multidose container

Read all of this leaflet carefully before you start taking this medicine. It contains important information for your treatment.
- If you have further questions or if you have a doubt, please ask your doctor or pharmacist for more information.
- Keep this leaflet; you may need to read it again.
- Ask your pharmacist if you need more information or advice.

In this leaflet:

1. WHAT IS ORAL BIVALENT TYPES 1 AND 3 POLIOMYELITIS VACCINE, AND WHAT IS IT USED FOR

Oral Bivalent Types 1 and 3 Poliomyelitis Vaccine, is indicated for poliomyelitis Supplementary Immunisation Activities (SIAs) in children from 0 to 5 years of age, to interrupt types 1 and 3 poliovirus transmission in remaining polio endemic areas. The routine poliomyelitis vaccination programme should continue to use trivalent vaccines according to national policy.

2. BEFORE YOU TAKE ORAL BIVALENT TYPES 1 AND 3 POLIOMYELITIS VACCINE

Do not take Oral Bivalent Types 1 and 3 Poliomyelitis Vaccine in the following cases:
- Known hypersensitivity to any component of the vaccine, to neomycin, streptomycin and polymyxin B, or serious reactions after previous administration of an oral poliomyelitis vaccine.
- Primary immune deficiency disease or immune deficiency subsequent to treatment, leukaemia, lymphoma or advanced malignancy in the subject to be vaccinated or his/her close contacts.

Take special care with Oral Bivalent Types 1 and 3 Poliomyelitis Vaccine:
- In the event of vomiting or diarrhoea at the time of or immediately after administration, a second dose may be given after the symptoms have disappeared.
- In the event of fever or acute disease, it may be recommended to postpone vaccination according to national policy.
- Vaccine viruses can be excreted by vaccine recipients and reach contact persons, including pregnant or lactating women. However, the safety of Oral Bivalent Types 1 and 3 Poliomyelitis Vaccine in pregnant or lactating women is not known. Clinical epidemiological studies have not revealed any congenital malformations or foetotoxic effects related to the use of the Oral Bivalent Types 1 and 3 Poliomyelitis Vaccine in exposed pregnant women.
- This vaccine should not be used for routine vaccination.
- This vaccine should not be injected.

Taking or using other medicines:
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
This vaccine is intended for paediatric use only.
Ask your doctor or your pharmacist for advice before taking any medicine.

3. HOW TO TAKE ORAL BIVALENT TYPES 1 AND 3 POLIOMYELITIS VACCINE

The vial must first be shaken gently, to avoid foaming, but sufficiently to obtain a homogeneous mixture of the contents.
One or several vaccine doses may be obtained from a multidose vial depending on the care of the handling.

Posology
The vaccine dose is 2 drops (0.1 ml) measured using the multi-dose dropper supplied with the vaccine, directly into the mouth. Care should be taken not to contaminate the multi-dose dropper with the saliva of the vaccinee.

Route of administration
The vaccine should be administered exclusively by the oral route.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Oral Bivalent Types 1 and 3 Poliomyelitis Vaccine can cause side effects although not everybody gets them.
Oral Bivalent Types 1 and 3 Poliomyelitis Vaccine contains two of the three components of the trivalent oral poliomyelitis vaccine. It is anticipated to exhibit the same side effects than the trivalent oral poliomyelitis vaccine.
- General reactions: fever, rigors, asthenia (tiredness), myalgia (muscle pain) and arthralgia (joint pain).
- Rare cases of neurological disorders: paresthesia (tingling sensations, pins and needles), paresis (mild paralysis), neuritis (nerve inflammation) and myelitis (spinal cord inflammation).
- Exceptionally, Guillain-Barré syndrome
- In exceptional cases, post-vaccination paralysis may result from reversion to neurovirulence of the vaccine virus. These cases occur within 4 to 8 weeks following vaccination.

Based on historical clinical data with trivalent OPV the risk of vaccine-associated paralytic poliomyelitis (VAPP) per million persons vaccinated is estimated to be 0.42.
In babies born very prematurely (at or before 28 weeks of gestation) longer gaps than normal between breaths may occur for 2-3 days after vaccination.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ORAL BIVALENT TYPES 1 AND 3 POLIOMYELITIS VACCINE

Keep out of the reach and sight of children.
Do not use Oral Bivalent Types 1 and 3 Poliomyelitis Vaccine after the expiry date which is stated on the box.
The expiry date refers to the last day of that month.
Store in a freezer (-20°C).
After thawing, the product can be stored for 6 months in a refrigerator (between +2°C and +8°C).

Vaccine Vial Monitors (VVM)

The Vaccine Vial Monitors (VVMs) are on the label of Oral Bivalent Types 1 and 3 Poliomyelitis Vaccine supplied through WHO.
The colour dot which appears on the label of the vial is a VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.

Inner square lighter than outer circle.
If the expiry date has not been passed, USE the vaccine.

Discard point:
Inner square matches colour of outer circle.
DO NOT use the vaccine.

Beyond the discard point:
Inner square darker than outer circle.
DO NOT use the vaccine.

The interpretation of the VVM is simple. Focus on the central square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the circle, then the vaccine can be used. As soon as the colour of the central square is the same colour as the circle or of a darker colour than the circle, then the vial should be discarded.

6. FURTHER INFORMATION

What ORAL BIVALENT TYPES 1 and 3 POLIOMYELITIS VACCINE contains

The active substance is:
Poliomyelitis virus type 1*, LS c2ab strain, (live, attenuated) at least 6.0 log† $CCID_{50}$‡
Poliomyelitis virus type 3*, Leon 12a1b strain, (live, attenuated) at least 5.8 log† $CCID_{50}$‡
For each 0.1-ml dose (2 drops)
* Produced in Vero cells
† Previously expressed as "at least 10^x $CCID_{50}$"
‡ $CCID_{50}$: 50% Cell Culture Infective Doses (viral infectious units).

The other ingredients are:
Human albumin, HEPES buffer solution, magnesium chloride solution (containing polysorbate 80 and phenol red).
The vaccine fulfils WHO requirements.

What ORAL BIVALENT TYPES 1 and 3 POLIOMYELITIS VACCINE looks like and contents of the pack?

This vaccine is an oral suspension in a multidose vial (20 doses (2 ml) – Pack of 10)

Marketing Authorisation Holder
SANOFI PASTEUR
2, AVENUE PONT PASTEUR
69007 LYON
FRANCE
Manufacturer:
SANOFI PASTEUR
PARC INDUSTRIEL D'INCARVILLE
27100 VAL-DE-REUIL - FRANCE

This leaflet was last approved on: 02/2011.

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VACUNA ANTIPOLIOMIELÍTICA ORAL BIVALENTE DE TIPOS 1 Y 3

Suspensión bebible en recipiente multidosis

Lea todo el prospecto detenidamente porque contiene información importante para usted
- Si tiene alguna duda, consulte a su médico o farmacéutico
- Conserve este prospecto, ya que puede tener que volver a leerlo.
- Si necesita consejo o más información, consulte a su farmacéutico.

En este prospecto:

1. QUE ES LA VACUNA ANTIPOLIOMIELÍTICA ORAL BIVALENTE DE TIPOS 1 Y 3 Y PARA QUE SE UTILIZA

La Vacuna Antipoliomielítica Oral Bivalente de Tipos 1 y 3 está indicada en las Actividades Suplementarias de Vacunación (SIAs) contra la poliomielitis en los niños de 0 a 5 años para interrumpir la transmisión de los viruses de tipos 1 y 3 de la polio en zonas aún endémicas. El programa de vacunación antipoliomielítica de rutina debe seguir utilizando las vacunas trivalentes según las recomendaciones nacionales.

2. ANTES DE TOMAR LA VACUNA ANTIPOLIOMIELÍTICA ORAL BIVALENTE DE TIPOS 1 Y 3

No tome la VACUNA ANTIPOLIOMIELÍTICA ORAL BIVALENTE DE TIPOS 1 Y 3 en caso:
- de hipersensibilidad conocida a uno de los componentes de la vacuna, a la neomicina, la estreptomicina y la polimixina B, o reacciones graves luego de una administración anterior de una vacuna antipoliomielítica.
- de déficit inmunitario primario o secundario a un tratamiento, una leucemia, un linfoma o una enfermedad maligna avanzada en el sujeto que va a ser vacunado o su entorno

Tenga especial cuidado con la VACUNA ANTIPOLIOMIELÍTICA ORAL BIVALENTE DE TIPOS 1 Y 3:
- En caso de vómitos o diarrea en el momento de la administración o inmediatamente después, se puede administrar una segunda dosis después de la desaparición de los síntomas.
- Se puede recomendar aplazar la vacunación en caso de fiebre o de enfermedad aguda según las recomendaciones nacionales.
- Los virus contenidos en la vacuna pueden ser excretados para las personas vacunadas y pueden alcanzar a las personas del entorno, incluyendo mujeres embarazadas o que dan de lactar. Sin embargo, se desconoce la tolerancia de la Vacuna Antipoliomielítica Oral Bivalente de Tipos 1 y 3 en las mujeres embarazadas o que dan de lactar. En el ámbito clínico, los estudios epidemiológicos relacionados al uso de la vacuna poliomielítica oral trivalente no han puesto en manifiesto efectos malformativos ni fetotóxicos asociados a la exposición de mujeres embarazadas a la Vacuna Antipoliomielítica Oral Bivalente de Tipos 1 y 3.
- Esta vacuna no debe utilizarse como vacunación de rutina.
- Esta vacuna no debe inyectarse.

