1458

F. Opmerkingen vragenlijst en project

Tot slot willen wij graag weten wat uw mening over de vragenlijst is en of u nog opmerkingen heeft.

56. Welke vragen uit de vragenlijst vond u onduidelijk?
Vraagnummer(s):
1. ☐
2. ○ Alle vragen waren duidelijk

57. Heeft u nog opmerkingen over de vragenlijst of het onderzoek?

U bent klaar met het invullen van de vragenlijst.
Wilt u de vragenlijst nog een keer doorlopen om te kijken of u alle vragen heeft beantwoord?

Ten slotte ter herinnering:

Meenemen naar het spreekuur

- Het inentingsboekje en andere vaccinatiebewijzen, zoals het geel internationaal vaccinatieboekje en het militair paspoort;
- De ingevulde vragenlijst;
- De ondertekende toestemmingverklaring
- Let op, voor deelnemers jonger dan 18 jaar dienen *beide* ouders/verzorgers **ook** een toestemmingsverklaring te ondertekenen;

Hartelijk bedankt voor uw medewerking!

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Appendix 12 Evaluation and recommendations

Questionnaire

- Questions that were not included were questions for example about smoking and breastfeeding.
- Questions about which vaccinations one had received could have better geared to LCR as some vaccinations were not clear for the participants.
- The question about which specific Protestant Christian religion one practices was found to be too difficult to answer. Participants, call centre and project team members did not have enough knowledge on this subject.
- Some questions were not very relevant for babies (e.g. vegetarian, eating raw meat products and unwashed vegetables).
- In case a child was adopted it was not clear whether the questions for parents/caretakers were meant for the biological parents or the adoption parents.

Design

- Not all provinces were included in the sample, e.g. no municipalities were drawn in Friesland and Drenthe. If a better regional representation of the Netherlands would be preferable (e.g. infectious diseases with large regional differences in incidence) then the study design should be adapted by choosing smaller regions and/or clusters.
- Municipalities have expanded compared to ten years ago (P1 study), which could have resulted into a lower response rate. To increase the response rate smaller clusters or more locations per municipality should be arranged.

Communication

- At the start of the project we would have preferred more input from the communication department of the RIVM.
- We regret the negative advice from the communication department to bring the P2 project to public notice in the nationwide newspapers and television.

Contacts with municipalities

- It is easier (always at the same way and quicker) when RIVM draws the sample from the population register of a municipality.
- It would be preferable to have access to the population registers of all municipalities in the Netherlands. In that case, we did not have to ask each municipality to draw a sample from its population register

Contacts with public health services (PHSs)

- The cooperation with the PHSs was good, we think the actions below have contributed to that:
  - Announcement of the start of the P2 project at the LOI meeting;
  - Article in bulletin of infectious diseases;
  - Kick-off meeting was organized, which was also accessible for the PHSs

Call centre

- For the consistency in the approach of invited individuals it is important to have the same group operating during the whole study.
- The communication between call centre and RIVM could be improved. More feed-back was needed about difficulties experienced by the call centre team members and on how to deal with those difficulties. This call centre was located in Leeuwarden (contact person lived nearby), maybe it would have been better if the call centre was located nearer to the RIVM.

Printing office RIVM

- It was very practical to have the printing office at the RIVM because there were many situations where the time was limited or some extra printing had to be done. In most cases this was possible.
- Often several project members had to help with the mailing packages. On the one hand this took a lot of time, on the other hand this created commitment.
- Vulnerable, because if the head of the printing office was sick there was no one to replace him.

External medical workers

- Good choice, nice and qualified personnel.
- It is important to have a good procedure about the work at the clinics and the blood sampling. The team member of the RIVM at the clinics should keep an eye on how things are going and report this at the weekly meetings of the project team members.

PIENTER 2 database

- Nice and practical database.
- Company, designing the database, was chosen on advice of EMI; we regret that EMI did not want to build a more general database that could have been used for many other studies.
- Communication between company and RIVM was good.
- Most difficulties occurred with the import (from municipality and call centre) and export (to call centre and repro) of documents. Probably help of a data manager at the RIVM could have solved these problems easier. It would be preferable to involve a data manager already at the start of building a database.

Location clinics

- Next time it would be nice to have a mobile location or to have more different locations in one municipality to decrease the travel distance for the participants.

Clinics

- More instructions were needed with copying of vaccination data (vaccination data were not complete or not readable). Hopefully next time Praeventis (i.e. nationwide database containing information from all local authorities for registration of vaccinations) can be used for retrieving vaccination data of the participants.
- Better check of date of birth, gender and unanswered questions in the questionnaire.

Materials

- More support needed from communication department (e.g. posters).

Over sampling migrants

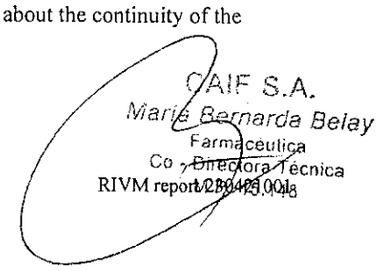
- Different approach is needed for the migrants than for the indigenous Dutch persons (e.g. fully translated materials) as the response was lower in migrants than in indigenous Dutch persons. We think that the flyer with date, time and address of the consultations hours, a street map with a photograph of the clinics and three photographs for clarifying this study (about blood sampling, filling in the questionnaire and receiving a gift voucher), which was sent to the migrants, had increased the response of the migrants.

Sample

- Wrong addresses especially in the larger cities (movements and many migrants).

Pienter telephone

- In the beginning of the study the invited individuals could call the Pienter telephone during the whole day and five days per week. During the study we changed this to only mornings. In this way the project team members were less interrupted in their daily work. Voicemail was sometimes difficult to analyze.
- Should be done by the project team members themselves.
- Meetings
- Weekly meetings with the project team members were good.
- Twice a year a meeting with a larger group of project members about the continuity of the project, was also adequate.
- Other



- External workers were also asked for the blood processing at the lab, which was very helpful.
- The day after each consultation hour the gathered materials should be checked on inconsistencies and solved right away.
- Import of questionnaire answers by import bureau was practical, again better feed-back should have taken place about difficulties experienced by the import of questionnaire answers and how to deal with these difficulties.
- Vaccination data should have been imported right away (after receiving) and the missing vaccination data should have been retrieved much earlier (import of vaccination data and retrieving of vaccination data from the local authorities for registration of vaccination was a big effort for two project team members and also for the local authorities for registration of vaccinations). Next time, the day the vaccination was given should also be registered in stead of only the month and year. Vaccinations which were given after the blood sampling date should not be imported into the db.
- HIV was excluded in the laboratory tests for the following reasons: it was not found ethical as the test results would be available several years after the blood sampling; it was thought that it would not be approved by the medical ethical committee; already a lot information is available on HIV and in the P1 study HIV was also not tested for.

ERRATUM by report 230421001 (2009): PIENTER 2-project: second research project on the protection against infectious diseases offered by the national immunization programme in the Netherlands

In section 3.3.6 in the second paragraph, in Tables 3.11 and 3.12 and in the footnote below Table 3.11, the abbreviations RB and RC have accidentally been reversed and should be RC and RB. In the same section in the text below Table 3.10 in the second paragraph three times the abbreviation RB has been used, which should be RC.

Agreement, 2 March 2010

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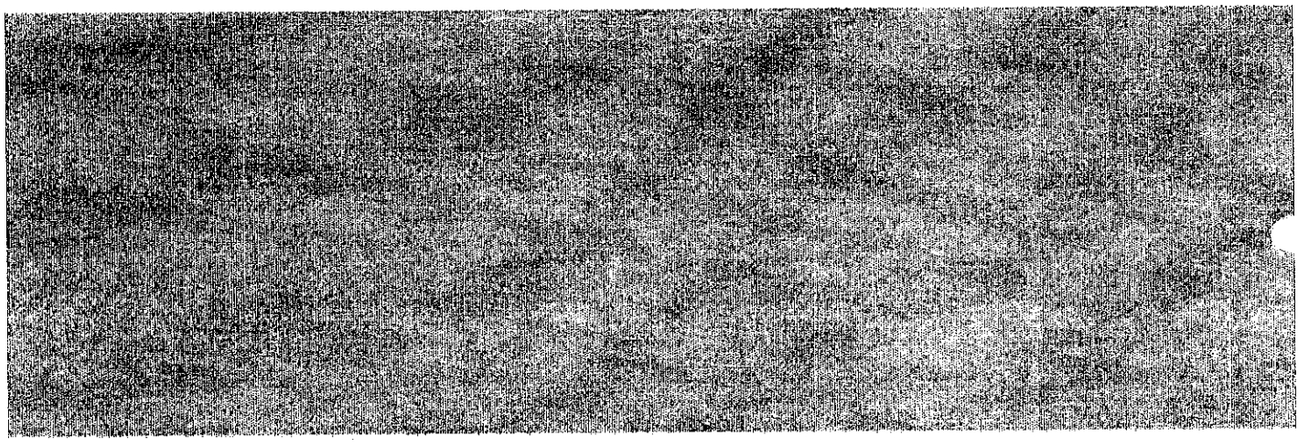

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VACCINES

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ELSEVIER
SAUNDERS

Poliovirus vaccine—inactivated

27

Emmanuel Vidor
Stanley A. Plotkin

Historical introduction

Not since the introduction of rabies vaccine by Louis Pasteur was public interest in vaccines stirred as much as by the development and testing of inactivated poliovirus vaccine (IPV), and not since Einstein did a scientist receive the public adulation accorded to Jonas Salk, the vaccine's inventor. Contributing to this phenomenon were the rise of poliomyelitis as an epidemic disease, its notoriety with the public (augmented by the paralysis suffered by US President Franklin Roosevelt), the publicity diffused by the March of Dimes Foundation in its efforts to raise money for research, and the involvement of hundreds of thousands of US children in the field trial that demonstrated the efficacy of IPV.

The efficacy trial was organized by Dr. Thomas Francis and sponsored by the National Foundation for Infantile Paralysis. It was a hallmark in vaccinology and the prototype for many later efficacy trials.[1–4] Francis insisted on a double-blind protocol, with partial success. Of 217 study areas in 44 states, 90 followed a placebo-controlled design, but they involved 419,000 vaccinees and 330,000 placebo recipients. Unblinded observations were also made on more than 1 million children, 232,000 of whom were vaccinated. The trial began in April 1954, and the successful results were announced on April 12, 1955.[5] Licensure followed rapidly, with rapid and broad vaccine adoption.

Nevertheless, in the early 1960s, IPV was eclipsed by oral poliovirus vaccine (OPV), except in some northern European countries. More than 50 years after its initial development IPV is renascent, owing to improvement in its manufacture, its outstanding safety record, the accelerating disappearance of poliomyelitis as an epidemic disease, and recognition of both sporadic vaccine-associated paralytic poliomyelitis (VAPP) cases and epidemics of circulating vaccine-derived poliovirus causing paralysis due to the continuing use of OPV. A large number of countries have adopted the use of IPV and more are likely to do so as the world moves toward the eradication of poliovirus.[6]

The disease itself is ancient. A famous Egyptian stele dating from 1403 to 1365 BC shows a man with flaccid paralysis of a leg. However, presumably owing to almost universal infection under the protection of maternal antibodies, only sporadic cases were described until the 19th century. Early in that century, small outbreaks were noted in Europe, usually among infants living in rural areas. In 1870, Jean-Martin Charcot described the pathologic lesions in the gray matter of the spinal cord, and in 1890 Oscar Medin described a major outbreak in Sweden, where epidemics subsequently continued to occur. Epidemics were reported in the United States at the end of the century, and in 1916 thousands of children were paralyzed during an epidemic in the northeastern United States. Fortunately, in 1908 Karl Landsteiner and Eric Popper isolated the virus of poliomyelitis, and scientific study of the agent began.[7]

The key discoveries that led to IPV development were as follows:

1. Definition of the three serotypes of poliovirus by Bodian, Burnet, and colleagues.[8]
2. Determination that poliovirus viremia precedes paralysis.[9]
3. Confirmation that neutralizing antibodies protect against disease.[10]
4. Demonstration by Enders and colleagues that the virus could be grown in cell culture.[11]

These discoveries permitted Salk, fresh from his success in developing an inactivated influenza vaccine and also experienced in working with poliovirus, to start IPV development. Large quantities of virus were grown in roller tubes from monkey testicular and kidney cells, and the kinetics of inactivation by formalin were studied. Salk concluded that if aggregates of virus were removed by filtration, poliovirus could be inactivated at a constant first-order rate, permitting complete killing if the process was of sufficient duration. Pools of trivalent vaccine were prepared at Connaught Laboratories in Toronto for use in a field trial of efficacy, which was conducted by Francis and his associates in 1954. Although it did have some flaws,[12] the trial decisively demonstrated that IPV was protective, and in 1955 IPV was licensed and launched in the United States.[13] Very soon after, other IPVs derived from the same concepts were launched in different countries.[14] The Cutter incident, described in the following section, in which recipients of IPV were paralyzed by residual live virus in the vaccine, underlined the necessity of removing viral aggregates to permit inactivation, but did not stop the use of IPV.

Years later, major developments improved the quality of IPV. The first, by van Wezel of Holland, was the development of techniques to select the best sources of monkey kidney cells, to grow the cells to high density on microbeads, and to concentrate the virus produced.[15] The second development was the adaptation of the Vero continuous African green monkey kidney cell line to the production of poliovirus by Montagnon and colleagues at the Institut Mérieux (now Sanofi Pasteur) of Lyon, France.[16] The result of these improvements was the historically named enhanced-potency IPV (referred to as eIPV), which is the subject of this chapter.