Toma o uso de otros medicamentos

Si toma o ha tomado recientemente otro medicamento, incluyendo medicamentos obtenidos sin receta, infórmeselo a su médico o farmacéutico.

Embarazo y lactancia

Vacuna para uso pediátrico solamente.

Pida consejo a su médico o farmacéutico antes de tomar cualquier medicamento.

3. COMO TOMAR LA VACUNA ANTIPOLIOMIELÍTICA ORAL BIVALENTE DE TIPOS 1 Y 3

Primero se deberá agitar el frasco suavemente para evitar la formación de espuma, pero suficientemente para obtener una mezcla homogénea del contenido.

La obtención de una o varias dosis de vacuna de un solo frasco multidosis depende principalmente del cuidado durante la manipulación.

Posología

La dosis vacunal es de 2 gotas (0,1 ml), se mide con el gotero provisto con la vacuna y se administra directamente en la boca. Tenga cuidado en no contaminar el gotero con la saliva de la persona vacunada.

Forma y vía(s) de administración

La vacuna debe administrarse exclusivamente por vía oral.

4. POSIBLES EFECTOS ADVERSOS:

Al igual que todos los medicamentos, la Vacuna Antipoliomielítica Oral Bivalente de Tipos 1 y 3 puede producir efectos adversos, aunque no todas las personas los sufran.

La Vacuna Antipoliomielítica Oral Bivalente de Tipos 1 y 3 contiene dos de los tres componentes de la vacuna antipoliomielítica oral trivalente. Se espera que presente el mismo perfil de tolerancia que la vacuna antipoliomielítica oral trivalente.
- Reacciones generales: fiebre, escalofríos, astenia (cansancio), mialgia (dolores musculares) y artralgia (dolores articulares).
- Casos raros de daño neurológico: parestesia (sensación de hormigueo), paresia (parálisis ligera), neuritis (inflamación de un nervio) y mielitis (inflamación de la médula espinal).
- Excepcionalmente: síndrome de Guillain Barré.
- Excepcionalmente, puede producirse una parálisis post vacunal debido a la reversión de la virulencia del virus vacunal. Estos casos ocurren en las 4-8 semanas siguientes a la vacunación.

Según los datos clínicos históricos relativos a la vacuna antipoliomielítica oral trivalente, el riesgo de poliomielitis paralítica asociada a la vacuna (PPAV) se estima a 0,42 por un millón de personas vacunadas.

En los bebés nacidos muy prematuramente (en la semana 28 del embarazo, o antes), pueden ocurrir pausas respiratorias durante los 2 ó 3 días siguientes a la vacunación.

Si considera que alguno de los efectos adversos que sufre es grave o si aprecia cualquier efecto adverso no mencionado en este prospecto, informe a su médico o farmacéutico.

5. CONSERVACION DE LA VACUNA ANTIPOLIOMIELÍTICA ORAL BIVALENTE DE TIPOS 1 Y 3

Mantener fuera del alcance y de la vista de los niños

No utilice la Vacuna Antipoliomielítica Oral Bivalente De Tipos 1 y 3 después de la fecha de caducidad que aparece en el envase.

La fecha de caducidad es el último día del mes que se indica. Conservar en congelador (-20°C).

Una vez descongelado, el producto puede conservarse 6 meses en nevera (entre +2°C y +8°C).

Sensor de control de la vacuna (SCV)

Los Sensores de Control de la Vacuna (SCV) aparecen en la etiqueta de la Vacuna Antipoliomielítica Oral Bivalente de Tipos 1 y 3 proporcionada por la OMS.

El círculo de color que aparece en la etiqueta del frasco es un SCV. Es un círculo sensible a la combinación tiempo/temperatura que indica la acumulación de calor a la que se ha expuesto el frasco. Advierte al usuario final cuando la exposición al calor puede haber producido una degradación de la vacuna más allá del límite aceptable.

El color del cuadrado interno es más claro que el color del círculo externo.
USE la vacuna cuando no ha pasado la fecha de caducidad.

Punto de eliminación:
El color del cuadrado interno se confunde con el color del círculo externo.
NO use la vacuna.

Después del punto de eliminación:
El color del cuadrado interno es más intenso que el color del círculo externo.
NO use la vacuna.

La interpretación del SCV es simple: mirar el cuadrado central. Su color cambia progresivamente. Mientras que el color de este cuadrado es más claro que el del círculo, se puede usar la vacuna.

Se debe destruir el frasco apenas el color del cuadrado central sea idéntico al del círculo o más oscuro.

6. INFORMACIÓN ADICIONAL

Composición de la VACUNA ANTIPOLIOMIELÍTICA ORAL BIVALENTE DE TIPOS 1 Y 3

El principio activo es:

Virus de la poliomielitis tipo 1*, cepa LS-c2ab (vivo, atenuado) al menos 6.0 log† $DICC_{50}$‡

Virus de la poliomielitis tipo 3*, cepa Leon-12a1b (vivo, atenuado) al menos 5.8 log† $DICC_{50}$‡

Por cada dosis de 0,1 ml (2 gotas)

* Producida en células Vero.

† Expresado anteriormente en "al menos 10^6 $DICC_{50}$"

‡ $DICC_{50}$: Dosis infectante para 50% de los cultivos celulares (unidades virales infecciosas).

Los demás componentes son:

Albúmina humana, solución de tampón HEPES, solución de cloruro de magnesio (contiene polisorbato 80 y rojo de fenol).

Vacuna conforme a las normas de la OMS

Aspecto del producto y contenido del envase

Esta vacuna es una suspensión bebible en frasco multidosis (20 dosis (2 ml) – caja de 10).

Titular de la autorización de comercialización

SANOFI PASTEUR
2, AVENUE PONT PASTEUR - 69007 LYON - FRANCIA

Fabricante

SANOFI PASTEUR
PARC INDUSTRIEL D'INCARVILLE
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Este prospecto ha sido aprobado en 02/2011

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WHO PACKAGE INSERT

1. NAME OF THE MEDICINAL PRODUCT

Polio Sabin™ Mono Two (oral)
Monovalent Oral Poliomyelitis vaccine Type 2 (mOPV2)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Polio Sabin™ Mono Two (oral) is a monovalent, live attenuated poliomyelitis virus vaccine of the Sabin strain Type 2 (P 712, Ch, 2ab), propagated in MRC5 human diploid cells.

Each dose (0.1 ml) contains not less than $10^{5.0}$ $CCID_{50}$ of Type 2. Magnesium chloride is used as a stabilizer.
Polio Sabin™ Mono Two (Oral) contains trace amounts of neomycin sulphate and polymyxin B sulphate.

3. PHARMACEUTICAL FORM

Oral suspension.
The vaccine is presented as a clear and colourless suspension for oral administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Polio Sabin™ Mono Two (oral) is indicated for active immunisation in all age groups against infection caused by Type 2 poliomyelitis virus.

This vaccine may be used in two instances:
- Eradication of poliomyelitis, to supplement vaccination against poliomyelitis with a trivalent vaccine in areas where the Type 2 poliomyelitis virus is circulating.
- Reappearance of the Type 2 poliomyelitis virus in an area previously recognised as poliomyelitis Type 2 free.

4.2 Posology and method of administration

Posology

In a multidose container, one immunising dose (0.1 ml) is contained in two drops.

Monovalent Oral Poliomyelitis vaccine Type 2 is not intended for routine vaccination.
The advised vaccination schedule for each country must be in accordance with the national recommendations.

According to WHO recommendations, Polio Sabin™ Mono Two (oral) is indicated for poliomyelitis Supplementary Immunisation Activities (SIAs) in children from 0 to 5 years of age, to interrupt any potential Type 2 poliovirus transmission or control Type 2 circulating vaccine-derived poliovirus (cVDPV) outbreak. The routine poliomyelitis vaccination programme should continue to use trivalent vaccines according to national policy.

Polio Sabin™ Mono Two (oral) may also be given to children and adults when it is necessary to maintain or to reinforce the level of protection against infection caused by Type 2 poliovirus. The vaccine may also be administered to persons with a high risk of exposure to infection caused by Type 2 poliovirus. This vaccine does not act as a substitute for the trivalent poliomyelitis vaccine when this later is recommended.

Method of administration

Polio Sabin™ Mono Two (oral) is for oral use only.

POLIO SABIN™ MONO TWO (ORAL) SHOULD UNDER NO CIRCUMSTANCES BE INJECTED.

One dose of vaccine (0.1 ml) is contained in two drops which are delivered from the polyethylene dropper supplied with the multidose container.

The vaccine may be administered alone or mixed with beverages or foods provided that these do not contain substances that may inactivate polioviruses, such as preservatives. Suitable vehicles are simple syrup, milk, bread and a lump of sugar. Since the vaccine has a bitter salty taste, it may be given in syrup or on a lump of sugar, particularly when it is to be given to young children.

The vaccine should be administered to breastfed infants, preferably two hours before or after breastfeeding in order to avoid contact with the antibodies present in the breast milk.

Care should be taken not to contaminate a multidose dropper with saliva of the vaccinee.

4.3 Contraindications

Polio Sabin™ Mono Two (oral) is contraindicated in subjects with known hypersensitivity to neomycin or polymyxin, or to any other component of the vaccine. A history of contact dermatitis to neomycin or to polymyxin is not a contraindication.

Polio Sabin™ Mono Two (oral) is contraindicated in subjects having shown signs of hypersensitivity after previous administration of GlaxoSmithKline Biologicals' oral poliomyelitis vaccines.