Licensure of IPV was the first result of the cell culture revolution that permitted the development of many other vaccines. At the time of licensure, more than 20,000 cases of polio were reported annually in the United States, and polio was a

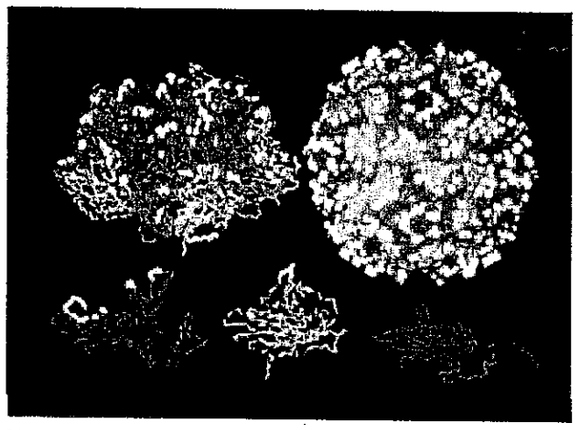

Figure 27-1 The antigenic sites of poliovirus are highlighted in white on the structure of the virus (top right), a pentamer consisting of five copies of each of the capsid subunits (top left), and the individual major capsid proteins VP1, VP2, and VP3 (bottom left to right). VP1, blue; VP2, yellow; and VP3, red. (Courtesy of James Hogle and Arthur Olson.)

worldwide disease with an incidence in the tropics that was as high as that in the developed world, but it was unrecognized due to the concentration of cases in infants younger than 2-years-old.[17,18]

The description of poliomyelitis as a disease, in addition to its virology, pathogenesis, and epidemiology, is covered in the Chapter 28. However, it is important to mention that the polioviruses are made of four capsid proteins, numbered VP1 to 4 (Figure 27-1). The first three are arranged on the surface with icosahedral symmetry, whereas VP4 is an internal protein.[19] There are five epitopes present on VP1 to 3 that are important to neutralization: sites 1, 2a, 2b, 3, and 4. These vary between serotypes and between strains.

Passive immunization

A field trial using human γ-globulin verified the importance of viremia in the pathogenesis of the disease and proved the concept that antibodies were protective. This experience, conducted in 1952 by Hammon and colleagues,[10] involved more than 54,000 children, half of whom received γ-globulin and half of whom received gelatin. From the second to the eighth week after injection, paralytic poliomyelitis was reduced by 80%. Unfortunately, despite the large γ-globulin dose used in subjects (0.3 mL/kg), the protection proved temporary (8 weeks), rendering γ-globulin impractical as a public health strategy except in household contacts.

Maternally produced antibodies transmitted via the placenta are also protective, but their half-life is only 28 days. By 6 months of age few unvaccinated infants remain protected.[20]

Active immunization

Prior approaches to inactivated poliovirus vaccines

Before the work of Salk, two disastrous attempts were made in the 1930s to inactivate polioviruses obtained from monkey spinal cords for the purposes of vaccination. Formalin was used by Brodie and Park,[21] whereas Kolmer[22] used ricinoleate. Both failed because of inadequate inactivation and probably also inadequate immunogenicity. The occurrence of polio cases likely caused by the vaccines terminated their development and instilled a sense of caution.

Description of inactivated poliovirus vaccine

IPV is a mixture of the three polioviruses made by harvesting cell culture supernatants and submitting them to purification and inactivation by formalin (one of the historical IPVs, developed by Lepine[23] at the Pasteur Institute in Paris, was inactivated by formalin and β-propioponolactone). The first versions of IPV were produced from primary rhesus monkey kidney cell cultures, with all of the problems of finding healthy monkeys and of excluding simian viruses that might be latent or replicating actively in cultured cells. The poliovirus strains used by Salk and still used by most current manufacturers are Mahoney (type 1, Brunenders strain (attenuated) is still used by one manufacturer in Denmark with no available information on antigenic and immunogenicity differences versus the Mahoney strain, see "IPV manufactured from Sabin strains"), MEF-1 (type 2), and Saukett (type 3). The final vaccine mixture is adjusted to achieve the right concentration of antigens (see the following section).

Although the results of the historical Francis trial were positive (see "Efficacy of IPV and correlates of protection"), the Cutter incident (see "Adverse events") led to a change in manufacturing processes that lowered the immunogenicity of the early vaccine.[24] The resurgence of paralytic polio in vaccinated children during the late 1950s weakened confidence in IPV.[25] However, several technical advances during the 1970s permitted the development of the eIPV, which, although based on principles similar to those of the first-generation vaccine, differs in three important aspects:

1. The cell substrate on which the virulent virus seeds are inoculated includes secondary or tertiary subcultures of kidney cells from pathogen-free monkeys, continuous culture of human diploid cell strains, or continuous culture of the Vero African green monkey kidney cell line, rather than primary cultures from newly captured monkeys.
2. To increase density, cells are grown on microbeads in large bioreactors.
3. The virus harvest is concentrated before inactivation to increase the final antigen content.

The production of eIPV in Vero cells is outlined in Figure 27-2.[26-32] The substrate cells are expanded from a working cell bank adapted to grow on microbeads (Figure 27-3) in large bioreactors until high cell density is reached (Figure 27-4). Growth medium is then removed, the cells are washed, and one of the three types of poliovirus is inoculated. By 72 to 96 hours of incubation at 37°C, the cells have been lysed by viral replication, and the supernatants are collected. After clarification, the virus is concentrated 500-fold by ultrafiltration. To remove cellular proteins and DNA, the concentrated virus is passed through size exclusion and ion exchange chromatography to yield purified material. At this point, there is less than 10 pg of DNA per human dose, a level considered to pose no hazard to recipients.[33]

The concentrated purified virus is inactivated by the addition of formalin to a final concentration of 1:4000, followed by incubation at 37°C for 12 days. By 4 days viral inactivation should be almost complete, as confirmed by sampling for residual live virus. During inactivation of the virus, it is important to avoid viral clumping and to maintain a neutral pH. An extra filtration is included during inactivation to remove viral clumps.[34]

Recently, polioviruses have been produced in Vero cells grown in serum-free medium.[35] The final monovalent material is subjected to tests for residual infectivity, which of course must be negative. The three monovalent antigenic materials are then mixed to form trivalent bulk antigen generally stored in concentrated form. Contents of the three vaccine types are adjusted by determination of the poliovirus D antigen (which is expressed only by intact poliovirus particles) historically using gel diffusion assay but now enzyme-linked immunosorbent assays (ELISA; in vitro potency). The final formula in D-antigen (D-Ag) units is targeting a content of 40 of type 1, 8 of type 2,

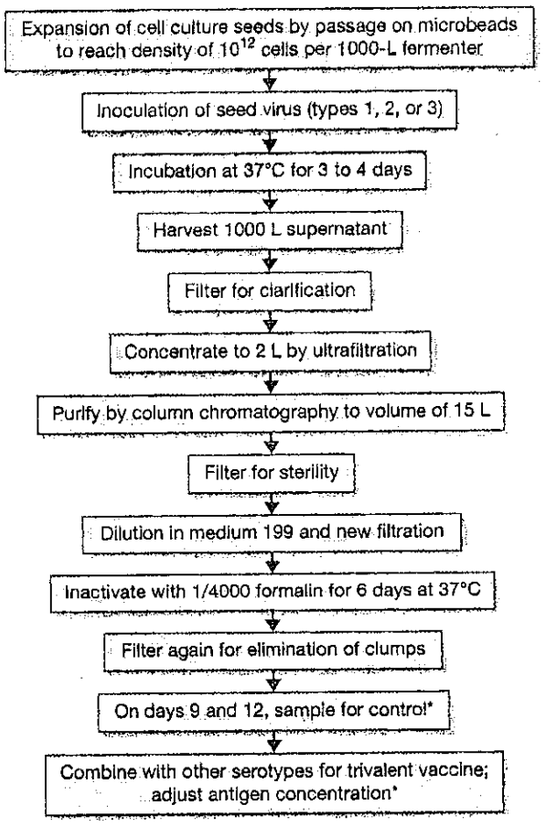

Figure 27-2 Production of enhanced-potency inactivated poliovirus vaccine. *, sampling of an equivalent of at least 1,500 human doses for control of effective inactivation

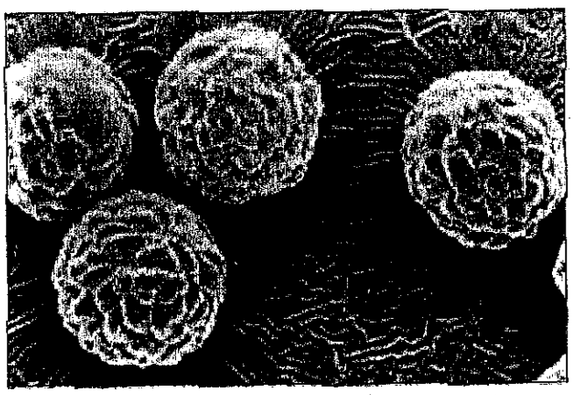

Figure 27-3 Kidney cells from African green monkeys (Vero cells) grown on microcarrier beads. (Courtesy of Dr. B. Montagnon, Institut Mérieux, Lyon.)

and 32 of type 3 polioviruses, respectively. The D-antigen contents of the original IPVs were variable, but all were below this current formula.

Determination and standardization of the D-antigen content is a key issue in making potent IPV. An international reference vaccine has been characterized by the World Health Organization (WHO) after a study showed test variability between laboratories.[36,37] Suggestions have been made for the improvement of the ELISA test that measures D-antigen content.[38] The key parameters in the performance of this assay include: (1) the nature (poly- or monoclonal and their specificity[ies]) of the antibodies used for antigen capture, (2) the nature (poly- or monoclonal and their specificity[ies]) of the antibodies used for antigen detection, (3) the method of calculation of results (sigmoid curve, parallel line, or four parameter curve methods), and (4) the nature of the reference antigen used in the assay. In addition, as some reagents may detect the presence of polio C antigens (associated with noninfectious viruses) and, consequently, provide a false evaluation of the D-antigen content of the vaccine, this can result in formulation and release of subpotent vaccines. Thus, the measured D-antigen content is the result of the combined activity of multiple antigenic sites, conceivably present in varying proportions in the tested preparations. Not all IPV manufacturers use the same set of reagents and methodologies to assess the D-antigen content of their routinely manufactured preparations, which makes it difficult for comparisons. With the development of Sabin IPV the situation is further complicated (see the following sections).[39] Moreover, prediction of immunogenicity from antigen content has been uncertain.[36] The immunogenicity (in vivo potency) of IPV preparations is measured by immune responses obtained in monkeys, rats, guinea pigs, mice, or chickens. The rat model is still used in some countries for release purposes, and different release specifications are described in various pharmacopeias. The variability of the methods of measuring neutralizing antibodies in these assays may also complicate the comparison of potencies of different IPVs. Finally, the relationship between immunogenicity observed in animal models (in vivo potencies measurements) and in humans might not be straightforward.

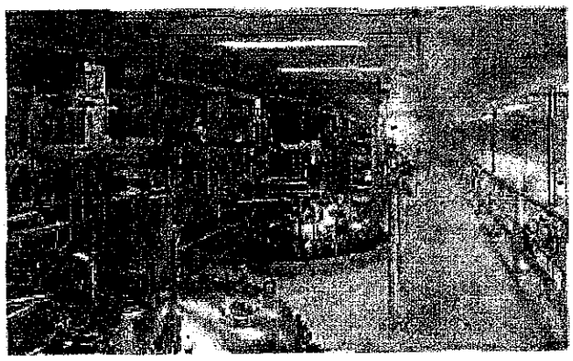

Figure 27-4 Bioreactors of 1,500-L capacity in which cells are grown for virus cultivation. (Courtesy of Sanofi Pasteur, Lyon.)