4.4 Special warnings and special precautions for use

POLIO SABIN™ MONO TWO (ORAL) SHOULD UNDER NO CIRCUMSTANCES BE INJECTED.

Polio Sabin™ Mono Two (oral) should not be used for routine immunization against poliomyelitis (see section 4.1).
The routine poliomyelitis vaccination programme should continue to use trivalent vaccines according to national policy.

Polio Sabin™ Mono Two (oral) may not prevent or modify the course of the disease in subjects already infected with a wild Type 2 poliovirus.

The administration of Polio Sabin™ Mono Two (oral) should be postponed in subjects suffering from acute severe febrile illness, or persistent diarrhoea or vomiting. However, the presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

Episodes of diarrhoea and/or vomiting (as well as any gastro-intestinal infection) may hinder the administration of Polio Sabin™ Mono Two (oral). In case of diarrhoea, the dose received will not be counted as part of the immunisation schedule and should be repeated after recovery.

The attenuated Type 2 poliomyelitis virus multiplies in the gut. The faecal excretion of the vaccine virus may persist for several weeks and may also be transmitted to the contacts of the vaccinees; contacts of vaccinees should therefore be warned about the need for strict personal hygiene.

Non-immune persons in close contact with a recently vaccinated subject may very rarely be at risk of vaccine-associated paralytic poliomyelitis.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

Where the person to be vaccinated or contacts of persons to be vaccinated suffer from spontaneous or iatrogenic immunodeficiency (hereditary immunodeficiency, hypogammaglobulinemia and dysgammaglobulinemia, blood dyscrasia, leukaemia, lymphoma, neoplasia of the bone marrow or of the lymphatic system, generalised malignancy, administration of ACTH, corticosteroids, immunosuppressive drugs, cytostatic drugs or radiation therapy) the risk benefit of the use of the vaccine should, in an epidemic context, be evaluated in comparison to the use of inactivated vaccines. However, individuals with asymptomatic or symptomatic human immunodeficiency virus (HIV) infection may be vaccinated with Polio Sabin™ Mono Two (oral).

4.5 Interaction with other medicinal products and other forms of interaction

Polio Sabin™ Mono Two (oral) can be administered at the same time as *Haemophilus influenzae* type b vaccine, hepatitis B vaccine, diphtheria, pertussis and/or tetanus vaccine, measles, rubella and/or mumps vaccine, yellow fever vaccine or BCG vaccine if this fits into the vaccination schedule.

Concomitant administration of oral poliomyelitis vaccine (OPV) and rotavirus vaccine does not affect the immune response to the polio antigens but may slightly reduce the immune response to rotavirus vaccine. A clinical trial involving more than 4200 subjects who received OPV concomitantly with GlaxoSmithKline Biologicals' rotavirus vaccine (Rotarix™) showed that clinical protection against severe rotavirus gastro-enteritis was maintained.

If Polio Sabin™ Mono ~~Three~~**Two** (oral) cannot be given at the same time as other live attenuated vaccines, an interval of at least one month should be left between both vaccinations.

Immunosuppressive treatment may reduce the immune response, may favour the multiplication of the vaccine virus and may increase the length of excretion of the vaccine virus in the stools (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy
During pregnancy and in an epidemic context, the risk benefit of the use of the vaccine should be evaluated in comparison to the use of inactivated vaccines.

Lactation
The vaccine may be administered to a lactating mother.

Women of childbearing potential/ Contraception
Non immune woman of child-bearing age should use contraception during 3 months following vaccination.

4.7 Effects on ability to drive and use machines

There have been no studies to investigate the effect of Polio Sabin™ Mono Two (oral) on driving performance or the ability to operate machinery. Nevertheless, considering the adverse event profile of Polio Sabin™ Mono Two (oral) it is unlikely that the vaccine has an effect on the ability to drive and use machines.

4.8 Undesirable effects

Very rarely, vaccine-associated paralysis has been observed with trivalent oral poliomyelitis vaccines (less than one case per 1 million doses administered). The majority of post vaccinal paralytic poliomyelitis occurred after the administration of the first dose.

Fever, vomiting, diarrhoea and allergic/anaphylactoid reactions have been described after immunisation with GlaxoSmithKline Biologicals' trivalent oral poliomyelitis vaccine.

4.9 Overdose

Occasional reports of overdose with GlaxoSmithKline Biologicals' trivalent oral poliomyelitis vaccine have been received. Overdose has not resulted in ill-effects.

Insufficient data on Polio Sabin™ Mono Two (oral) are available.

5. PHARMACOLOGICAL PARTICULARS

5.1 Pharmacodynamic properties

On the basis of literature, it can be estimated that the immune response against Type 2 poliomyelitis virus will be at least equal to the one obtained with a trivalent oral poliomyelitis vaccine.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetics is not required for vaccines.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on routine quality control tests performed in animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium chloride, L-arginine, polysorbate 80 and purified water.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf-life

The expiry date of the vaccine is indicated on the label and packaging. (see also section 6.4)

6.4 Special precautions for storage

The vaccine is potent if stored at not higher than –20°C until the expiry date indicated on the vial. It can be stored for up to six months between +2°C and +8°C.

Multidose vials of Polio Sabin™ Mono Two (oral) from which one or more doses of vaccine have been removed during an immunization session may be used in subsequent immunization sessions for up to a maximum of 4 weeks, provided that all of the following conditions are met (as described in the WHO policy statement: The use of opened multidose vials in subsequent immunization sessions. WHO/V&B/00.09):

- The expiry date has not passed;
- The vaccines are stored under appropriate cold chain conditions;
- The vaccine vial septum has not been submerged in water;
- Aseptic technique has been used to withdraw all doses;
- The vaccine vial monitor (VVM), if attached, has not reached the discard point.

In order to preserve optimal potency of Polio Sabin™ Mono Two (oral), exposure of the vaccine to ambient (non-refrigerated) temperatures should be kept to a minimum and exposure to sunlight should be avoided.

Shipment should be done under refrigerated conditions, particularly in hot climates.

Freezing and thawing does not affect the titre of the vaccine.

When distribution or administration is not imminent, it is advisable to store the vaccine, if possible, at temperatures of –20°C or less since this halts deterioration in vaccine potency.

If the vaccine has been accidentally exposed to high environmental temperatures it is recommended that the vaccine be used immediately or stored ideally at –20°C or at 2-8°C until administration under condition that the VVM allows its use.

Store in the original package in order to protect from light.

6.5 Nature and contents of container

The vaccine is presented in glass vials (multidose vials containing 10 doses or 20 doses).

6.6 Instructions for use and handling

Vaccines should be inspected visually for any particulate matter prior to administration.

6.7 Vaccine Vial Monitor (see VVM pictogram at the end of the leaflet)

The Vaccine Vial Monitor (VVM) is part of the label used for all Polio Sabin™ Mono Two (oral) batches supplied by GlaxoSmithKline Biologicals. The colour dot that appears on the label of the vial is a VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.

The interpretation of the VVM is simple. Focus on the central square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the ring, then the vaccine can be used. As soon as the colour of the central square is the same colour as the ring or of a darker colour than the ring, then the vial should be discarded.

It is absolutely critical to ensure that the storage conditions specified above (in particular the cold chain) are complied with. GlaxoSmithKline Biologicals will assume no liability in the event Polio Sabin™ Mono Two (oral) has not been stored in compliance with that storage instructions. Furthermore GlaxoSmithKline Biologicals assumes no responsibility in case a VVM is defective for any reason.

Inner square lighter than outer circle. **If the expiry date has not been passed, USE the vaccine.**

At a later time, inner square still lighter than outer circle. **If the expiry date has not been passed, USE the vaccine.**

Discard point: Inner square matches colour of outer circle. **DO NOT use the vaccine**.

Beyond the discard point: Inner square darker than outer ring. **DO NOT use the vaccine**.

For further information, please contact the manufacturer.

Polio Sabin is a trademark of the GlaxoSmithKline group of companies.

WHO Package Insert Version number: [GDS02/WHO Insert02] / Date of issue: 12/07/2010 © [2010] GlaxoSmithKline Group of Companies
Manufacturer: *GlaxoSmithKline Biologicals s.a.* Rue de l'Institut 89, B-1330 Rixensart, Belgium. Tel : (32.2) 656 81 11 Fax : (32.2) 656 80 00

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IMOVAX POLIO

VACCIN POLIOMYELITIQUE (INACTIVE)

Suspension injectable en flacon multidose

Lire attentivement l'intégralité de cette notice avant de vous faire vacciner.
Gardez cette notice jusqu'à ce que vous ayez terminé le schéma de vaccination complet. Vous pourriez avoir besoin de la relire.
Vous devez suivre attentivement les conseils de votre médecin ou de votre infirmier/ère. Si vous avez besoin de plus d'informations et de conseils, adressez-vous à votre médecin ou à votre infirmier/ère.
Assurez-vous de terminer le schéma de vaccination complet. Sinon, vous risquez de ne pas être complètement protégé(e).
Ce vaccin vous a été personnellement prescrit. Ne le donnez à personne d'autre.

Les substances actives sont :
Une dose (0,5 ml) contient :
Virus poliomyélitique# de type 1 souche Mahoney (inactivé) ..... 40 UI D*†
Virus poliomyélitique# de type 2 souche MEF-1 (inactivé) ..... 8 UI D*†
Virus poliomyélitique# de type 3 souche Saukett (inactivé) ..... 32 UI D*†

Ce vaccin est conforme aux spécifications de la Pharmacopée Européenne et aux recommandations de l'O.M.S.

produit sur cellules VERO
* UI D : Unité antigène D
† ou quantité d'antigène équivalente déterminée selon une méthode immunochimique appropriée.

Les autres composants sont : 2-phénoxyéthanol, éthanol, formaldéhyde, milieu 199 de Hanks (contenant notamment des acides aminés, des sels minéraux, des vitamines, du glucose, du polysorbate 80 et de l'eau pour préparations injectables), de l'acide chlorhydrique ou de l'hydroxyde de sodium pour ajustement du pH.

Titulaire/Fabricant :
SANOFI PASTEUR SA - 2, avenue Pont Pasteur - 69007 LYON

Veuillez indiquer à votre médecin ou à votre pharmacien si vous prenez ou avez pris récemment un autre médicament, même s'il s'agit d'un médicament obtenu sans ordonnance.

3. COMMENT UTILISER IMOVAX POLIO ?

Posologie :
Primo-vaccination :
A partir de l'âge de 2 mois, il convient d'administrer 3 doses successives de 0,5 ml à un ou deux mois d'intervalle.
A partir de 6 semaines, IMOVAX POLIO peut être administré à l'âge de 6, 10, 14 semaines selon les recommandations du programme étendu d'immunisation de l'Organisation Mondiale de la Santé.
Chez l'adulte non vacciné, il convient d'administrer 2 doses successives de 0,5 ml à un ou, de préférence, deux mois d'intervalle.
Rappel :
Chez les enfants au cours de la deuxième année, une 4ème dose (1er rappel) est administrée un an après la 3ème injection.
Chez l'adulte, une 3ème dose (1 er rappel) est administrée 8 à 12 mois après la 2ème injection.
Pour les rappels ultérieurs, une injection de rappel est faite tous les 5 ans chez l'enfant et l'adolescent et tous les 10 ans chez l'adulte.

Mode d'administration :
L'administration se fait par voie intramusculaire de préférence ou sous-cutanée.
L'injection intramusculaire se fera de préférence dans la face antérolatérale de la cuisse chez le jeune enfant et dans le deltoïde chez l'enfant, l'adolescent et l'adulte.

Si vous avez utilisé plus de IMOVAX POLIO que vous n'auriez dû : sans objet.
Si vous oubliez de prendre IMOVAX POLIO : votre médecin décidera quand administrer la dose manquante.

4. QUELS SONT LES EFFETS INDESIRABLES EVENTUELS ?

Comme tous les vaccins, IMOVAX POLIO est susceptible d'avoir des effets indésirables.
Les effets indésirables les plus fréquemment rapportés sont :
– Réactions locales au site d'injection : douleur, érythème (rougeur de la peau), induration.
– Fièvre modérée et transitoire.
D'autres effets indésirables rapportés avec une fréquence très rare (<0,01 %) sont :
– Réactions locales au site d'injection :
  – oedème pouvant survenir dans les 48 heures et persister un ou deux jours
  – lymphadénopathies (augmentation de la taille des ganglions lymphatiques)
– Réaction d'hypersensibilité (allergie) : urticaire, oedème de Quincke (oedème de la face), choc anaphylactique à l'un des composants du vaccin.
– Arthralgies (douleurs des articulations) modérées et transitoires et des myalgies (douleurs musculaires) dans les jours suivant la vaccination.
– Convulsions associées ou non à de la fièvre dans les jours suivant la vaccination, céphalées (maux de tête), paresthésies (sensations de fourmillement) modérées et transitoires (principalement des membres inférieurs) survenant dans les deux semaines après la vaccination.
– Agitation, somnolence et irritabilité dans la première heure ou les jours suivant la vaccination et disparaissant rapidement.
– Rash (éruption cutanée étendue).
Chez les nourrissons nés grands prématurés (à 28 semaines de grossesse ou moins) des pauses respiratoires peuvent survenir pendant 2 à 3 jours après la vaccination.
Si vous remarquez des effets indésirables non mentionnés dans cette notice, veuillez en informer votre médecin ou votre pharmacien.

1. QU'EST-CE QUE IMOVAX POLIO ET DANS QUEL CAS EST-IL UTILISE ?

IMOVAX POLIO se présente sous la forme d'une suspension injectable en flacon multidose (flacon de 10 doses de 0,5 ml) - boîte de 10.
Ce vaccin est indiqué pour la prévention de la poliomyélite chez le nourrisson, l'enfant et l'adulte, en primo-vaccination et en rappel.

2. QUELLES SONT LES INFORMATIONS NECESSAIRES A CONNAITRE AVANT D'UTILISER IMOVAX POLIO ?

Ne pas utiliser IMOVAX POLIO si vous ou votre enfant :
– Etes allergiques aux substances actives, à l'un des excipients, à la néomycine, à la streptomycine et à la polymyxine B ou avez présenté une réaction allergique à la suite d'une injection précédente de ce vaccin.
– Présentez de la fièvre, une maladie aiguë, la vaccination devra être différée.

Prendre des précautions particulières avec IMOVAX POLIO si vous ou votre enfant :
– présentez une thrombocytopénie (quantité insuffisante de plaquettes jouant un rôle important dans la coagulation) ou des troubles de la coagulation en raison de saignement qui peut survenir lors de l'administration intramusculaire du vaccin.
– suivez un traitement supprimant vos défenses immunitaires ou présentez des défenses immunitaires déficientes, la réponse immunitaire du vaccin peut alors être diminuée. Il est alors recommandé d'attendre la fin du traitement pour vacciner ou de s'assurer de la bonne protection du sujet. Néanmoins, la vaccination de sujets présentant une immunodépression chronique, telle qu'une infection par le VIH, est recommandée si la maladie sous-jacente permet une réponse en anticorps même limitée.
La vaccination peut également être recommandée chez les sujets pour lesquels le vaccin oral est contre-indiqué, ainsi qu'en rappel pour les sujets préalablement vaccinés avec le vaccin oral.
– Ne pas injecter par voie intravasculaire : s'assurer que l'aiguille ne pénètre pas dans un vaisseau sanguin.

Grossesse et allaitement :
Ce médicament peut être utilisé pendant la grossesse.
L'allaitement n'est pas une contre-indication.
Demandez conseil à votre médecin ou à votre pharmacien avant de prendre tout médicament.

Conduite de véhicules et utilisation de machines : sans objet.
Liste des excipients à effet notoire : formaldéhyde, phénylalanine.

Utilisation avec d'autres médicaments :
Il n'y a pas d'inconvénient connu à l'administration d'IMOVAX POLIO au cours de la même séance de vaccination avec d'autres vaccins usuels.

5. COMMENT CONSERVER IMOVAX POLIO ?

Tenir hors de la portée et de la vue des enfants.
A conserver au réfrigérateur (entre +2°C et +8°C) et à l'abri de la lumière. Ne pas congeler.
Après ouverture : une utilisation immédiate est recommandée.
Ne pas utiliser IMOVAX POLIO si vous constatez que le produit présente un aspect trouble.
Ne pas utiliser après la date de péremption figurant sur la boîte.

La dernière date à laquelle cette notice a été approuvée est le 16 avril 2009

IMOVAX POLIO

POLIOMYELITIS VACCINE (INACTIVATED)

Suspension for injection in multidose vial

Read this entire leaflet carefully before getting vaccinated.
Keep this leaflet until you have completed the entire vaccination regimen. You might need to read it again.
Follow the advice of your doctor or nurse carefully. If you need more information or advice, ask your doctor or nurse.
Make sure to complete the entire vaccination regimen. If you do not, you may not be completely protected.
This vaccine has been prescribed for you. Do not pass it on to others.

The active substances are:
One dose (0.5 ml) contains:
Poliovirus* type 1, Mahoney strain (inactivated) ..... 40 DU*†
Poliovirus* type 2, MEF-1 strain (inactivated) ..... 8 DU*†
Poliovirus* type 3, Saukett strain (inactivated) ..... 32 DU*†

This vaccine is in compliance with European Pharmacopoeia requirements and WHO recommendations.

* cultured on VERO cells
* DU: D-antigen Unit
† or the equivalent antigenic quantity, determined by suitable immunochemical method.

The other ingredients are: 2-phenoxyethanol, ethanol, formaldehyde, medium 199 Hanks (containing in particular amino acids, mineral salts, vitamins, glucose, polysorbate 80 and water for injections), hydrochloric acid or sodium hydroxide for pH adjustment.

Holder/Manufacturer:
SANOFI PASTEUR SA - 2, avenue Pont Pasteur - 69007 LYON

1. WHAT IMOVAX POLIO IS AND WHAT IT IS USED FOR

IMOVAX POLIO is presented in the form of a suspension for injection in a multidose vial (vial of 10 doses of 0.5 ml) – box of 10.
This vaccine is indicated for the prevention of poliomyelitis in infants, children and adults, for primary vaccination and as a booster.

2. BEFORE YOU TAKE IMOVAX POLIO

Do not use IMOVAX POLIO if you or your child:
- Are allergic to the active substances, to one of the excipients, to neomycin, to streptomycin or to polymyxine B or have had an allergic reaction following a previous injection of this vaccine.
- Have a fever or acute illness; in this case, vaccination should be postponed.