All of these parameters are correlates of the clinical protective effect anticipated in humans vaccinated with IPV. To more closely approximate that effect, mice transgenic for the CD-155 poliovirus receptor[40] have been employed to determine relative immunogenicity before clinical trials.[41,42]

IPV manufactured from Sabin strains

The methods described earlier have become even more important in view of the WHO's efforts to promote the emergence of new IPV manufacturers relying on the use of attenuated strains for fear of inadvertent release of wild viruses from facilities (see "Rationale for the Use of IPV").[43] This push has led to the emergence of several initiatives, some of them benefiting from the experience of technology transfer.[44] Several studies have evaluated the biochemical differences between Sabin strain–derived and Salk strain–derived IPVs, and particularly the effect of formaldehyde inactivation on the antigenic structures of polioviruses.[45] Using reactivity to monoclonal antibodies profiled by enzyme immunoassay (EIA), it has been shown that inactivation with formaldehyde destroys some antigenic sites of the polioviruses.[46,47] Depending on the characteristics (reagents) of the D-antigen assay to measure the potency of

resulting inactivated viruses, such alterations might not necessarily be measured.[41,48] Due to their genomic differences, the epitopes presented by the Sabin strains are different from the epitopes presented by the Salk strains; therefore, they have a different sensitivity to formalin inactivation. A study[46] documented that the antigenic site 1 of the Sabin poliovirus 1 can be damaged by formalin, whereas the same antigenic site present at the surface of the wild-type Mahoney poliovirus 1 strain is not. One consequence of this difference in antigenicity in terms of immunogenicity is that the repertoire of antibodies induced in humans by Salk IPV or OPV are different.[49,50]

Historically, the first attempts to validate the concept in man were made at the Japanese Poliomyelitis Research Institute (JPRI) during the mid-1980s[51,52] and at the Lederle Laboratories in the United States[59] followed by the Rijksinstituut voor Volksgezondheid en Milieu (RIVM) in the Netherlands, which is still particularly active in the development of Sabin strain–derived IPVs.[48] More recently, a group from the Institute of Medical Biology, Chinese Academy of Medical sciences (Kunming Institute) has embarked on such development.[53,54] Other poliovirus vaccine manufacturers claim to be engaged in the development of Sabin strain–derived IPVs, but no concrete information is publicly available. Since 2011, the WHO-promoted approach followed by RIVM has embarked on a stepwise phase I clinical program in the European Union (EU). This step should be followed by further developments from RIVM partners through technology transfer projects following the WHO-awarded Request For Proposals. The requirements and challenges in the clinical development of this novel IPV have been recently reviewed.[55,56]

Studies done using transgenic mice have shown that whereas an immunogenic IPV can be made from Sabin strains, differences in neutralizing epitopes result in antibody specificities that are less broad than those produced by wild strains.[41–46,57] The importance of this difference was illustrated by a study done at the US Food and Drug Administration (FDA) using the transgenic poliovirus receptor mice model to evaluate a Sabin type 2 IPV prepared by the JPRI.[42] In this study, a type 2 IPV prepared from MEF-1 strain (Salk strain) elicited broader immune responses (heterotypic) and better protection against paralysis after virulent challenge than an IPV prepared from Sabin polio type 2 strain. Similar findings were observed previously with a Sabin strain–derived type 3 IPV,[58] but not for Sabin strain–derived type 1 IPV.[41] These findings raise the issue of the antigenic match between the inactivated Salk strains and the inactivated Sabin strains and of its potential consequence in terms of clinical protection against wild-type poliovirus strains that can be induced in humans by Sabin IPV versus Salk IPV. Therefore, the criteria on which national regulatory agencies will base their future reviews for licensing such vaccines are not yet fully clear.

Producers

Table 27-1 lists the current manufacturers of IPV drug substance (bulk antigen) that are principally based in Europe. The majority of the IPV antigens currently manufactured are from viruses grown on the Vero cell line. The only other cell substrate in use for IPV production is a human diploid cell line (MRC-5). Because all IPV now in use is eIPV, hereafter the designation IPV will be used to refer to eIPV vaccines. Current (2010) global production capacity for bulk antigen is at more than 100 million doses of final product equivalent per year. Considering that the currently existing facilities can produce 400 to 450 million doses per year after full scale-up of facilities utilization, large demand can be satisfied.[65,66]

Table 27-1 Manufacturers of IPV (bulk antigen)

Manufacturer	Where made	Cell substrate
Sanofi Pasteur	France, Canada	Vero, MRC-5
GlaxoSmithKline	Belgium	Vero
Novartis	Italy	Vero
NVI	The Netherlands	Vero
Statens Serum Institut	Denmark	Vero

Dosage and route

Salk established that the immune response to IPV is directly related to the dose of viral antigen (Table 27-2).[67] When IPV is used for primary vaccination of infants, the ideal schedule is two to three doses administered during the first 6 months of life, followed by a first booster given during the second year of life and another booster before school entry. The formulation of all current IPVs proceeds from a series of several dose-response clinical studies[68–70] performed in infants from 1977 to 1979, which were aimed at determining the optimal D-antigen content necessary for providing reliable protection after two doses of the IPV antigens combined with other vaccine antigens (D, T, and whole cell pertussis (wP), which were already routinely administered in infants at that age). This strategy was implemented by Jonas Salk and Charles Mérieux with the objective of developing an IPV formulation that was useful in Africa and that required two doses with a relatively long interval between them that could overcome the negative effect of circulating maternally transmitted poliovirus antibodies on the immune responses.

This work was made possible by the pioneering work done at the RIVM (the ancestor structure of the Netherlands Vaccine Institute; NVI) by van Wezel on large-scale culture of cells on microbeads. These studies led to the current IPV formula with 40-8-32 D-Ag units for poliovirus type 1, 2, and 3, respectively. Two doses are sufficient as priming for a first booster in the second year. When IPV is included in DTP-backboned combination vaccines, up to three doses can be given during the first year of life. In any case, the first two doses should be followed by a third dose at least 6 months later (acting as a booster) to generate persistent immunity.[71] It should be noted that some of the historical studies have documented the capacity of IPV to induce antibody levels even after the first dose[68,74] confirmed also by a one-dose clinical efficacy of 36% (95% confidence limits, 0% to 67%) measured in Senegal[208–210] (see "Efficacy of IPV and correlates of protection").

In the United States, infants immunized with IPV receive doses at ages 2 months, 4 months, 6 to 18 months, and at preschool age (4-6 years). In most European countries the first three doses are given earlier at 2, 3 and 4 or 2, 4 and 6 months of age, whereas in Scandinavia and Italy the schedule is spread out, with only two doses before 1 year of age. The different pediatric routine primary series schedules used in various countries are shown in Table 27-3. The subject of additional boosters after the preschool age is discussed later (see "Duration of immunity"). In some countries, along with routine pediatric IPV-only schedules, supplemental immunization activities (SIAs) with OPV are organized (see "Results of vaccination programs").

Ideal dosage for IPV in truly unvaccinated adolescents and adults is three doses. The first two doses can be given 1 or preferably 2 months apart, with the third dose given 6 to 12 months later. If there is urgency, the third dose can be given earlier, but the achieved antibody titers will not be as high (Sanofi Pasteur, unpublished data).

Adolescents or adults who are already primed and whose last polio vaccination occurred ten to twenty years ago need only one booster dose to redevelop high titers (Sanofi Pasteur, unpublished data).[72] In subjects with an unknown polio vaccination two doses of any kind of IPV-containing combination vaccines given 1 month apart are sufficient to induce very high seroprotection rates and lasting circulating antibodies.[73,74]

Table 27-2 Determination of Dose of Poliovirus Type 1 Detectable Serum Antibody Versus Secondary-type Responsiveness

No. of subjects*	Primary dose†	% of group with detectable antibody (≥1:4) 2 weeks after one dose	% of group with detectable antibody (≥1:4) 1 year after two doses	% of group with secondary-type antibody response (≥1:32)‡ 2 weeks after booster doses§
33	None	—	—	6
24	2	100	92	100
21	1	100	85	100
26	1/2	96	60	96
27	1/4	93	73	100
30	1/8	87	45	93
26	1/16	77	35	96

*In the group evaluated 2 weeks after booster dose.
†Milliliters of reference vaccine A given in each of two doses 2 weeks apart.
‡Antibody titer of 1:32 arbitrarily chosen as criterion for hyperreactive secondary-type antibody response.
§One milliliter of vaccine.
From Salk J, Salk D. Vaccination against poliomyelitis. In: Voller A, Friedman H, eds. New Trends and Developments in Vaccines. Lancashire, UK: MTP Press; 117-154, 1978. With permission.

Table 27-3 Schedules of IPV Administration for Primary Immunization in Infant/Toddlers/Children in Countries Recommending IPV-only schedules†

Schedule†		Countries
2 + 1 + 1	2, 4, and 18 months, 4-6 years*	United States
	3, 5, and 11-12 months, 5-6 years	Sweden, Slovakia, Italy, Norway, Denmark, Finland
	3, 5, and 12 months, 14 years	Iceland
	2, 4, and 6-18 months, 4-6 years	Greece
3 + 1 + 0	2, 4, 6, and 18 months	Spain
	2, 3, 5, and 18 months	Malaysia
3 + 0 + 1	2, 4, and 6 months, 4 years	Australia, Ireland, Portugal, Korea
	2, 3, and 4 months, 4-6 years	United Kingdom
	2, 4, and 6 months, 4-6 years*	United States
3 + 1 + 1	2, 4, 6, and 18 months, 4-6 years	Switzerland, Austria, Canada, Croatia, Israel, Romania
	2, 3, 4, and 11-18 months, 5-7 years	Hungary, Belgium, France, Luxembourg
	2, 3, 4, and 11-14 months, 9 years	Germany
	3, 4, 5, and 18 months, 10 years	Czech Republic
	3, 4, 5, and 12 months, 4 years	Netherland
	3, 4.5, 6, and 18-24 months, 6-7 years	Estonia, Latvia, Lithuania

*The current recommendations call for a 2 + 1 + 1 or a 3 + 0 + 1 schedule as the third dose can be given any time between 6 and 18 months of age.
†As of May 2012, see http://apps.who.int/immunization_monitoring/en/globalsummary/ScheduleSelect.cfm

IPV may be given subcutaneously or intramuscularly, and there is no published information on the relative immunogenicity of IPV administered intramuscularly versus subcutaneously through randomized controlled trials; however, as it is administered more and more frequently as IPV-containing multivalent DTP-based vaccines (including possibly also Hib and hepatitis B antigens), and with the objective to minimize local adverse events, IPV is now almost exclusively administered intramuscularly even when used as a stand-alone vaccine.

Available vaccines

IPV is available as a stand-alone vaccine and as tetravalent, pentavalent, and hexavalent combination vaccines with diphtheria, tetanus, acellular pertussis, hepatitis B, or Hib antigens. In the United States, IPV is available as a stand-alone vaccine and as a tetravalent and two pentavalent combinations with diphtheria, tetanus, acellular pertussis, Hib, or hepatitis B antigens. In the rest of the world, IPV is available as a stand-alone vaccine and as tetravalent, pentavalent, or hexavalent combinations with diphtheria, tetanus, acellular pertussis, Hib, and hepatitis B antigens with variable situations across countries depending on licensure status of these products. In some countries stand-alone IPV vaccines formulated, filled, and packaged by local manufacturers and using IPV bulk antigens imported from another manufacturer are licensed and used. Most of the IPV stand-alone vaccines are WHO prequalified, and are starting to be used in a number of UNICEF-driven vaccination programs. The most widely used IPV-containing combinations are produced by Sanofi Pasteur and GlaxoSmithKline. For a more comprehensive review of the available IPV-containing combination vaccines, see Chapter 40. Several whole-cell pertussis IPV-containing combinations were available, but there are none now. Some manufacturers have embarked on the (re)development of whole-cell pertussis-based combination vaccines including IPV antigens.

Vaccine constituents other than immunizing antigens

Regarding the vaccines produced in Vero cells, streptomycin, neomycin, and polymyxin B are used during the manufacturing process to control bacterial contamination, but they are

largely eliminated during purification. The use of polymyxin B has been shown to have some effect on the quality of the viral replication, which can be achieved in the process.[75] Trace amounts of these antibiotics (≤200 ng of streptomycin, ≤5 ng of neomycin, and ≤25 ng of polymyxin B) may still be present. Preservation of the final product is conferred by residual formalin (0.02%) and 2-phenoxyethanol (0.5%). Thimerosal cannot be used to preserve polio-containing vaccines because it destroys the polio antigens.[83] The MRC-5-produced vaccine contains trace amounts of streptomycin and neomycin as well as formalin (27 ppm), 2-phenoxyethanol (0.5%), human albumin (0.5%), and Tween 80 (20 ppm). When used as part of multivalent combination vaccines, the quality of the IPV bulk antigens and of their other constituents are of extreme importance in the behavior, potency, and stability of the formulated final drug product.

The role of adjuvant on the immunogenicity of IPV antigen has been known since the pioneering work done with mineral oil and oxide aluminum salts.[77,78] Later, through several IPV-containing wP-based combinations, the positive role of calcium aluminum salts has been advocated.[79] Since then, it has been confirmed through several randomized controlled studies that the immunogenicity of the IPV antigens is improved when the antigens are injected in the presence of aluminum salts.[116–120] In recent years, through the strong pressure of WHO (see "Rationale for the use of IPV"), new adjuvants are being considered for IPV. Preclinical studies with conventional IPV or with Sabin-IPV have shown that some new adjuvants (squalene-based emulsions supplemented or not with TLR-agonists; polymers) may decrease the amount of antigen needed to achieve desired immunogenicity with the potential of lowering costs per dose, and some adjuvants may enhance the mucosal immune response to IPV.[80–82]

Stability

IPV is relatively heat stable. The vaccine is stable for 4 years at 4°C and for 1 month at 25°C. At 37°C, there is loss of potency of the type 1 component after 1 to 2 days, and of types 2 and 3 after 2 weeks. Freezing diminishes the potency of IPV and should be avoided. All manufacturing intermediates are also relatively heat stable, allowing flexibility in managing manufacture.

Results of vaccination

Immune responses

Although it is possible to measure serum antibodies to poliovirus by a variety of methods, poliovirus-neutralizing antibodies are considered the best correlate of protection[84] and are the only responses considered here.

IPV is a killed antigen vaccine, and immune responses depend on the concentration of antigens, the number of doses (when used for primary immunization), the interval between doses, the age at first dose (and, consequently, the level of maternally acquired poliovirus antibodies present at time of vaccination that can suppress the immune response), and finally the type of IPV-containing product used (stand-alone unadjuvanted versus aluminum-adjuvanted IPV-containing combinations). Several parameters are used to express the levels of seroneutralizing antibodies against polioviruses when assessing the overall responses obtained in a group of vaccinated individuals: the geometric mean titers (GMTs) (sometimes median titers are used which can lead to different results compared with GMTs); the percentage of subjects with neutralizing antibodies above the 1:8 threshold now considered as the serologic correlate of protection (historically the 1:4 threshold has been used) and very often referred to as the seroprotection rate; and the percentages of subjects presenting with a greater than or equal fourfold rise in their neutralizing antibody titers between their prevaccination titers and postvaccination titers, adjusted or not for maternally derived antibody decay, and referred as to the seroconversion rate. If maternal antibody decay is not factored in, calculated seroconversion rates could be lower than the actual proportion of persons who make a significant immune response. On the other hand, it is known that maternal antibody does inhibit the immune response to IPV.[96] The percentage of subjects with neutralizing antibodies above the 1:8 threshold at a time when maternally transmitted antibodies should have disappeared probably gives the best measure of the proportion of persons with protective immune responses to IPV.

The neutralization antibody assay is used by the vast majority of laboratories assessing the immunogenicity of these vaccines.[85] The assay procedures are variable and have been shown to be sensitive to the nature of the cells used to grow the target virus (HEp-2 or Vero), viral inoculums' size, the duration and temperature of serum–virus interaction before cell culture, the number of serial dilutions of the tested sera, and the nature of the viral strains (Sabin or wild-type) used in the test.[86,87] In addition, the type of assay readout (cytopathic effect or metabolic inhibition) has an influence. Numerous attempts have been made to standardize this assay,[88,89] but there is no broad-based acceptance of international standards for its use.[90] Under some assay conditions neutralizing titers are higher when sera from subjects vaccinated with IPV manufactured from wild-type strains are tested against wild-type strains than those tested against Sabin strains.[86,87] Lack of specific description of the serum panels used in standardization studies makes evaluation difficult. Some studies refer to the use of the trivalent reference serum lot IIA4 from the FDA that was prepared from vaccinated monkeys, whereas others refer to pools of sera obtained from humans in the United Kingdom probably vaccinated with OPV or naturally infected. As described in "IPV manufactured from Sabin strains", it is conceivable that the paratopes (antigen binding sites) of the neutralizing antibodies exhibited by OPV-vaccinated subjects or by IPV manufactured from Sabin strains might differ from the paratopes exhibited by Salk-derived–IPV vaccinated subjects, and that the overall levels of neutralizing antibodies measured in these subjects might be influenced by the nature of the viral strains used in the detection system. All of the landmark historical studies, which led to the current IPVs,[68–70] have based their neutralization assay on wild-type–derived poliovirus strains. The absence of clear indication that this variable might be important and the progressive logistical constraints imposed on the laboratories manipulating the wild-type–derived strains, particularly for those located in polio-free areas or in tropical low or middle-income countries, have induced most of the laboratories to switch to the use of the Sabin strains for this assay. This parameter should be considered when interpreting and comparing immunogenicity data from different clinical trials, particularly trials done with IPVs manufactured from Sabin strains.

An enormous number of studies and trials have been conducted over the last 30 years with IPV-containing vaccines given in schedules of two or three doses during the first year of life. These studies used different formulations of IPV, study designs, and schedules and were conducted in a variety of countries with different ethno-ecological situations. A number of reviews of these studies have been published.[91–94,203] For example, data collected from 30 study groups where IPV-containing vaccines were administered to more than 4,500 subjects in a two-dose primary series, usually at 2 and 4 months of age, are summarized in Table 27-4. At completion of the immunization series, seroprotection rates ranged from 89% to 100% for poliovirus type 1, from 92% to 100% for poliovirus type 2, and from 70% to 100% for poliovirus type 3. Table 27-4 also summarizes responses after three doses. Seroprotection rates after

Table 27-4 Summary of Immunogenicity of IPV After Two or Three Doses in the First Year of Life One Month After Last Vaccination

	Type 1		Type 2		Type 3			
Schedule	Seropositives	GMT*	Seropositives	GMT	Seropositives	GMT	Study groups	Approximate no. subjects
2-4 months	89-100%	17-355	92-100%	17-709	70-100%	50-1200	30	4500
2-4, and 12-18 months	94-100%	495-2629	98-100%	1518-6637	97-100%	1256-4332	10	2000
2-4-6 months	96-100%	143-2459	96-100%	78-2597	95-100%	187-3010	48	6000
3-4-5 months	85-100%	110-475	98-100%	92-944	86-100%	89-1244	8	500
2-3-4 months	93-100%	143-595	89-100%	91-561	95-100%	221-1493	18	2200

*GMT, geometric mean antibody titer.
IPV, inactivated polio virus.

three doses are clearly better than after two, particularly when the schedule is 2-4-6 months. However, schedules of 3-4-5 and 2-3-4 months also give good responses, although lower than after 2-4-6, particularly when responses are described using the GMT parameter (the Expanded Programme on Immunization [EPI] schedule will be discussed in the next section). After two or three doses in the first 6 months of life, antibody levels fall although the vaccinees usually retain seroprotective titers until the first booster is given during the second year of life and this third or fourth injection gives a marked anamnestic response. Five studies conducted in the United States are presented in Table 27-5. Nearly all infants were already seropositive after the second dose, although their antibody titers were generally below 100 (1/dil). Data on MRC-5 cells or in primary monkey kidney cell (PMKC)-produced IPV are provided in Table 27-6 and demonstrate similar immunogenicity for such products.

Cellular-mediated immune responses and other components of acquired immunity have not been comprehensively studied and may not be critical for protection.[95,170] Ethnicity background has never been observed to play a role in the immunogenicity profile of IPV.

In some studies, immune responses have been detected even after the first dose of IPV-containing vaccines[68-70,76,162,183] and, depending on study designs and on seroconversion criteria definition, up to 90% seroprotection rates and above 50% seroconversion rates have been observed. As summarized under "Efficacy of IPV and correlates of protection", a one-dose schedule has been shown to provide limited clinical efficacy (36% with 95% confidence limits ranging from 0% to 67%) against poliovirus type 1. Nevertheless, these data are important in the context of current efforts by WHO toward development of affordable IPV solutions for the developing world (see "Rationale for the use of IPV"). The role that could be played by sequential schedules of IPV followed by OPV is discussed in the chapter on oral polio vaccines (See Chapter 28).

Clinical experience with Sabin-derived IPVs

The first version of the JPRI Sabin strain–derived IPV (sIPV) was formulated to contain 30-45-45 D-Ag units for poliovirus type 1, 2, and 3, respectively (formulation using monovalent bulks titrated against the WHO reference 91/672 and using the parallel line method for titer calculations) per 0.5 mL. This formula was determined mainly from in vivo potency studies done on rats with the objective of having a formulation able to induce neutralizing antibodies against wild-type strains.

In comparison, wild-type–derived IPV-containing products (wt-IPV) are now all formulated to contain 40-8-32 D-Ag units for poliovirus types 1, 2, and 3, respectively. Strict comparison of the relative D-antigen contents between JPRI vaccine (and all other sIPVs) and conventional IPVs is not possible due to the different characteristics of the in vitro and in vivo potency assays used to formulate and release these vaccines (D-Ag determination by EIA and immunogenicity in animals).[36,37,48,58,60] With regard to clinical experience, JPRI reported only two studies including 118 subjects.[60] In the first trial, the vaccine was given in two subcutaneous doses to 10 seropositive adults at 4-week intervals. Safety was excellent. Antibody data obtained 2 weeks after the second dose (against Sabin strains and wild-type strains) showed high neutralizing responses in all volunteers. In the second trial, the vaccine was given by the same regimen to 108 infants (3-90-months-old). Most infants were seronegative (SN titer < 1:4) before immunization, except for type 2 where 40% were seropositive. Immunogenicity results 2 weeks after the second dose showed high neutralizing response in all infants against types 1 and 3, but low for type 2. Seroneutralizing GMTs against the homotypic Sabin strains were about 2,000 for polio type 1, 300 for polio type 2, and 500 for polio type 3. SN titers were 4 to 1.3-fold lower against wt strains than against the homotypic Sabin strains.

Later, JPRI worked on animal models (rat and green monkeys) to refine the D-Ag content of the sIPV to target a 3-100-100 D-Ag units per human dose formula, and is now embarked on an antigen supply agreement or has licensed its technology with several Japanese DTaP manufacturers (Biken, Kaketsuken, and Takeda) who are developing DTaP-sIPV combinations for Japan. Phase II and III trials are in progress but no results are available from these DTaP-sIPV vaccines.

Murph et al[59] at Lederle in the United States manufactured a Sabin strain–derived trivalent IPV containing 20-12.5-35 of D-Ag units (per 0.5 mL) of polioviruses type 1, 2, and 3 grown on PMKC. A study done in 1986 comprised 18 seropositive adults who received vaccine containing 10-6.25-17.5 of D-Ag units, 20-12.5-35 of D-Ag units, or 40-25-70 of D-Ag units per dose and 9 seronegative adults who received one dose of a 20-12.5-35 of D-Ag units formulation. In the seropositive adults, the three vaccine formulations were able to boost serum neutralizing antibody levels with a noticeable dose-response effect. In seronegative adults, a response against the three polioviruses was observed. The drawback of this study was that no subject was naive to polio antigens as they all had previously received OPV or IPV during infancy. Infant studies with this vaccine were never reported.

Finally, scientists at the Kunming Institute have performed a multistep phase I study in adults, children, and infants with several formulations of sIPVs containing from 15-16-22.5 to 45-64-67.5 D-Ag units for poliovirus types 1, 2, and 3, respectively, with good immunogenicity data and a dose-response effect.[61] Following this study, a dose-response and comparative against OPV and conventional IPV study was done in infants with very preliminary reported results.[62] Optimal content of D Ag units for this Chinese vaccine were defined for

Table 27-5 Studies of IPV Given Alone or in Mixed IPV/OPV Sequential Schedules

		% of Neutralizing antibody to indicated strain ≥1/8 (Geometric Mean Titer)															
		Vaccine administered at given age				After second dose			After third dose[1]			Before booster			After booster[2]		
Investigators and reference	No.*	2 Months	4 Months	6 Months	Booster 12–18 Months	Type 1	Type 2	Type 3	Type 1	Type 2	Type 3	Type 1	Type 2	Type 3	Type 1	Type 2	Type 3
Faden et al.[152,153]	116	IPV	IPV		IPV	96 (184)	100 (631)	96 (634)				90 (61)	96 (135)	92 (102)	96 (1954)	100 (5835)	100 (5187)
	34	IPV	IPV		OPV	100 (283)	100 (481)	100 (1132)				100 (128)	100 (334)	100 (151)	100 (3044)	100 (10,693)	100 (2347)
Blatter and Starr[155]	94	IPV	IPV		IPV	97 (44)	96 (105)	95 (83)				92 (22)	95 (42)	87 (23)	100 (2070)	100 (3419)	100 (1968)
	68	IPV	IPV		IPV	98 (88)	100 (256)	98 (162)				100 (41)	100 (71)	93 (35)	100 (2029)	100 (4388)	100 (2580)
Halsey et al.[156]	75	IPV	IPV		OPV	94 (28)	98 (91)	96 (63)				85 (18)	96 (47)	81 (20)	100 (1568)	100 (7199)	96 (297)
	99	IPV	IPV		OPV	99 (90)	99 (120)	95 (126)				98 (47)	96 (61)	88 (29)	100 (1765)	100 (7516)	99 (709)
McBean et al.[164]	87	IPV	IPV	IPV	OPV	97 (74)	98 (82)	100 (110)	100 (463)	100 (652)	100 (605)	100 (72)	100 (98)	100 (91)	100 (2141)	100 (7169)	100 (1824)
	331	IPV	IPV		IPV	99	99	99							99	100	100
Modlin et al.[157]	332	IPV	IPV		IPV	99	100	100							100	100	100
	101	IPV	IPV		IPV	97	92	78							100	100	100
Asturias E et al.[158]	113	IPV	IPV	IPV		100 (1011)	99 (517)	99 (859)	100 (2542)	100 (2675)	100 (3248)						
	920	IPV	IPV	OPV		99 (1264)	100 (798)	99 (1089)	100 (1821)	100 (4294)	100 (2828)						
	101	OPV	OPV	OPV		97 (575)	100 (1641)	94 (350)	99 (685)	100 (1768)	98 (415)						

*Number of enrolled subjects at beginning of study.
[1]In infancy.
[2]Booster is third or fourth dose, depending on the schedule.
IPV, inactivated poliovirus vaccine; OPV, live oral poliovirus vaccine.