Take special care with IMOVAX POLIO if you or your child:
- Have thrombocytopenia (insufficient blood platelets, which play an important role in coagulation) or a bleeding disorder, because of the bleeding that can occur during intramuscular administration of the vaccine.
- Are taking a treatment that suppresses your immune response or presenting with an immune deficiency disorder, in which case the immune response to the vaccine may be reduced. In such cases it is recommended to postpone vaccination until the end of the treatment or to make sure the subject is well protected. Vaccination of subjects with chronic immunodeficiency, such as HIV infection, is nevertheless recommended even if the immune response might be limited by the underlying illness.
  This vaccine may also be indicated for subjects for whom the oral vaccine is contraindicated and as a booster for subjects previously vaccinated with the oral vaccine.
- Do not inject by the intravascular route: make sure the needle does not penetrate a blood vessel.

Pregnancy and Breast Feeding:
This vaccine may be used during pregnancy, if required. Breast feeding is not a contraindication.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and Using Machines: Not applicable.

List of Excipients with Known Effect: formaldehyde, phenylalanine.

Use with Other Medicines:
There is no documented evidence against administration of IMOVAX POLIO with other usual vaccines in a single vaccination session.
Please tell your doctor or pharmacist if you are taking or have recently taken another medicine, including medicines obtained without a prescription.

3. HOW TO USE IMOVAX POLIO

Dosage:
Primary vaccination:
From 2 months of age, 3 successive injections of 0.5 ml should be administered at intervals of one or two months.
From 6 weeks of age, IMOVAX POLIO may be administered following the 6, 10, 14-week schedule, as per the recommendations of the Expanded Programme on Immunisation of the World Health Organisation.
For nonvaccinated adults, 2 successive injections of 0.5 ml must be given at intervals of one or, preferably, two months.

Booster:
In children in the second year of life, a 4th dose (1st booster) is administered one year after the 3rd injection.
For adults, a 3rd dose (1st booster) is administered 8 to 12 months after the 2nd injection.
A booster is given every 5 years in children and adolescents and every 10 years in adults.

Method of Administration:
The preferred route of administration is intramuscular, though the vaccine may also be given subcutaneously.
The preferred site of intramuscular injection is the mid-lateral aspect of the thigh in infants and toddlers and the deltoid muscle in children, adolescents and adults.

If you use more IMOVAX POLIO than you should have: Not applicable.

If you forget to take IMOVAX POLIO:
Your doctor will decide when to administer the missing dose.

4. POSSIBLE SIDE EFFECTS

Like all vaccines, IMOVAX POLIO may cause side effects.
The most frequently reported side effects are:
- Local reactions at the injection site: pain, erythema (skin redness), induration.
- Moderate, transient fever.

Other side effects, reported very rarely (<0.01 %), are:
- Local reactions at the injection site:
  - oedema that can occur within 48 hours and persist for one or two days
  - lymphadenopathy (increase in the size of lymph nodes)
- Hypersensitivity reaction (allergy): urticaria, Quincke's oedema (facial oedema), anaphylactic shock in response to one of the vaccine components.
- Moderate and transient arthralgia (joint pain) and myalgia (muscular pain) in the days following vaccination.
- Convulsions (isolated or associated with fever) in the days following vaccination, headaches, moderate and transient paresthesia (a tingling sensation, primarily in the lower limbs) occurring in the two weeks following vaccination.
- Agitation, somnolence and irritability in the first hours or days following vaccination and disappearing rapidly.
- Widespread skin rash.

In babies born very prematurely (at or before 28 weeks of gestation) longer gaps than normal between breaths may occur for 2-3 days after vaccination.
If you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE IMOVAX POLIO

Keep out of the reach and sight of children.
Store in a refrigerator (between +2°C and +8°C), protected from light. Do not freeze.
It is best to use the vaccine immediately after opening it.
Do not use IMOVAX POLIO if it has a cloudy appearance.
Do not use after the expiry date listed on the package.

This leaflet was last approved on 16 April 2009

IMOVAX POLIO

VACUNA ANTIPOLIOMIELITICA (INACTIVADA)

Suspensión inyectable en frasco multidosis

Lea todo el prospecto detenidamente antes de proceder a la vacunación.
Conserve este prospecto hasta que haya terminado el calendario completo de vacunación ya que puede tener que volver a leerlo.
Debe seguir atentamente los consejos de su médico o de su enfermero(a). Si necesita información adicional o consejo, consulte a su médico o enfermero(a).
Asegúrese de terminar el calendario completo de vacunación. De lo contrario, podría no quedar totalmente protegido(a).
Esta vacuna se le ha recetado a usted personalmente. No debe dársela a otras personas.

Los principios activos son:
Una dosis (0,5 ml) contiene:
Virus poliomielítico* de tipo 1 cepa Mahoney (inactivado) ..... 40 UD*†
Virus poliomielítico* de tipo 2 cepa MEF-1 (inactivado) ..... 8 UD*†
Virus poliomielítico* de tipo 3 cepa Saukett (inactivado) ..... 32 UD*†

Esta vacuna está en conformidad con las especificaciones de la Farmacopea Europea y con las recomendaciones de la OMS.

* producido en células VERO
* UD: Unidad antígeno D.
† o cantidad equivalente de antígenos determinada según un método inmunoquímico apropiado

Los demás componentes son: 2-fenoxietanol, etanol, formaldehído, medio 199 de Hanks (que contiene aminoácidos, sales minerales, vitaminas, glucosa, polisorbato 80 y agua para preparaciones inyectables, entre otros), ácido clorhídrico o hidróxido de sodio para ajuste del pH.

Titular / Fabricante:
SANOFI PASTEUR SA - 2, avenue Pont Pasteur - 69007 LYON

1. QUÉ ES IMOVAX POLIO Y PARA QUÉ SE UTILIZA

IMOVAX POLIO se presenta bajo forma de suspensión inyectable en frasco multidosis (frasco de 10 dosis de 0,5 ml) - caja de 10.
Esta vacuna está indicada para la prevención de la poliomielitis en el lactante, el niño y el adulto, tanto en primovacunación como en refuerzo.

2. ANTES DE USAR IMOVAX POLIO

No use IMOVAX POLIO si Ud. o su hijo(a):
- Es alérgico(a) a los principios activos a uno de los excipientes, a la neomicina, a la estreptomicina o a la polimixina B o ha presentado una reacción alérgica tras una inyección anterior de esta vacuna.
- Presenta fiebre o una enfermedad aguda, deberá posponerse la vacunación.

Tenga especial cuidado con **IMOVAX POLIO** si Ud. o su hijo(a):
- Presenta una trombocitopenia (cantidad insuficiente de plaquetas que juegan un papel importante en la coagulación) o trastornos de coagulación debido al sangrado que puede ocurrir durante la administración intramuscular de la vacuna.
- Sigue un tratamiento que suprime sus defensas inmunitarias o si presenta defensas inmunitarias deficientes, la respuesta inmunitaria de la vacuna puede verse reducida. En tales casos se recomienda esperar al final del tratamiento para vacunar o asegurarse de la buena protección del sujeto. Sin embargo, se recomienda la vacunación de sujetos que presentan una inmunodepresión crónica, como una infección por VIH, si la enfermedad subyacente permite una respuesta de anticuerpos aunque ésta sea limitada.

Esta vacuna puede recomendarse igualmente en sujetos para los cuales la vacuna oral está contraindicada, al igual que en refuerzo para los sujetos previamente vacunados con la vacuna oral.
- No inyectar por vía intravascular: asegurarse de que la aguja no penetre en un vaso sanguíneo.

Embarazo y lactancia:
Este medicamento puede utilizarse durante el embarazo en caso de necesidad.
La lactancia no es una contraindicación.
Consulte a su médico o farmacéutico antes de tomar cualquier medicamento.

Conducción y uso de máquinas: No procede.

Lista de los excipientes con efecto conocido: formaldehído, fenilalanina.

Uso de otros medicamentos:
No hay inconveniente conocido en administrar IMOVAX POLIO en el transcurso de la misma sesión de vacunación con otras vacunas habituales.
Informe a su médico o farmacéutico si está tomando o ha tomado recientemente otros medicamentos, incluso los adquiridos sin receta.

3. CÓMO USAR IMOVAX POLIO

Posología:
Primovacunación:
A partir de los 2 meses de edad, es conveniente administrar 3 dosis sucesivas de 0,5 ml con uno o dos meses de intervalo.
A partir de las 6 semanas de edad, IMOVAX POLIO puede ser administrada a las 6, 10 y 14 semanas según las recomendaciones del programa extendido de inmunización de la Organización Mundial de la Salud.
En el adulto no vacunado es conveniente administrar 2 dosis sucesivas de 0,5 ml con uno o preferentemente, dos meses de intervalo.

Refuerzo:
En los niños, se administra una 4ª dosis (1er refuerzo) en el transcurso del segundo año, un año después de la 3ª inyección.
En el adulto, se administra una 3ª dosis (1er refuerzo) entre 8 y 12 meses después de la 2ª inyección.
Para los refuerzos posteriores, se le aplica al niño y al adolescente una inyección de refuerzo cada 5 años, y cada 10 años al adulto.

Forma de administración:
La administración se realiza por vía intramuscular (vía recomendada), o por vía subcutánea.
La inyección intramuscular se realizará preferentemente en la cara anterolateral del muslo en el niño pequeño y en el deltoides en el niño más mayor, el adolescente y el adulto.

Si Ud. toma más **IMOVAX POLIO** del que debiera: no procede.

Si olvidó usar **IMOVAX POLIO**: su médico deberá decidir cuándo administrar la dosis que falta.