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Table 27-6 Neutralization Antibody Responses to Non-Vero-Cell–Produced IPVs*

IPV used†	Age at vaccination (mo)	Country	No. of subjects‡	% Positive for neutralizing antibodies to indicated strain								
				After 2nd dose			After 3rd dose			At pre-school age, before additional booster		
				Type 1	Type 2	Type 3	Type 1	Type 2	Type 3	Type 1	Type 2	Type 3
PMKC 40/8/32	1.5, 10 or 2.5, 5, 11	India	114	97	88	97						
PMKC 40/8/32	3, 8-9, 14	Burkina Faso	179	94	99	78						
PMKC 40/8/32	2, 4, 6	Kenya	84	94	88	97	100	98	100			
PMKC 40/8/32	2, 4, 6	Thailand	94	100	99	97	100	100	100			
MRC-5 40/8/32	2, 4, 6	Canada	120	90	99	97	99	100	100			
MRC-5 40/8/32	2, 4, 15	United States	279	92	94	74	81	92	53	99	100	100
PMKC 40/4/16	2, 3.5, 10	Israel	115	100	97	100	97	95	96	100	100	100
MRC-5 40/8/32	2, 4, 18	United States	377	99	100	99	98	99	99	100	100	100
PMKC 40/4/16	2, 4, 18	United States	371	99	99	99	99	99	98	99	100	100
MRC-5 40/8/32	2, 4, 18	Canada	329	99	99	99	98	95	97	87	99	100
MRC-5 40/8/32	2, 4, 6, 18	Canada	443	94	97	96	99	99	99	100	100	100
MRC-5 40/8/32	2, 4, 6, 18	Canada	211	NA	NA	NA	NA	100	99	100	94	88
MRC-5 40/8/32	2, 4, 6, 18	Canada	211	NA	NA	NA	100	99	100	95	90	98
PMKC 40/4/8	3, 4, 5, 18	Netherlands	118	NA	NA	NA	97	95	94	100	99	96

* Two or three doses of IPV were administered during the first year of life, with or without a booster dose during the second year of life.
† Cell substrate and poliovirus D antigen formulation of the used vaccine.
‡ Number of subjects enrolled at beginning of study.
IPV, inactivated poliovirus vaccine; MRC-5, Medical Research Council strain 5 of human diploid fibroblasts; NA, data not available or analysis not performed; PMKC, primary monkey kidney culture.
From Vidor, E, Meschievitz C, Plotkin SA. Pediatr Infect Dis J 16:312-322,1997. With permission

the Phase III as 30 for type 1, 32 for type 2 and 45 for type 3. The dose-response effect was confirmed and some differences were reported between the antigenicities of sIPV formulations and conventional IPV (wild-type derived). Cross-neutralization evaluation of vaccinees' sera against a large panel of poliovirus strains (Salk, Sabin, wild-type isolates, and vaccine-derived polioviruses [VDPV] isolates) are under investigation.

Although Sabin strains can mutate on circulation and acquire the phenotypic neurovirulence and transmissibility characteristics of wild viruses,[63] the public health risk of a break in containment from a manufacturing plant using Sabin viruses is much less than a break with wild strains in areas of low vaccination coverage, making Sabin strains potentially attractive for use and expanding the base of IPV manufacturers. The regulatory pathway for licensure of Sabin strain–derived IPVs is far from clear.[64] Due to differences in the breadth of antibodies induced between inactivated Salk strains and inactivated Sabin strains because of differences in the viruses,[89] it will be critical to assure that antibody response in humans is broadly cross-reactive against wild-type strains. In addition, the industrial feasibility (large capacity of viral culture attaining the yield of currently existing processes at an affordable cost of goods) of such an approach still needs to be demonstrated.

Effect of maternal antibodies and of neonatal vaccination

Many studies have documented that high levels of maternally transmitted poliovirus antibodies present during the course of primary series diminish the height of the antibody response to an IPV primary series schedule and can decrease seroconversion rates.[97–105] This is particularly evident when seroconversion rates are used but less so if evaluating seroprotection. This effect can be minimized by giving three doses of IPV during the first year of life.

Neonatal vaccination with IPV has been evaluated on several occasions. Swartz and colleagues[55] showed that a single dose of IPV at birth primed infants for a uniform response to a second dose given at age 6 months. Israeli infants immunized at birth with IPV concomitantly with hepatitis B vaccine showed higher mean antibody levels for polio types 2 and 3 at 1 and 3 months of age than infants who received IPV at 2 months of age, but the difference disappeared at 7 months of age after both groups had received one additional dose of IPV and two doses of OPV.[101]

Hovi et al[107] showed priming for higher titers in Pakistani infants whose three OPV doses at 8, 12, and 16 weeks of age were preceded by a birth dose of IPV. Linder et al[168] documented the immunogenicity of IPV given at 2 months of age with or without a preceding IPV given at 5 to 10 days of age in premature Israeli infants. In infants who received IPV within the first 2 weeks of life, 100%, 100%, and 97.9% presented neutralizing antibodies at titers greater or equal to 1:8 against poliovirus type 1, 2, and 3, respectively, 1 month after the dose given at 2 months of age versus 96%, 100%, and 71% of infants who had not received prior IPV.

Jain et al[108] documented the immunogenicity of a pure IPV schedule given at 0, 6, and 10 weeks of age in Indian neonates and was able to demonstrate better seroconversion (80% seroconverted against all three poliovirus types) with this schedule than with an EPI schedule using OPV (at 6, 10, and 14 weeks of age) supplemented by IPV or OPV at birth (72% and 72% seroconverted against all three poliovirus types, respectively).

Thus IPV at birth appears to prime the immune system, but this vaccination strategy has not been implemented in public health practice. When IPV immunization is started early in life after birth (eg, 6 weeks of age as in the EPI schedule) and in the presence of high levels of maternally transmitted poliovirus antibodies, seroconversion rates decrease compared to vaccination of infants with low levels of maternal antibodies.

Combination vaccines containing IPV

IPV has been combined with DTwP (first combination of such nature was licensed in 1964 in France, but today these DTwP-IPV-containing combinations no longer exist), DTaP, hepatitis B, and Hib vaccines[91,109–113] (see also Chapter 40) and those combinations are now used worldwide for primary series use in infants and toddlers (Table 27-7). New DTwP-IPV backboned combinations are currently in development (ref). One of the technical challenges is the effect on antigen potencies of the residual (thimerosal), or pro-actively introduced (thimerosal, 2-phenoxyethanol), preservatives in the final formulation particularly if multidose presentations are targeted.[113a] The combined vaccines containing IPV induce immune responses against polioviruses superior to IPV stand-alone vaccines due to the effect of the aluminum adjuvant present in such combinations.[114–120] This is particularly visible after primary immunization of infants in which randomized control trials (RCTs) have consistently shown GMT approximately twofold higher with combined vaccines.

When considering all of the factors, data clearly indicate that the main drivers of the immunogenicity of the IPV antigens when used for primary series vaccination are the following (in decreasing importance): use of an IPV-containing combination vaccine (the role of the quantity and of the quality of aluminum salts is still poorly known), the number of primary series injections, the age at first dose, the interval between doses, and ethno-ecological factors (passively transmitted antibodies, etc.).

In addition to the pediatric combinations, several combinations of IPV with low-dose diphtheria, tetanus, and low-dose acellular pertussis antigens have also been developed and licensed for preschool, adolescent, and adult (including elderly) booster immunization with good immunogenicity records.[121–125]

Intradermal use of IPV

The first report of use of the intradermal route with the IPV antigen came from Salk.[126,127] These studies showed that the intradermal injection of 0.1 mL of aqueous formulation of IPV was immunogenic in children and adults. Soon after the availability of the first commercial IPVs in 1955, several countries obtained good epidemiological results from vaccination programs with IPV delivered intradermally (using the Mantoux technique) to maximize the use of the limited quantity available at that time.[128–134]

Table 27-7 Licensed IPV-Containing Combinations

Manufacturer	Other valences in combination	Where licensed*
Sanofi Pasteur	DTaP2	EU, LA, AA
	DTaP5	CA, LA, AA
	DTaP2/Hib	EU, LA, AA
	DTaP5/Hib	US, CA, LA, AA
	DT	EU†
	Tdap5	US, CA, AA, EU
	Td	EU, AA, LA
GlaxoSmithKline	DT	EU
	DTaP3	CA, EU, LA, AA
	DTaP3/Hib	EU, LA, AA
	DTaP3/HepB	EU, AA, US
	DTaP3-HepB/Hib	EU, LA, AA, CA
	Tdap3	EU, CA, LA, AA
Statens Serum Inst.	DTaP1	EU
	DTaP1/Hib	EU

*AA, Asia and Africa; CA, Canada; EU, Europe; LA, Latin America; US, United States.
†Only in France.
DTaP, diphtheria, tetanus, and acellular pertussis vaccine; HepB, hepatitis B vaccine; Hib, Haemophilus influenzae type b vaccine.

Later, three successful proof-of-concept studies were conducted during the early 1990s by John's team in India using the modern IPV. These studies demonstrated that one fifth of the intramuscular dose is immunogenic in humans when delivered intradermally with needles, but none of these studies were randomized against full intramuscular dose.[135–137]

More recently, WHO sponsored two RCT studies in Cuba and in Oman with two different IPV vaccines using two different schedules (6-10-14 weeks and 2-4-6 months).[138,139] The vaccines were administered by the intradermal route with a DCJI jet-injector (Biojector 2000 from Bioject, customized for intradermal administration) or by the intramuscular route with regular syringe and needle. The primary study objectives were to show noninferiority (using a low stringent definition for noninferiority) of the responses in the intradermal groups versus the intramuscular groups. The primary end point was seroconversion against poliovirus. Both studies demonstrated clinically relevant immunogenicity but lower responses with the 6-10-14-week schedule than with to the 2-4-6-month schedule. In the Oman study, infants were challenged at 7 months of age with monovalent type 1 OPV, and 7 days later shedding prevalence was 74.8% in the ID group versus 63.1% in the IM group. A third RCT done in the Philippines compared the two routes of administration using the classical Mantoux technique for the intradermal injection and with vaccines administered in a 6-10-14-week schedule,[140] again demonstrating noninferiority of responses of the intradermal group versus the intramuscular group.

A study conducted in India (Moradabad district) reported inferior immune responses with IPV administered by the intradermal route by a similar jet-injector (Pharmajet) customized for intradermal administration. The study design included vaccination of several groups of infants, aged 6 to 9 month, who had previously received multiple monovalent OPV type 1 and tOPV doses, randomized to receive one of two different IPV vaccines delivered intramuscularly, an IPV vaccine administered intradermally (one fifth of the IM dose), or one of two different monovalent OPV type 1 vaccines. Due to the very high levels of prevaccination antibodies against all three polioviruses and to a suspected high failure of the injection device to deliver the full 0.1 mL volume of vaccine intradermally, the study failed to show that a fractional dose of IPV by the intradermal route was as immunogenic as full-dose IPV intramuscularly, but did reveal an undisputable booster effect of the intradermal administration.[141]

Finally, a recent study from Cuba[142] evaluated whether a schedule of two fractional 0.1 mL IPV doses administered intradermally (jet-injector; Pharmajet) provides comparable seroconversion with a two-dose schedule of full 0.5 mL IPV doses administered intramuscularly at 4 and 8 months of age. Seroconversion was assessed in each group after the first and second dose of study vaccines, and the proportion of subjects that responded with a priming immune response after the first dose of IPV was determined. Results showed high seroconversion after the first dose of both fractional and full-dose IPV, with significantly lower median titer for intradermal arms, and priming evidence in more than 90% of the subjects who did not seroconvert after first dose. The second IPV dose, delivered by either route closed the remaining seroconversion gaps and resulted in high antibody titers, although the titers were higher in children vaccinated by the intramuscular route.

Nelson et al[142a] recently reviewed studies of intradermal IPV and concluded that the route was promising but still required optimization of dose and of administration. However, a critical factor in making intradermal IPV use practical would be the development and licensure of a simple delivery device. In addition, a clear and feasible licensing pathway is still not clear. First, the nature of the safety and of the immunogenicity data to be submitted to National Regulatory Agencies is not yet defined. Second, this licensure pathway implies partnership between a given vaccine manufacturer and a given device manufacturer to assemble a specific application file claiming for the use of a given IPV with a given ID device in a given ID regimen. The WHO is supporting substantial research to develop affordable and effective intradermal delivery devices.

IPV in the expanded program on immunization schedule

To achieve rapid immunization in developing countries with high endemicity, vaccines are given on a 6-10-14-week schedule, which is not optimal for immune response against a variety of antigens due to the early age for starting immunization and the short interval between doses.

Since the early studies sponsored by the WHO,[102,103,143] several studies have been done in a wide range of epidemiological settings with IPV-containing vaccines. The results, which must be interpreted considering the previously listed variables (including the fact that many of these studies were conducted in countries where OPV was the standard vaccine used and could therefore have exposed vaccinees to OPV via contact with vaccines or their contacts) are summarized in Table 27-8.[102,103,143,145–154] One should note particularly the predominantly high seroprotection rates achieved at completion of immunization in addition to the more variable seroconversion rates probably due to the high maternal antibody levels observed in some studies.[104,144]

In one study in South Africa, antibodies were measured at 17 months of age after three doses of IPV contained in a hexavalent combination vaccine given in infancy, and persistence of antibodies with good anamnestic response to a fourth dose were noted.[149] In infants who received DTaP-IPV-HepB-Hib at 6-10-14 weeks of age, 100%, 99.5%, and 97.8% of them still had neutralizing antibodies at titers greater than or equal to 1:8 against poliovirus type 1, 2, and 3, respectively, at 17 months of age, and a 40 to 56-fold increase in their GMT was observed from prebooster to postbooster.

A direct comparative study of the 2-4-6-month schedule (the standard schedule in the United States) and the EPI schedules was performed in Puerto Rico, where OPV is no longer given.[151] Seroconversion rates for types 1, 2, and 3, respectively, after three doses on the US standard schedule were 100%, 100%, and 99%, whereas after the EPI schedule they were 86%, 86%, and 97%.

Overall, the data clearly demonstrate that IPV is immunogenic in an EPI schedule although the titers achieved and the seroconversion rates may be lower compared with vaccination of children at older ages. The immunogenicity of IPV in an EPI schedule appears to be superior to the use of OPV in such schedules in developing countries.

Immunogenicity of sequential schedules with IPV and OPV

From 1997 to 1999 the United States relied on sequential use of IPV and OPV vaccines, in which two doses of IPV were administered at 2 and 4 months of age, followed by two doses of OPV administered at 6 to 18 months of age and again at school entry.[155–158] Table 27-5 summarizes the excellent immunogenicity obtained with this schedule.