4. POSIBLES EFECTOS ADVERSOS

Al igual que todos los medicamentos, IMOVAX POLIO puede producir efectos adversos.
Los efectos adversos informados con más frecuencia son:
- Reacciones locales en el lugar de la inyección: dolor, eritema (enrojecimiento de la piel), induración.
- fiebre moderada y transitoria.

Otros efectos adversos informados muy raramente (<0,01 %) son:
- Reacciones locales en el lugar de la inyección:
  - edema que puede sobrevenir en las siguientes 48 horas y persistir uno o dos días
  - linfadenopatías (aumento del tamaño de los ganglios linfáticos)
- Reacción de hipersensibilidad (alergia): urticaria, edema de Quincke (edema facial), choque anafiláctico a uno de los componentes de la vacuna.
- Se han informado artralgias (dolores en las articulaciones) moderadas y transitorias y mialgias (dolores musculares) en los días siguientes a la vacunación.
- Convulsiones asociadas o no a fiebre en los días siguientes a la vacunación, cefaleas (dolores de cabeza), parestesias (sensaciones de hormigueo) moderadas y transitorias (principalmente de los miembros inferiores) que sobrevienen en las dos semanas siguientes a la vacunación.
- Agitación, somnolencia e irritabilidad en las primeras horas o en los días siguientes a la vacunación y que desaparecen rápidamente.
- Rash (erupción cutánea extendida).

En los bebés nacidos muy prematuramente (en la semana 28 del embarazo, o antes), pueden ocurrir pausas respiratorias durante los 2 ó 3 días siguientes a la vacunación.
Si aprecia efectos adversos no mencionados en este prospecto, comuníqueselo a su médico o farmacéutico.

5. CONSERVACIÓN DE IMOVAX POLIO

Mantener fuera del alcance y de la vista de los niños.
Consérvese en nevera (entre +2°C y +8°C) para protegerlo de la luz. No congelar.
Una vez abierta, se recomienda que se utilice inmediatamente.
No utilice IMOVAX POLIO si Ud. observa que el producto presenta un aspecto turbio.
No use esta vacuna después de la fecha de caducidad que figura en la caja.

Este prospecto fue aprobado por última vez el 16 de abril de 2009

sanofi pasteur

059 94242-0

AHFS Category 80:12

Poliovirus Vaccine Inactivated

IPOL®

IPV

℞ only

DESCRIPTION

IPOL®, Poliovirus Vaccine Inactivated, produced by Sanofi Pasteur SA, is a sterile suspension of three types of poliovirus: Type 1 (Mahoney), Type 2 (MEF-1), and Type 3 (Saukett). IPOL vaccine is a highly purified, inactivated poliovirus vaccine with enhanced potency. Each of the three strains of poliovirus is individually grown in vero cells, a continuous line of monkey kidney cells cultivated on microcarriers.[1,2] The cells are grown in Eagle MEM modified medium, supplemented with newborn calf serum tested for adventitious agents prior to use, originated from countries free of bovine spongiform encephalopathy. For viral growth the culture medium is replaced by M-199, without calf serum. This culture technique and improvements in purification, concentration and standardization of poliovirus antigen produce a more potent and consistent immunogenic vaccine than the inactivated poliovirus vaccine (IPV) available in the US prior to 1988.[3,4]

After clarification and filtration, viral suspensions are concentrated by ultrafiltration, and purified by three liquid chromatography steps; one column of anion exchanger, one column of gel filtration and again one column of anion exchanger. After re-equilibration of the purified viral suspension, with Medium M-199 and adjustment of the antigen titer, the monovalent viral suspensions are inactivated at +37°C for at least 12 days with 1:4000 formalin.

Each dose (0.5 mL) of trivalent vaccine is formulated to contain 40 D antigen units of Type 1, 8 D antigen units of Type 2, and 32 D antigen units of Type 3 poliovirus. For each lot of IPOL vaccine, D-antigen content is determined *in vitro* using the D-antigen ELISA assay and immunogenicity is determined by *in vivo* testing in animals. IPOL vaccine is produced from vaccine concentrates diluted with M-199 medium. Also present are 0.5% of 2-phenoxyethanol and a maximum of 0.02% of formaldehyde per dose as preservatives. Neomycin, streptomycin and polymyxin B are used in vaccine production, and although purification procedures eliminate measurable amounts, less than 5 ng neomycin, 200 ng streptomycin and 25 ng polymyxin B per dose may still be present. The residual calf serum protein is less than 1 ppm in the final vaccine.

The vaccine is clear and colorless and should be administered intramuscularly or subcutaneously.

CLINICAL PHARMACOLOGY

Poliomyelitis is caused by poliovirus Types 1, 2, or 3. It is primarily spread by the fecal-oral route of transmission but may also be spread by the pharyngeal route.

Approximately 90% to 95% of poliovirus infections are asymptomatic. Nonspecific illness with low-grade fever and sore throat (minor illness) occurs in 4% to 8% of infections. Aseptic meningitis occurs in 1% to 5% of patients a few days after the minor illness has resolved. Rapid onset of asymmetric acute flaccid paralysis occurs in 0.1% to 2% of infections, and residual paralytic disease involving motor neurons (paralytic poliomyelitis) occurs in approximately 1 per 1,000 infections.[5]

Prior to the introduction of inactivated poliovirus vaccines in 1955, large outbreaks of poliomyelitis occurred each year in the United States (US). The annual incidence of paralytic disease of 11.4 cases/100,000 population declined to 0.5 cases by the time oral poliovirus vaccine (OPV) was introduced in 1961. Incidence continued to decline thereafter to a rate of 0.002 to 0.005 cases per 100,000 population. Of the 127 cases of paralytic poliomyelitis reported in the US between 1980 and 1994, six were imported cases (caused by wild polioviruses), two were “indeterminate” cases, and 119 were vaccine associated paralytic poliomyelitis (VAPP) cases associated with the use of live, attenuated oral poliovirus vaccine (OPV).[6] An all IPV schedule was adopted in 1999, to eliminate VAPP cases.[7]

Poliovirus Vaccine Inactivated induces the production of neutralizing antibodies against each type of virus which are related to protective efficacy. Antibody response in most children were induced after receiving fewer doses[8] of IPV vaccine than the vaccine available in the United States prior to 1988.

Studies in developed[8] and developing[9,10] countries with a similar enhanced IPV manufactured by the same process as IPOL vaccine in primary monkey kidney cells have shown a direct relationship exists between the antigenic content of the vaccine, the frequency of seroconversion, and resulting antibody titer. Approval in the US was based upon demonstration of immunogenicity and safety in US children.[11]

In the US, 219 infants received three doses of a similar enhanced IPV at two, four and eighteen months of age manufactured by the same process as IPOL vaccine except the cell substrate for IPV was using primary monkey kidney cells. Seroconversion to all three types of poliovirus was demonstrated in 99% of these infants after two doses of vaccine given at 2 and 4 months of age. Following the third dose of vaccine at 18 months of age, neutralizing antibodies were present at a level of ≥1:10 in 99.1% of children to Type 1 and 100% of children to Types 2 and 3 polioviruses.[3]

IPOL vaccine was administered to more than 700 infants between 2 to 18 months of age during three clinical studies conducted in the US using IPV only schedules and sequential IPV-OPV schedules.[12,13] Seroprevalence rates for detectable serum neutralizing antibody (DA) at a ≥1:4 dilution were 95% to 100% (Type 1); 97% to 100% (Type 2) and 96% to 100% (Type 3) after two doses of IPOL vaccine depending on studies.

TABLE 1 US STUDIES WITH IPOL VACCINE ADMINISTERED USING IPV ONLY OR SEQUENTIAL IPV-OPV SCHEDULES

Age (months) for 2 Dose 1	4 Dose 2	6 Dose 3	12 to 18 Booster	Post Dose 2 N*	Post Dose 2 Type 1 %DA**	Post Dose 2 Type 2 %DA	Post Dose 2 Type 3 %DA	Post Dose 3 N*	Post Dose 3 Type 1 %DA	Post Dose 3 Type 2 %DA	Post Dose 3 Type 3 %DA	Pre Booster N*	Pre Booster Type 1 %DA	Pre Booster Type 2 %DA	Pre Booster Type 3 %DA	Post Booster N*	Post Booster Type 1 %DA	Post Booster Type 2 %DA	Post Booster Type 3 %DA
STUDY 1[11¶]																			
I(s)	I(s)	NA†	I(s)	56	97	100	97		–	–	–	53	91	97	93	53	97	100	100
O	O	NA	O	22	100	100	100		–	–	–	22	78	91	78	20	100	100	100
I(s)	O	NA	O	17	95	100	95		–	–	–	17	95	100	95	17	100	100	100
I(s)	I(s)	NA	O	17	100	100	100		–	–	–	16	100	100	94	16	100	100	100
STUDY 2[10§]																			
I(c)	I(c)	NA	I(s)	94	98	97	96		–	–	–	100	92	95	88	97	100	100	100
I(s)	I(s)	NA	I(s)	68	99	100	99		–	–	–	72	100	100	94	75	100	100	100
I(c)	I(c)	NA	O	75	95	99	96		–	–	–	77	86	97	82	78	100	100	97
I(s)	I(s)	NA	O	101	99	99	95		–	–	–	103	99	97	89	107	100	100	100
STUDY 3[10§]																			
I(c)	I(c)	I(c)	O	91	98	99	100	91	100	100	100	41	100	100	100	40	100	100	100
I(c)	I(c)	O	O	96	100	98	99	94	100	100	99	47	100	100	100	45	100	100	100
I(c)	I(c)	I(c) + O	O	91	96	97	100	85	100	100	100	47	100	100	100	46	100	100	100

* N = Number of children from whom serum was available
** Detectable antibody (neutralizing titer ≥1:4)
† NA – No poliovirus vaccine administered
¶ IPOL vaccine given subcutaneously
§ IPOL vaccine given intramuscularly
I IPOL vaccine given either separately in association with DTP in two sites (s) or combined (c) with DTP in a dual chambered syringe
O OPV

In one study,[13] the persistence of DA in infants receiving two doses of IPOL vaccine at 2 and 4 months of age was 91% to 100% (Type 1), 97% to 100% (Type 2), and 93% to 94% (Type 3) at twelve months of age. In another study,[12] 86% to 100% (Type 1), 95% to 100% (Type 2), and 82% to 94% (Type 3) of infants still had DA at 18 months of age.

In trials and field studies conducted outside the US, IPOL vaccine, or a combination vaccine containing IPOL vaccine and DTP, was administered to more than 3,000 infants between 2 to 18 months of age using IPV only schedules and immunogenicity data are available from 1,485 infants. After two doses of vaccine given during the first year of life, seroprevalence rates for detectable serum neutralizing antibody (neutralizing titer ≥1:4) were 88% to 100% (Type 1); 84% to 100% (Type 2) and 94% to 100% (Type 3) of infants, depending on studies. When three doses were given during the first year of life, post-dose 3 DA ranged between 93% to 100% (Type 1); 89% to 100% (Type 2) and 97% to 100% (Type 3) and reached 100% for Types 1, 2, and 3 after the fourth dose given during the second year of life (12 to 18 months of age).[14]

In infants immunized with three doses of an unlicensed combination vaccine containing IPOL vaccine and DTP given during the first year of life, and a fourth dose given during the second year of life, the persistence of detectable neutralizing antibodies was 96%, 96% and 97% against poliovirus Types 1, 2, and 3, respectively, at six years of age. DA reached 100% for all types after a booster dose of IPOL vaccine combined with DTP vaccine.[11] A survey of Swedish children and young adults given a Swedish IPV only schedule demonstrated persistence of detectable serum neutralizing antibody for at least 10 years to all three types of poliovirus.[15]

IPV is able to induce secretory antibody (IgA) produced in the pharynx and gut and reduces pharyngeal excretion of poliovirus Type 1 from 75% in children with neutralizing antibodies at levels less than 1:8 to 25% in children with neutralizing antibodies at levels more than 1:64.[4,14,16-22] There is also evidence of induction of herd immunity with IPV,[15,23-26] and that this herd immunity is sufficiently maintained in a population vaccinated only with IPV.[26]

VAPP has not been reported in association with administration of IPOL vaccine.[27] It is expected that an IPV only schedule will eliminate the risk of VAPP in both recipients and contacts compared to a schedule that included OPV.[7]

INDICATIONS AND USAGE
IPOL vaccine is indicated for active immunization of infants (as young as 6 weeks of age), children and adults for the prevention of poliomyelitis caused by poliovirus Types 1, 2, and 3.[28]

INFANTS, CHILDREN AND ADOLESCENTS

General Recommendations

It is recommended that all infants (as young as 6 weeks of age), unimmunized children and adolescents not previously immunized be vaccinated routinely against paralytic poliomyelitis.[29] Following the eradication of poliomyelitis caused by wild poliovirus from the Western Hemisphere (including North and South America).[30] An IPV-only schedule was recommended to eliminate VAPP.[7]

All children should receive four doses of IPV at ages 2, 4, 6 to 18 months and 4 to 6 years. OPV is no longer available in the US and is not recommended for routine immunization.[7] OPV is only recommended for special circumstances including the control of outbreaks.

Previous clinical poliomyelitis (usually due to only a single poliovirus type) or incomplete immunization with OPV are not contraindications to completing the primary series of immunization with IPOL vaccine.

Children Incompletely Immunized

Children of all ages should have their immunization status reviewed and be considered for supplemental immunization as follows for adults. Time intervals between doses longer than those recommended for routine primary immunization do not necessitate additional doses as long as a final total of four doses is reached (see **DOSAGE AND ADMINISTRATION** section).

ADULTS

General Recommendations

Routine primary poliovirus vaccination of adults (generally those 18 years of age or older) residing in the US is not recommended. Unimmunized adults who are potentially exposed to wild poliovirus and have not been adequately immunized should receive polio vaccination in accordance with the schedule given in the **DOSAGE AND ADMINISTRATION** section.[28]

Persons with previous wild poliovirus disease who are incompletely immunized or unimmunized should be given additional doses of IPOL vaccine if they fall into one or more categories listed previously.

The following categories of adults are at an increased risk of exposure to wild polioviruses:[28,31]

- Travelers to regions or countries where poliomyelitis is endemic or epidemic.
- Health-care workers in close contact with patients who may be excreting polioviruses.
- Laboratory workers handling specimens that may contain polioviruses.
- Members of communities or specific population groups with disease caused by wild polioviruses.

IMMUNODEFICIENCY AND ALTERED IMMUNE STATUS

IPOL vaccine should be used in all patients with immunodeficiency diseases and members of such patients' households when vaccination of such persons is indicated. This includes patients with asymptomatic HIV infection, AIDS or AIDS-Related Complex, severe combined immunodeficiency, hypogammaglobulinemia, or agammaglobulinemia; altered immune states due to diseases such as leukemia, lymphoma, or generalized malignancy; or an immune system compromised by treatment with corticosteroids, alkylating drugs, antimetabolites or radiation. Immunogenicity of IPOL vaccine in individuals receiving immunoglobulin could be impaired and patients with an altered immune state may or may not develop a protective response against paralytic poliomyelitis after administration of IPV.[32]

As with any vaccine, vaccination with IPOL vaccine may not protect 100% of individuals.

Use with other vaccines: refer to **DOSAGE AND ADMINISTRATION** section for this information.

CONTRAINDICATIONS

IPOL vaccine is contraindicated in persons with a history of hypersensitivity to any component of the vaccine, including 2-phenoxyethanol, formaldehyde, neomycin, streptomycin and polymyxin B.

No further doses should be given if anaphylaxis or anaphylactic shock occurs within 24 hours of administration of one dose of vaccine.

Vaccination of persons with an acute, febrile illness should be deferred until after recovery; however, minor illness, such as mild upper respiratory infection, with or without low grade fever, are not reasons for postponing vaccine administration.

WARNINGS

Neomycin, streptomycin, polymyxin B, 2-phenoxyethanol, and formaldehyde are used in the production of this vaccine. Although purification procedures eliminate measurable amounts of these substances, traces may be present (see **DESCRIPTION** section) and allergic reactions may occur in persons sensitive to these substances (see **CONTRAINDICATIONS** section).

Systemic adverse reactions reported in infants receiving IPV concomitantly at separate sites or combined with DTP have been similar to those associated with administration of DTP alone.[11] Local reactions are usually mild and transient in nature.

Although no causal relationship between IPOL vaccine and Guillain-Barré Syndrome (GBS) has been established,[28] GBS has been temporally related to administration of another inactivated poliovirus vaccine. Deaths have been reported in temporal association with the administration of IPV (see **ADVERSE REACTIONS** section).

PRECAUTIONS

GENERAL

Prior to an injection of any vaccine, all known precautions should be taken to prevent adverse reactions. This includes a review of the patient's history with respect to possible sensitivity to the vaccine or similar vaccines.

Health-care providers should question the patient, parent or guardian about reactions to a previous dose of this product, or similar product.

Epinephrine Injection (1:1000) and other appropriate agents should be available to control immediate allergic reactions.

Health-care providers should obtain the previous immunization history of the vaccinee, and inquire about the current health status of the vaccinee.

Immunodeficient patients or patients under immunosuppressive therapy may not develop a protective immune response against paralytic poliomyelitis after administration of IPV.

Administration of IPOL vaccine is not contraindicated in individuals infected with HIV.[33,34,35]

Special care should be taken to ensure that the injection does not enter a blood vessel.

INFORMATION FOR PATIENTS

Patients, parents, or guardians should be instructed to report any serious adverse reactions to their health-care provider.

The health-care provider should inform the patient, parent, or guardian of the benefits and risks of the vaccine.

The health-care provider should inform the patient, parent, or guardian of the importance of completing the immunization series.

The health-care provider should provide the Vaccine Information Statements (VISs) which are required to be given with each immunization.

DRUG INTERACTIONS

There are no known interactions of IPOL vaccine with drugs or foods. Concomitant administration, of other parenteral vaccines, with separate syringes at separate sites, is not contraindicated. The first two doses of IPOL vaccine may be administered at separate sites using separate syringes concomitantly with DTaP, acellular pertussis, *Haemophilus influenzae* type b (Hib), and hepatitis B vaccines. From historical data on the antibody responses to diphtheria, tetanus, acellular pertussis, Hib, or hepatitis B vaccines used concomitantly or in combination with IPOL vaccine, no interferences have been observed on the immunological end points accepted for clinical protection.[11,16,36] (See **DOSAGE AND ADMINISTRATION** section.)

If IPOL vaccine has been administered to persons receiving immunosuppressive therapy, an adequate immunologic response may not be obtained. (See **PRECAUTIONS** – GENERAL section.)

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Long-term studies in animals to evaluate carcinogenic potential or impairment of fertility have not been conducted.