Israel and Denmark have also used mixed schedules, with successful induction of immune responses and protection. In Israel, two schedules have been used: IPV at 2, 4, 6, and 12 months of age with OPV administered at 7 and 13 months of age or IPV at 2, 4, and 12 months plus OPV at 4, 6, and 12 months. Persistent polio in the Gaza strip despite extensive use of OPV induced the authorities to change to a mixed sequential and combined schedule, which caused a prompt drop in wild strain isolations.[159]

A study in the United Kingdom showed the advantages of a mixed schedule comprised of one dose of IPV followed by two doses of OPV in terms of immunogenicity.[160]

A particular use of mixed schedules was undertaken in Romania because of an unusually high rate of VAPP due to

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Table 27-8 GMT and Percentages of Subjects with Poliovirus NA After IPV Vaccines Given at 6, 10, and 14 Weeks of Age

	Poliovirus antibodies					
	Pre-dose 1			Post-dose 3		
Country, date (reference)	Type 1	Type 2	Type 3	Type 1	Type 2	Type 3
Oman, 1990-1992[101,102,143]				24 weeks; N = 161-169		
Product used		DTwP-IPV				
GMT		NA		447	571	251
% with NA ≥ 1: 8				88%	92%	91%
Gambia, 1990-1991[101,102,143]				24 weeks ; N=87-105		
Product used		DTwP-IPV				
GMT		NA		79	144	241
% with NA ≥ 1: 8				81%	82%	98%
Thailand, 1991-1992[101,102,143]				24 weeks; N = 92-134		
Product used		DTwP-IPV				
GMT		NA		49	68	136
% with NA ≥ 1: 8				66%	63%	92%
South Africa, 1998[145]		6 weeks; N = 119			18 weeks; N = 119	
Product used		DTwP-IPV/Hib				
GMT	20.3	23.1	16.0	116	93	166
% with NA ≥ 1: 8	63.1%	73.0%	46.7%	99.2%	99.2%	99.2%
Philippines, 2000[147]		6 weeks; N = 65			18 weeks; N = 65	
Product used		DTaP-IPV-Hib				
GMT	34.5	36.4	13.5	863	768	901
% with NA ≥ 1: 8	81.5%	81.5%	76.9%	100%	100%	100%
Moldavia, 1998[145]					18 weeks; N = 150	
Product used		DTaP-IPV-HepB				
GMT		NA		535	154	731
% with NA ≥ 1: 8				98.7%	98%	98.7%
Moldavia, 1998[145]					18 weeks; N = 136-137	
Product used		DTwP-IPV/Hib				
GMT		NA		170	88	544
% with NA ≥ 1: 8				99.3%	97.2%	100%
Cuba, 2001[148]		6 weeks; N = 52			18 weeks; N = 52	
Product used		DTwP-IPV/Hib				
GMT	33	22	< 8	304	304	858
% with NA ≥ 1: 8	NA	NA	NA	94%	83%	100%
South Africa, 2001[149]		6 weeks; N = 184-190			18 weeks; N = 213-214	
Product used		DTaP-IPV-HepB-Hib				
GMT	7.8	16	4.8	1226	661	1249
% with NA ≥ 1: 4	51%	72%	30%	100%	100%	100%
Philippines, 2003[150]		6 weeks; N = 191-193			18 weeks; N = 192-194	
Product used		DTaP-IPV/Hib				
GMT	10	14	10	533	789	1968
% with NA ≥ 1: 8	58%	65%	58%	100%	100%	100%

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Table 27-8 GMT and Percentages of Subjects with Poliovirus NA After IPV Vaccines Given at 6, 10, and 14 Weeks of Age—cont'd

	Poliovirus antibodies					
	Pre-dose 1			Post-dose 3		
Country, date (reference)	Type 1	Type 2	Type 3	Type 1	Type 2	Type 3
Philippines, 2003[150]	6 weeks; N = 191-193			18 weeks; N = 192-194		
Product used	DTaP-IPV/Hib					
GMT	10	14	10	533	789	1968
% with NA ≥ 1: 8	58%	65%	58%	100%	100%	100%
Puerto Rico, 2003[151]				18 weeks; N = 225		
Product used	IPV					
GMT	NA			222	147	724
% with NA ≥ 1: 8				85.8%	86.2%	96.9%
South Africa, 2005[152]				18 weeks; N = 202-206		
Product used	DTaP-IPV/Hib					
GMT	NA			1453	1699	2395
% with NA ≥ 1: 8				100%	100%	100%
India, 2006[153]	6 weeks; N = 213			18 weeks; N = 212-213		
Product used	DTaP-IPV/Hib					
GMT	18	20	10	440	458	1510
% with NA ≥ 1: 8	74.6%	74.2%	61.5%	100%	99.1%	100%
South Africa, 2006[154]				18 weeks; N = 220		
Product used	DTaP-IPV-HepB-Hib					
GMT	NA			579	620	975
% with NA ≥ 1: 8				100%	98.5%	100%

DTaP, diphtheria, tetanus, and acellular pertussis vaccine; GMT, geometric mean antibody titer; HepB, hepatitis B vaccine; Hib, Haemophilus influenzae type b vaccine, IPV, inactivated polio vaccine; NA, neutralizing antibodies

concurrent intramuscular injections.[161] For a time, infants in one province of Romania received IPV at 2, 3, and 4 months of age together with OPV at 4 and 9 months of age.[162] The schedule was well tolerated and highly immunogenic. No cases of polio occurred subsequently in this region, but too few children were involved to draw conclusions about the prevention of VAPP.

The previously mentioned WHO study[102,103,143] compared four doses of OPV, three doses of IPV, and a mixed schedule consisting of four doses of OPV and three doses of IPV. Seroconversion rates and GMTs were highest in the mixed OPV/IPV groups. In addition, when children of the three groups were challenged with another dose of OPV, virus fecal excretion was as low in the mixed vaccine group as in the OPV group, confirming the presence of intestinal immunity.

Another mixed schedule was tested in the Ivory Coast, with the objective of correcting deficiencies in response to OPV in tropical settings.[163] A single dose of IPV or OPV was given after three doses of OPV. Of those 9-month-old children who remained seronegative after the third dose of OPV, 81%, 100%, and 67% seroconverted to types 1, 2, and 3 polio, respectively, after the IPV booster. The corresponding percentages for an OPV booster were 14, 27, and 5.

Similarly Sutter et al[165] evaluated the performance of IPV versus three formulations of OPV (monovalent OPV type 3, Lederle tOPV, and GlaxoSmithKline tOPV) used as a booster in 9-month-old Omani infants who had received five previous doses of OPV. This supplemental dose of IPV had excellent immunogenicity and led to higher increases in polio type 3 antibodies than did OPV. In addition, mucosal immunity was assessed by administering a challenge dose of monovalent poliovirus type 3 OPV at the 15-month visit. Overall, 13.2% of the infants excreted poliovirus type 3 and there were no significant differences in the rate of excretion of poliovirus type 3 among the study groups.

In Pakistan, infants were randomly vaccinated with OPV alone; OPV and IPV at 6, 10, and 14 weeks of age; or were given OPV at those times plus a single dose of IPV at 14 weeks. The immune responses were better for types 1 and 3 for the mixed OPV/IPV association, but the single dose of IPV at 14 weeks did not improve the OPV-only responses.[141]

More recently, the WHO conducted a study in India in which 6- to 9-month-old infants who had previously received multiple doses of trivalent OPV and monovalent OPV type 1 were given a single dose of IPV. Nearly 100% of children who were seronegative to types 2 and 3 at the time of the dose seroconverted.[141]

Finally, a study in the Netherlands showed that IPV vaccination was able to boost systemic and salivary IgA responses in previously OPV-vaccinated people. In contrast, persons who received only past IPV did not produce a salivary IgA response.[166]

To conclude, several types of IPV/OPV sequential and combined schedules have been created and are being used throughout the world with good immunogenicity.

Immunogenicity of IPV in the immunocompromised subject and in preterm infants

Due to its nature and because IPV is the indicated polio vaccine for immunocompromised subjects even in countries that recommend OPV, the immunogenicity of IPV in these subjects is an important issue.

Prematurity does not appear to reduce the response to IPV-containing vaccines when the vaccines are given at the usual

postnatal age. Preterm infants all develop neutralizing antibodies after three doses of IPV, although titers might be lower than in term infants[167–172] particularly if the infants are chronically ill.[173]

Vaccination of full-term infants at birth results in lower immune responses than does vaccination later in life, presumably because maternal antibody levels are higher in newborns, and not due to immune immaturity[168] (see "Effect of maternal antibodies and neonatal vaccination").

Children infected with HIV who were given two doses of IPV in early infancy responded reasonably well, probably because their immune systems were largely intact.[174] In hemophiliac adults, however, HIV seropositivity had a negative effect on titer levels after IPV, although all adults responded to some degree.[175] Chronic renal dialysis patients also seroconverted in 90% or more of cases.[176] In patients who had undergone bone marrow transplantation and were reimmunized after transplantation, vaccination was usually successful in inducing antibodies, although at least two and often three doses were needed.[177,178]

Follow-up of 134 stem cell transplant recipients who were given three doses of IPV at 12 months after transplantation found that 94%, 94%, and 90% were seroprotected for types 1, 2, and 3, respectively. Those patients who had chronic graft versus host disease had less persistent antibody.[179]

Taken together, these results demonstrate that IPV can be immunogenic in many immunocompromised subjects.

Mucosal immunity

In general, nasopharyngeal immunity induced by IPV, as measured by the levels of secretory IgA in secretions, may be less than the levels of such antibodies induced by OPV. However, nasopharyngeal immunity as measured by resistance to challenge by OPV viruses appears equivalent to such immunity induced by OPV. On the other hand, intestinal immunity induced by IPV, whether measured by secretory IgA or resistance to challenge, appears to be inferior to such immunity generated by OPV. Many of these data come from Ogra,[180] who found that OPV recipients developed nasopharyngeal and sometimes duodenal poliovirus-specific secretory IgA, whereas IPV recipients produced lower quantities.[181,182]

Serum IgG can transit into the nasopharynx and intestine after both vaccines. Local (nasopharyngeal) and systemic antibody responses after three doses of IPV, OPV, or a mixed IPV/OPV schedule have been observed (summarized in Table 27-9[183]), but nasopharyngeal mean antibody levels were the highest following the OPV-only schedule. Another study showed equal secretory IgA levels in pharyngeal and stool samples of prior IPV and OPV vaccinees.[184]

Both premature and full-term infants developed nasopharyngeal IgA after immunization in about 90% of the cases.[185] Hovi[98] has studied IgA production in the intestine of IPV vaccinees, but found little IgA until the vaccinees had been challenged with OPV. A correlation was found between the detection of intestinal IgA and diminution of virus excretion.

Effect of IPV on poliovirus excretion after natural or experimental challenge

Early in the history of IPV, it was shown that IPV vaccinees could excrete poliovirus in the stools and in nasopharyngeal secretions after challenge,[186–189] which has been considered an important disadvantage versus OPV. Time has tempered this vision particularly due to the progressive observation that IPV-induced nasopharyngeal immunity could limit the virus shedding from this site after challenge. Thus, in epidemiological settings where the primary mode of interhuman transmission in affected communities is oral to oral (vs. fecal to oral), IPV can effectively terminate transmission.

Studies in monkeys demonstrated that pharyngeal excretion of poliovirus was inhibited in IPV vaccinees equally or even more than in OPV vaccinees.[190–192] Then, Marine,[193] who followed families exposed to natural wild-type 1 virus, found that pharyngeal infection was prevented by low levels of circulating neutralizing antibodies induced by IPV; higher levels were associated with reduced intestinal infection (Table 27-10). A similar correlation between the height of the serum antibody titer and prevention of excretion was seen in Israel.[194] In a more recent study, children who had received three doses of IPV or OPV were challenged with two different doses of type 1 monovalent OPV.[184] The results (summarized in Table 27-11) reveal that, whereas few subjects in either group excreted virus from the pharynx, intestinal infection occurred in both groups but was significantly lower in the OPV group (82% vs. 31% for the high titer challenge and 46% vs. 18% for the low titer challenge). Nevertheless, the fact that high serum-neutralizing antibodies are a correlate of intestinal or nasopharyngeal immunity is still debated. The persistence of local immunity after polio vaccination has not been well studied, but there is evidence that resistance to reinfection wanes and that protection against paralysis ultimately depends on the level of serum antibodies.[127,195,196]

Table 27-10 Percent Excretion of Wild Poliovirus Type 1 in Children According to Level of Vaccine-Induced Serum Neutralizing Antibody

	% excretion at given time after infection		
	1-2 weeks	3-4 weeks	5-6 weeks
Antibody titer	P, S	S	S
<8	75, 93	82	60
8-64	38, 97	81	54
>64	25, 88	59	28

P, pharynx sample; S, stool sample.
Data from Marine WM, Chin TDY, Gravelle CR Am J Hyg 76:173-195, 1962.

Table 27-9 Levels of Serum Neutralizing or Nasopharyngeal IgA Antibodies in Children After Three Doses of IPV, OPV, or a Sequential Schedule

	OPV-OPV-OPV			IPV-IPV-IPV			IPV-IPV-OPV		
	Type 1	Type 2	Type 3	Type 1	Type 2	Type 3	Type 1	Type 2	Type 3
Serum neutralizing antibodies (%)	100	100	100	96	100	100	100	100	100
GMT	1,470	3,578	1,522	1,954	5,835	5,187	3,044	10,693	2,348
Nasopharyngeal sIgA antibodies (%)	100	100	100	89	91	89	75	81	81
GMT	69	97	129	24	25	31	19	22	23

GMT, geometric mean titer; IPV, inactivated poliovirus vaccine; OPV, oral poliovirus vaccine.
From Faden, H, Modlin J, Thomas ML, et al. J Infect Dis 162:1291-1297, 1990. With permission.

Table 27-11 Isolation of Poliovirus From Stool or Pharynx of Prior Recipients of IPV or OPV After Challenge with Type 1 OPV

Challenge dose	No. of pharyngeal isolations (%)		No. of stool isolations (%)	
	IPV	OPV	IPV	OPV
High (560,000-600,000 TCID50)	1/45 (2)	3/45 (7)	37/45 (82)	14/45 (31)
Low (500-800 TCID50)	0/48 (0)	0/34 (0)	22/48 (46)	6/34 (18)
Total	1/93 (1)	3/79 (4)	59/93 (63)	20/79 (25)

IPV, inactivated poliovirus vaccine; OPV, oral poliovirus vaccine; TCID50, median tissue culture infective dose.
From Onorato IM, Modlin JF, McBean AM, et al. J Infect Dis 163:1-6, 1991. With permission.

Several challenge studies of IPV vaccinees have been conducted using type 3 monovalent OPV. In one, 93% of IPV-only vaccinated Finnish infants excreted type 3 virus in stools after challenge with 300,000 median tissue culture infective doses ($TCID_{50}$), but there was no control group.[274] The median length of poliovirus excretion was 35 to 42 days, and the excreted peak virus titers were $10^{5.6}$ $TCID_{50}$ per gram.[98] In the second study, a challenge with 600,000 $TCID_{50}$ induced only 5% to 10% stool excretion in Pakistani infants who received OPV alone or a sequential and mixed IPV/OPV schedule.[164]

One study done in the United States had the advantage of a control group that was unvaccinated. In this study, two doses of IPV or OPV were followed by a dose of OPV.[197] Stool excretion was measured after that dose, in comparison to a group receiving OPV for the first time. The results are summarized in Table 27-12, which shows, in line with prior studies, that excretion of poliovirus in IPV vaccinees is significantly lower and shorter than in the unvaccinated, but more than in OPV vaccinees.

The recent Cuban study of IPV given by the EPI schedule showed virus isolation rates 1 week after challenge with OPV of 94%, and a mean $\log_{10}$ viral titer of any serotype of 3.46. The titers of virus shed were about 0.5 log lower in IPV-vaccinated children post challenge compared to unvaccinated children being vaccinated for the first time with OPV.[148]

Until recently, OPV was the only polio vaccine used in Mexico. A study done in contiguous border towns showed that IPV-vaccinated American infants did not become infected with OPV despite high-level poliovirus importation.[225]

In the city of Cordoba, Argentina, use of IPV much reduced the circulation of OPV strains; although Sabin viruses were still occasionally detected in sewage, some of which had reverted to a more neurovirulent phenotype, no circulating VDPVs (cVDPVs) were detected.[226] Mexico now routinely immunizes infants with IPV supplemented by biannual national immunization days with OPV. A study showed that revertant and nonrevertant Sabin-strain viruses could be isolated from IPV-vaccinated infants 10 weeks after the campaign and from sewage for at least 13 weeks.[227]

The controversial question is whether or not the decreased titers of polioviruses shed in stool and duration of shedding observed in IPV vaccinees, results in less risk of transmission than in unvaccinated populations or OPV vaccinees, and therefore could contribute to the herd protection effect[195] (see "Herd immunity"). A recent review of intestinal excretion of polioviruses after IPV vaccination concluded that IPV does not reduce the incidence of excretion but does reduce the quantity of virus shed.[227a] The unresolved issue is whether or not decreased quantity means decreased transmission.

Studies have also examined the effect of IPV on the mutation profile of OPV strains in the intestinal tract.[198-200] This phenomenon, referred to as reversion to virulence, is a regular feature of the replication of attenuated poliovirus strains, whereby the mutations in those strains responsible for attenuation in humans revert to the virulent genotype. Although the suggestion has been made that prior IPV immunization potentiates that reversion,[201,202] a relatively large study failed to show a significant difference in the mutation of excreted virus between IPV and OPV-vaccinated groups.[203] Recent analysis made on the virus samples isolated during use of a sequential schedule in the United Kingdom[160] found that reversion occurred faster in vaccinees given IPV or OPV than in previously unvaccinated infants, suggesting that the virus attempts to increase its fitness in the presence of antibodies.[204,205]

Efficacy of IPV and correlates of protection

The efficacy of IPV in its original version was proved beyond a doubt in the original field trial conducted by Francis et al.[1-4,206] In that trial, ~400,000 children randomly received vaccine or placebo, and another 200,000 were vaccinated and observed together with unvaccinated children. There were 71 cases of paralytic polio in vaccinees versus 445 in control subjects. In the placebo-controlled part of the study, 70 cases occurred in the placebo arm versus 11 in the vaccinated arm.[206] The calculated efficacy of the vaccine was 80% to 90% against paralytic polio and 60% to 70% against all forms of polio.

The efficacy of IPV was later confirmed in several settings. Melnick[207] calculated an efficacy of 96% through two polio seasons in Houston. In Senegal, two doses of a DTwP-IPV combination vaccine were given in the Kolda area, which subsequently suffered an outbreak of type 1 polio. A case-control analysis revealed an efficacy for one dose of 36% (95% confidence limits, 0%-67%) and for two doses of 89% (95% confidence limits, 62%-97%).[208-210] In another study conducted in the North Arcot region of India, John[211] compared OPV in one district with IPV vaccination in two other districts. Vaccination coverage with three doses rose to 85% to 90% in the OPV districts and 75%

Table 27-12 Viral Shedding in Stool of Any Type After Trivalent OPV Administration to IPV Vaccinees, OPV Vaccines, or Unvaccinated Infants

Prior vaccination	1 week post OPV		3 weeks post OPV			
	N	% PCR pos. (CI).	N	% PCR pos. (CI)	Geometric Mean copy no.*	
None	48	92 (80-98)	48	81 (67-91)	627	1143
OPV × 2	41	22 (11-38)	42	5 (1-16)	NA	
IPV × 2	42	76 (61-88)	38	37 (22-54)	155	

*Of positive stools.
IPV, inactivated polio vaccine; OPV, oral poliovirus vaccine; PCR, polymerase change reaction.
Adapted from Laassri M, Lottenbach K, Belshe R, et al., J Infect Dis 192:2092-2098, 2005. With permission.

to 80% in the IPV districts. Case-control analysis revealed an efficacy of 92% for IPV and 66% for OPV. During the introduction of IPV into Canada, efficacy of the vaccine was calculated at more than 90%.[212]

Correlate of protection

Neutralizing antibody levels above the 1:8 dilution threshold are now well accepted by all national regulatory agencies as correlates of protection when reviewing license applications for IPV-containing vaccines,[213] although a 1:4 dilution may also be protective.

Herd immunity

The best evidence for a herd immunity effect of IPV is the experience in the United States where IPV was introduced into routine use in 1955 and was replaced by OPV in 1962. A sharp drop in the numbers of cases of paralytic and nonparalytic polio was evident during the years 1955 to 1962 (Figure 27-5). The apparent reduction in the number of cases observed exceeded the expectation based on the percentage of children vaccinated (Figure 27-6).[214] More specific regional data were published that suggested a greater than expected reduction in polio cases.[215]

The second example of herd immunity comes from the Netherlands where vaccination is refused by a religious community that is well dispersed throughout the country, although IPV is routinely administered to the rest of the population. Two outbreaks of polio have occurred in this religious group, one caused by type 1 virus in 1978 (110 cases) and the second by type 3 virus from 1992 to 1993 (71 cases). Despite the wide circulation of the virus in this community, there was only one case of polio in other Dutch communities. Approximately 400,000 unvaccinated individuals not belonging to this religious community also remained unaffected.[216–220,270] The virulent viruses also spread to similar religious groups in North America, but cases only resulted from the 1978 outbreak.[221–223] Oostvogel et al[224] did an analysis of the circulating viruses in schools affected by the outbreak from 1992 to 1993. Proof of recent type 3 infection was found in 59.5% of the unvaccinated children and in 22.2% of the vaccinated children.

The evidence for herd immunity comes from countries where oral-to-oral transmission was probably the dominant mode of interhuman poliovirus transmission. It is less clear if IPV is able to induce herd immunity in countries where the fecal-to-oral route is thought to be the primary role in transmission.

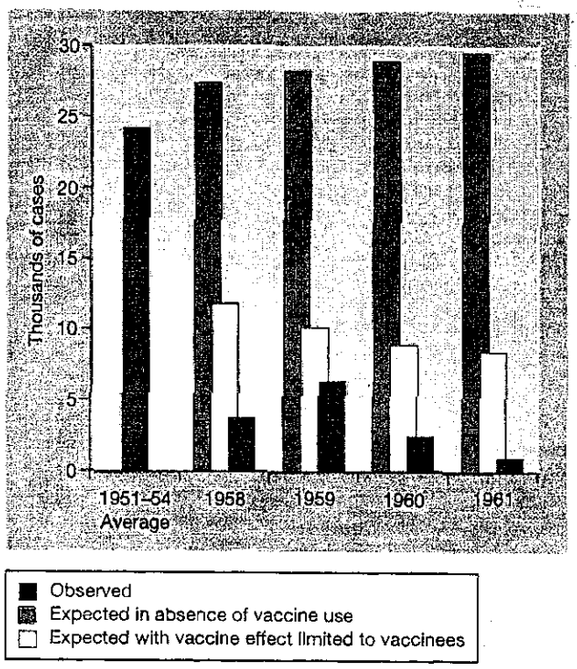

Figure 27-6 Herd effect induced by IPV in the United States from 1958-1961. The number of observed cases of paralytic poliomyelitis was consistently lower than the number that would have been expected if vaccination had benefited only vaccinated individuals. (From Stickle, G. Am J Public Health 54:222-229, 1964. With permission.)

Duration of immunity

Several studies have been conducted to assess the long-term persistence of antibodies following different infant regimens for the primary series with IPV-containing vaccines with or without boosters with IPV-containing vaccines administered

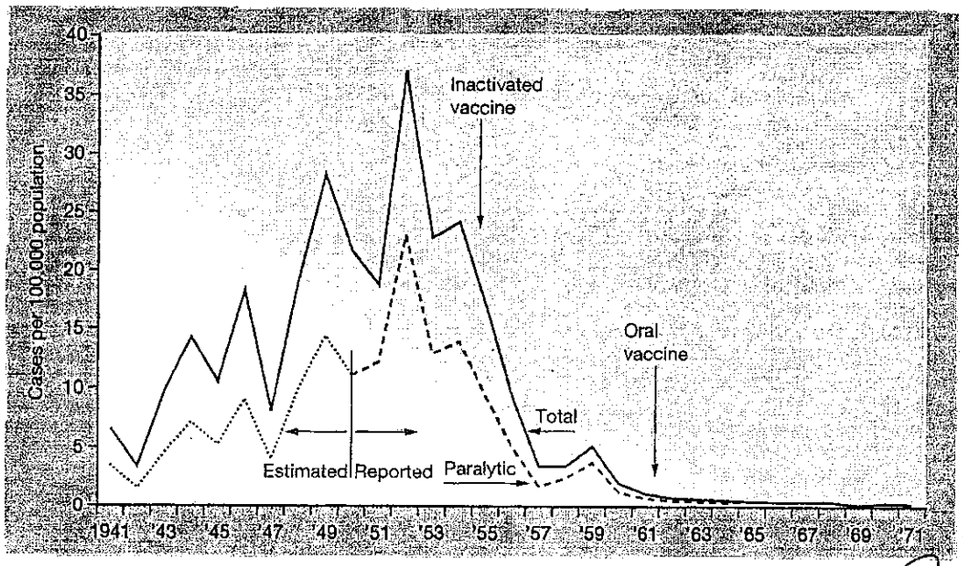

Figure 27-5 Incidence of polio in the United States. The OPV was introduced from 1961 to 1962. The dashed line indicates the incidence of paralytic polio only; the solid line measures the incidence of both paralytic and nonparalytic polio. (From Centers for Disease Control and Prevention. Immunization Against Disease—1972. Atlanta, Centers for Disease Control and Prevention, 1973.)

during the second year of life and/or during preschool age. This section will not review long-term persistence data from studies where primary series polio immunizations have been done with sequential IPV/OPV schedules, because they are much less frequent and because their overall conclusions do not differ from the ones described in the following sections. The vast majority of studies have involved cohorts of subjects followed for varying periods of time that have been vaccinated within the context of clinical trials aimed at documenting the early responses induced by IPV-containing vaccines under development and/or licensure. The studies have been grouped by type of IPV vaccine used and then subgrouped by type of primary series regimen.

The first group includes studies done with the older IPV-containing vaccines formulated before eIPV was available. These low-potency vaccines contained quantities of antigen that were lower than the current formulations. Bottiger[228] evaluated 30 Swedish children given two primary doses of IPV at approximately 9 and 10 months of age and a booster dose at 2 years of age. When tested at 10 years of age (8 years after the last dose), 100% of the children still had seroprotective levels (≥1:4) of antibody to all three poliovirus serotypes. In addition, in the same study, Bottiger evaluated 220 Swedish children given the same low-dose vaccine with three doses at 9 months, 10 months, and 2 years of age, and a later booster dose at 6 years of age. At 18 years of age (12 years after the last dose), 100% of subjects were still seropositive (≥1:4) to all three serotypes. The decline of antibody titers was greater during the first 3 years after the 6-year booster (0.13-0.22 $\log_{10}$ fold-reduction per year) than during the next 9 years (0.05-0.10 $\log_{10}$ fold-reduction per year). In another study conducted in Sweden by Taranger et al,[229] two primary series immunization schedules were evaluated. All subjects were given an older low-dose 20-4-16 D-Ag units IPV concomitantly but at separate sites from DTaP and Hib vaccines. One group of 103 children were immunized using the standard Swedish schedule at 3, 5, and 12 months of age; the other group of 118 children were immunized at 2, 4, 6, and 15 months of age. At 4 years of age, 93% to 100% of children on the 3-5-12-month schedule and 96% to 100% of children on the 2-4-6-15-month schedule still had seroprotective titers (≥1:4) to the three poliovirus serotypes.