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with IPOL vaccine. It is also not known whether IPOL vaccine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. IPOL vaccine should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

It is not known whether IPOL vaccine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when IPOL vaccine is administered to a nursing woman.

PEDIATRIC USE

SAFETY AND EFFECTIVENESS OF IPOL VACCINE IN INFANTS BELOW SIX WEEKS OF AGE HAVE NOT BEEN ESTABLISHED.[12,20] (See **DOSAGE AND ADMINISTRATION** section.)

In the US, infants receiving two doses of IPV at 2 and 4 months of age, the seroprevalence to all three types of poliovirus was demonstrated in 95% to 100% of these infants after two doses of vaccine.[12,13]

ADVERSE REACTIONS

BODY SYSTEM AS A WHOLE

In earlier studies with the vaccine grown in primary monkey kidney cells, transient local reactions at the site of injection were observed.[3] Erythema, induration and pain occurred in 3.2%, 1% and 13%, respectively, of vaccinees within 48 hours post-vaccination. Temperatures of ≥39°C (≥102°F) were reported in 38% of vaccinees. Other symptoms included irritability, sleepiness, fussiness, and crying. Because IPV was given in a different site but concurrently with Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (DTP), these systemic reactions could not be attributed to a specific vaccine. However, these systemic reactions were comparable in frequency and severity to that reported for DTP given alone without IPV.[12] Although no causal relationship has been established, deaths have occurred in temporal association after vaccination of infants with IPV.[37]

Four additional US studies using IPOL vaccine in more than 1,300 infants,[12] between 2 to 18 months of age administered with DTP at the same time at separate sites or combined have demonstrated that local and systemic reactions were similar when DTP was given alone.

TABLE 2[12] PERCENTAGE OF INFANTS PRESENTING WITH LOCAL OR SYSTEMIC REACTIONS AT 6, 24, AND 48 HOURS OF IMMUNIZATION WITH IPOL VACCINE ADMINISTERED INTRAMUSCULARLY CONCOMITANTLY AT SEPARATE SITES WITH SANOFI¶ WHOLE-CELL DTP VACCINE AT 2 AND 4 MONTHS OF AGE AND WITH SANOFI ACELLULAR PERTUSSIS VACCINE (TRIPEDIA®) AT 18 MONTHS OF AGE

REACTION	AGE AT IMMUNIZATION								
	2 Months (n=211)			4 Months (n=206)			18 Months† (n=74)		
	6 Hrs.	24 Hrs.	48 Hrs.	6 Hrs.	24 Hrs.	48 Hrs.	6 Hrs.	24 Hrs.	48 Hrs.
Local, IPOL vaccine alone§									
Erythema >1"	0.5%	0.5%	0.5%	1.0%	0.0%	0.0%	1.4%	0.0%	0.0%
Swelling	11.4%	5.7%	0.9%	11.2%	4.9%	1.9%	2.7%	0.0%	0.0%
Tenderness	29.4%	8.5%	2.8%	22.8%	4.4%	1.0%	13.5%	4.1%	0.0%
Systemic*									
Fever >102.2°F	1.0%	0.5%	0.5%	2.0%	0.5%	0.0%	0.0%	0.0%	4.2%
Irritability	64.5%	24.6%	17.5%	49.5%	25.7%	11.7%	14.7%	6.7%	8.0%
Tiredness	60.7%	31.8%	7.1%	38.8%	18.4%	6.3%	9.3%	5.3%	4.0%
Anorexia	16.6%	8.1%	4.3%	6.3%	4.4%	2.4%	2.7%	1.3%	2.7%
Vomiting	1.9%	2.8%	2.8%	1.9%	1.5%	1.0%	1.3%	1.3%	0.0%
Persistent Crying	Percentage of infants within 72 hours after immunization was 0.0% after dose one, 1.4% after dose two, and 0.0% after dose three.								

¶ Sanofi Pasteur Inc. formerly known as Aventis Pasteur Inc.
§ Data are from the IPOL vaccine administration site, given intramuscularly.
* The adverse reaction profile includes the concomitant use of Sanofi whole-cell DTP vaccine or Tripedia vaccine with IPOL vaccine. Rates are comparable in frequency and severity to that reported for whole-cell DTP given alone.
† Children who have been vaccinated with Tripedia vaccine.

DIGESTIVE SYSTEM
Anorexia and vomiting occurred with frequencies not significantly different as reported when DTP was given alone without IPV or OPV.[12]

NERVOUS SYSTEM
Although no causal relationship between IPOL vaccine and GBS has been established,[28] GBS has been temporally related to administration of another inactivated poliovirus vaccine.

Reporting of Adverse Events
The National Vaccine Injury Compensation Program, established by the National Childhood Vaccine Injury Act of 1986, requires physicians and other health-care providers who administer vaccines to maintain permanent vaccination records and to report occurrences of certain adverse events to the US Department of Health and Human Services. Reportable events include those listed in the Act for each vaccine and events specified in the package insert as contraindications to further doses of that vaccine.[38,39,40]

Reporting by parents or guardians of all adverse events after vaccine administration should be encouraged. Adverse events following immunization with vaccine should be reported by health-care providers to the US Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS). Reporting forms and information about reporting requirements or completion of the form can be obtained from VAERS through a toll-free number 1-800-822-7967.[38,39,40]

Health-care providers also should report these events to the Pharmacovigilance Department, Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 or call 1-800-822-2463.

DOSAGE AND ADMINISTRATION
Before administration, parenteral drug products should be checked visually for any deviation from normal appearance including container integrity. The syringe or vial and its packaging should be inspected prior to use for evidence of leakage, premature activation of the plunger, or a faulty tip seal. If evidence of such defects are observed, the syringe should not be used.

After preparation of the injection site, immediately administer IPOL vaccine intramuscularly or subcutaneously. In infants and small children, the mid-lateral aspect of the thigh is the preferred site. In older children and adults IPOL vaccine should be administered intramuscularly or subcutaneously in the deltoid area.

The syringe is intended for single use only, must not be reused, and must be disposed of properly and promptly following its use.

To help avoid HIV (AIDS), HBV (Hepatitis), and other infectious diseases due to accidental needlesticks, contaminated needles should not be recapped or removed, unless there is no alternative or that such action is required by a specific medical procedure.

Care should be taken to avoid administering the injection into or near blood vessels and nerves. If blood or any suspicious discoloration appears in the syringe, do not inject but discard contents and repeat procedures using a new dose of vaccine administered at a different site.

DO NOT ADMINISTER VACCINE INTRAVENOUSLY.

Children
The primary series of IPOL vaccine consists of three 0.5 mL doses administered intramuscularly or subcutaneously, preferably eight or more weeks apart and usually at ages 2, 4, and 6 to 18 months. Under no circumstances should the vaccine be given more frequently than four weeks apart. The first immunization may be administered as early as six weeks of age. For this series, a booster dose of IPOL vaccine is administered at 4 to 6 years of age.[41]

Use with Other Vaccines
From historical data on the antibody responses to diphtheria, tetanus, whole-cell or acellular pertussis, Hib, or hepatitis B vaccines used concomitantly with IPOL vaccine, no interferences have been observed on the immunological end points accepted for clinical protection.[11,16,36] (See DRUG INTERACTIONS section.)

If the third dose of IPOL vaccine is given between 12 to 18 months of age, it may be desirable to administer this dose with Measles, Mumps, and Rubella (MMR) vaccine and/or other vaccines using separate syringes at separate sites,[28] but no data on the immunological interference between IPOL vaccine and these vaccines exist.

Use in Previously Vaccinated Children
Children and adolescents with a previously incomplete series of polio vaccine should receive sufficient additional doses of IPOL vaccine to complete the series. OPV is no longer recommended for routine immunization and is recommended only in special circumstances[7] (see **General Recommendations** section).

Interruption of the recommended schedule with a delay between doses does not interfere with the final immunity. There is no need to start the series over again, regardless of the time elapsed between doses.

The need to routinely administer additional doses is unknown at this time.[28]

Adults
Unvaccinated Adults
A primary series of IPOL vaccine is recommended for unvaccinated adults at increased risk of exposure to poliovirus. While the responses of adults to primary series have not been studied, the recommended schedule for adults is two doses given at a 1 to 2 month interval and a third dose given 6 to 12 months later. If less than 3 months but more than 2 months are available before protection is needed, three doses of IPOL vaccine should be given at least 1 month apart. Likewise, if only 1 or 2 months are available, two doses of IPOL vaccine should be given at least 1 month apart. If less than 1 month is available, a single dose of IPOL vaccine is recommended.[28]

Incompletely Vaccinated Adults
Adults who are at an increased risk of exposure to poliovirus and who have had at least one dose of OPV, fewer than three doses of conventional IPV or a combination of conventional IPV or OPV totaling fewer than three doses should receive at least one dose of IPOL vaccine. Additional doses needed to complete a primary series should be given if time permits.[28]

Completely Vaccinated Adults
Adults who are at an increased risk of exposure to poliovirus and who have previously completed a primary series with one or a combination of polio vaccines can be given a dose of IPOL vaccine.

The preferred injection site of IPOL vaccine for adults is in the deltoid area.

HOW SUPPLIED
Syringe, without needle, 0.5 mL (10 per package).
Product No. 49281-860-55

Vial, 10 Dose – Product No. 49281-860-10

CPT® Code: 90713

CPT is a registered trademark of the American Medical Association.

STORAGE
The vaccine is stable if stored in the refrigerator at 2°C to 8°C (35°F to 46°F). The vaccine must not be frozen.

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