The second group of studies includes studies done with modern IPV-containing vaccines, and is further subgrouped according to the type of infant/toddler schedule used. That is, two doses in infancy followed by one dose in the second year of life (2 + 1), three doses in infancy with no booster dose in the second year of life (3 + 0), or, finally, three doses in infancy (6-10-14 weeks of age, or 2-3-4 months, or 2-4-6 months of age) followed by a booster in the second year of life (3 + 1). Their results are summarized in Table 27-13.[203,230-242] All of the available data show persistence of antibodies only up to the preschool age, because all of these cohorts have received a preschool booster with an IPV-containing vaccine. No data are available in cohorts of subjects primed with these different infant/toddler schedules who have not received a preschool booster with an IPV-containing vaccine. Overall, these studies show that the persistence of poliovirus-neutralizing antibodies is well established at least until preschool age by the 3 + 1, 2 + 1, and 3 + 0 schedules, with slightly higher titers in favor of the most complete schedule (3 + 1). In all studies where evaluated, antibody titers declined more rapidly during the first 2 years after the last dose (0.45-0.60 $\log_{10}$ fold-reduction/year for each of the three serotypes) but remained more stable during the following years. When a preschool booster is given following these different infant-toddler primary immunization schedules, there is evidence of a marked anamnestic response with high titers when measured in the month following the preschool booster. Based on data from the historical Swedish data noted earlier, duration of protection is expected to be long term, if not lifelong. Whether additional boosters will enhance long-term protection is still debated,[300] but some countries recommend post preschool age additional doses. A compromise position would be to recommend four to five doses of IPV with the last one administered at preschool age, as, for example, in the current US schedule, which is ages 2, 4, and 6 to 18 months and 4 to 6 years (2 + 1 + 1 or 3 + 0 + 1); or in the UK, which is ages 2, 3, and 4 months and 3 to 6 years (3 + 0 + 1) (but in this case, the UK recommends a fifth dose at 13-18 years of age); or in some other European countries, which is ages 2, 4, 6, and 15 to 18 months and 4 to 6 years (3 + 1 + 1).

Experience is very limited with regard to duration of persistence of antibody in countries that do not recommend boosters at preschool age or later. Thus, it is not clear if immunity will persist long term in the absence of such preschool or later boosters.[243] Therefore, given the present state of knowledge, it seems prudent to recommend that a preschool booster be part of any IPV routine immunization schedule. The need for subsequent boosters in countries relying on five consecutive doses of IPV from birth to preschool entry (3 + 1 + 1 schedules) has not yet been established. The availability of IPV-containing combination vaccines licensed for adolescent and adult populations (Tdap-IPV) will facilitate adolescent and adult boosters, but available data do not suggest such boosters are needed. In fact, few countries recommend such boosters. However, few studies have evaluated persistence of poliovirus-neutralizing antibodies beyond childhood following primary immunizations[242] (see also Figure 27-7), as the first countries who put in place routine and exclusive use of modern IPV-containing vaccines schedules started in the mid-1980s. Thus, the cohorts of infants having received such schedules are just starting to reach their thirties.

Salk argued that immunologic memory is established by primary vaccination with IPV and that no further immunizations are necessary.[244-246] He showed that, whereas unprimed individuals reacted with only low responses to a single dose of IPV, previously vaccinated individuals, even those originally given fractional doses, developed anamnestic responses (see Table 27-2). In his opinion, the vaccinees would respond similarly to an infection, thus preventing viremia and disease. Swartz[106] and colleagues showed that newborns could be sensitized to develop an anamnestic response to IPV at age 6 months if they were given a dose at birth. In contrast, Dutch workers identified a group of elderly IPV-vaccinated but now seronegative subjects who were challenged with OPV.[247] Although a third had anamnestic serum antibody responses suggesting prior exposure to type 1 virus and immunological memory, those responses did not appear to protect them against intestinal infection with the virus.

Adverse events

IPV is a very well-tolerated antigen.[91,203] When infants are injected intramuscularly with IPV stand-alone vaccine, injection site erythema is seen in 0.5% to 1.5% of infants, induration in 3% to 11%, and tenderness in 14% to 29%.[93] The combination of IPV with other vaccines, such as DTwP/DTaP (supplemented or not by Hib and hepatitis B), does not seem to add to the reactions expected with those vaccines alone (Sanofi Pasteur and GlaxoSmithKline, published and unpublished data).[91,92,203]

IPV-containing vaccines are now licensed in more than 100 countries[248] and it is estimated (2010) that 25 to 30 million newborn infants and approximately 15 million children, adolescents, and adults receive them every year. Overall, the numbers of adverse events reported to the manufacturers have been low, and the types of reactions reported have been classical and without concentration in a single category.

The US CDC Vaccine Adverse Event Reporting System database assembled between 1991 and 1998 was reviewed for reactions attributed to IPV.[249] The putative reactions were compared with reports of reactions to OPV. No significant change was

Table 27-13 Long-Term Persistence of Antibodies After a Booster Dose in the Second Year of Life

Study	Ages of immunization	Vaccine used for polio primary immunizations	Age at serum collection	SP threshold	No. of subjects	% Seropositive (GMT)		
						Type 1	Type 2	Type 3
2 + 1 primary series infant/toddler schedule								
Murdin et al[203]	2, 4, and 18 months	IPV stand-alone	4-6 years	≥ 1:8	147	97% (426)	99% (722)	94% (276)
Faden et al[230]	2, 4, and 12 months	IPV stand-alone	5 years	≥ 1:10	27	100% (200)	100% (398)	100% (251)
Swartz[231]	2, 3.5, and 10 months	DTwP-IPV	4-5 years	≥ 1:4	~ 50	100% (NA)	100% (NA)	100% (NA)
Carlsson et al[232]	3, 5, and 12 months	DTaP-IPV/Hib	5.5 years	≥ 1:4	112	95% (72)	99% (133)	97% (98)
Black et al[233]	2, 4, and 6 or 2, 4, and 18 months	IPV stand-alone	4-6 years	≥ 1:8	837-841 260-262	88% (32) 85% (31)	92% (40) 87% (35)	85% (38) 85% (38)
3 + 0 primary series infant/toddler schedule								
Kitchin et al[234]	2, 3, and 4 months	DTaP-IPV-Hib	3.5-4.5 years	≥ 1:8	77	89% (37)	85% (52)	92% (47)
Guerra et al[241]	2, 4, and 6 months	IPV stand-alone	4-5 years	≥ 1:8	249	96% (63)	99% (84)	95% (61)
3 + 1 primary series infant/toddler schedule								
Langue et al[235]	2, 3, 4, and 14-16 months	DTwP-IPV/Hib and DTaP-IPV/Hib	5-6 years	≥ 1:5	162	94% (72)	96% (85)	99% (187)
Mallet et al[236]	2, 3, 4 or 2, 4, 6 and 12-16 months	DTaP-IPV/Hib	5-6 years	≥ 1:5	234	94% (58)	96% (78)	96% (123)
Carlsson et al[232]	2, 4, 6, and 13 months	DTaP-IPV/Hib	5.5 years	≥ 1:4	116	97% (92)	100% (125)	100% (202)
Danjou, Silier, and Dupuy[237]	2, 3, 4, and 16-18 months	DTwP-IPV	4-7 years	≥ 1:5	131	95% (88)	95% (72)	97% (121)
Danjou, Silier, and Dupuy[237]	2, 3, 4, and 16-18 months	DTaP-IPV/Hib	4-7 years	≥ 1:5	130	95% (86)	97% (94)	99% (109)
Gadjos et al[238]	2, 3, 4, and 16-18 months	DTaP-IPV/Hib	5.8-7 years	≥ 1:8	383	92% (87)	96% (109)	96% (136)
Gadjos et al[238]	2, 3, 4, and 16-18 months	DTaP-IPV/Hib	5.8-7 years	≥ 1:8	375	88% (67)	93% (83)	92% (99)
Sanofi Pasteur, Study A3R22[239]	2, 3, 4 or 2, 4, 6, and 15-17 months	DTaP-IPV-HepB-Hib	5-6 years	≥ 1:8	166	93% (91)	98% (115)	94% (138)
Guerra et al[241]	2, 4, 6, and 15 months	DTaP-IPV/Hib	4-5 years	≥ 1:8	76-77	95% (172)	99% (265)	97% (284)
Sanofi Pasteur, Study TD917[240]	2, 4, 6, and 15 months	DTaP-IPV/Hib	4-5 years	≥ 1:8	114	98% (157)	100% (226)	94% (170)
					106	92% (120)	99% (242)	95% (143)
	2, 4, and 6 or 2, 4, and 15 months	IPV stand-alone			328	99% (130)	99% (151)	95% (122)
					320	98% (134)	99% (152)	94% (111)
Zinke et al[242]	2, 3, 4 or 3, 4, 5 and 12-23 months	DTaP-IPV-HepB/Hib	4-6 years 7-9 years	≥ 1:8	174-185 144-148	> 95% (87) 91% (52)	> 95% (84) 91% (44)	97.2% (158) 97.2% (96)

*Not available.
DTaP, diphtheria, tetanus, and acellular pertussis vaccine; GMT, geometric mean antibody titer; HepB, hepatitis B vaccine; Hib, Haemophilus influenzae type b vaccine, IPV, inactivated polio vaccine.

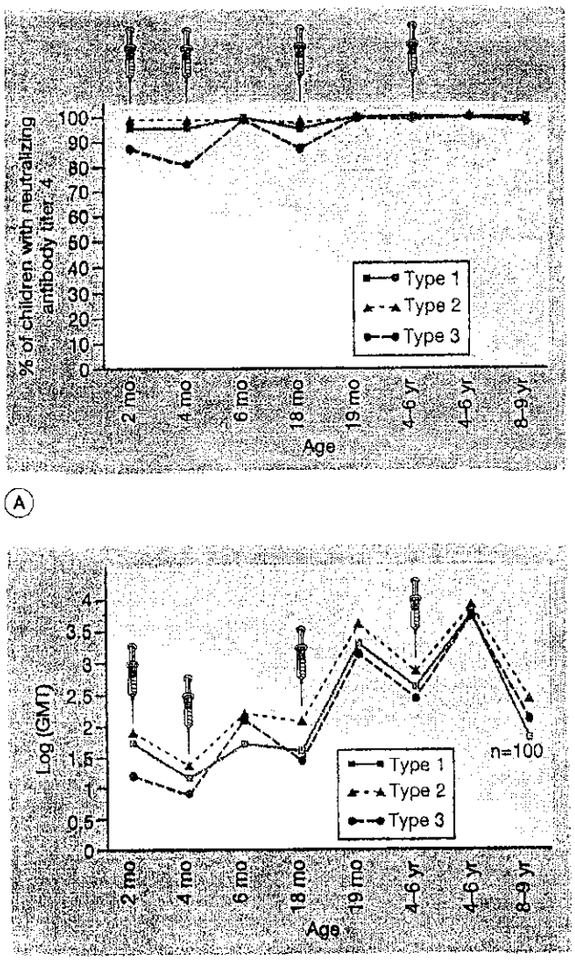

Figure 27-7 Eight- to nine-year follow-up study of poliovirus neutralizing antibodies in children immunized with MRC5-produced IPV. Vaccinees received a two-dose primary series at 2 and 4 months of age and booster vaccinations at 18 months and 4 to 6 years of age (indicated by the syringe symbol). (A) Percentage of children with a neutralizing antibody titer of 4 or greater. (B) Natural logarithm of the GMT. (Reprinted from Murdin AD, Barreto L, Plotkin SA. Vaccine 14:735-746, 1996. With permission from Elsevier Science.)

seen in the types or frequency of reactions such as fever, convulsions, and local reactions. Both vaccines generally were administered in association with other vaccines such as DTwP, so these events cannot be attributed necessarily to IPV or OPV.

Safety data accumulated by Sanofi Pasteur and GlaxoSmithKline on combination vaccines containing IPV also have not shown unexpected reactions attributable to the IPV vaccine. As one example, among dozens, in one study of 2,195 infants given a DTaP-IPV vaccine associated or combined with one Hib vaccine at 2, 3, and 4 months of age, there were no seizures and no hypotonic hyporesponsive episodes, fever higher than 40°C in only 0.1%, and inconsolable crying in only 0.15%.[250]

With regard to major adverse events, the events reported within the context of the "Cutter incident" are unique in the history of IPV. Between April and June 1955, shortly after licensure in the United States, 204 cases of type 1 polio were observed in association with use of the vaccine manufactured by Cutter Laboratories.[251,252] After investigation, 60 cases in vaccinees and 89 in family contacts were judged to be caused by two lots of vaccine in which infectious virus had not been completely inactivated. About 70,000 children received the two lots, and half were probably seronegative to type 1. Virologic studies revealed infection in 10% to 25% of vaccinated children and found an incidence of 1 paralytic case in every 100 to 600 infections. The incriminated lots all had passed release tests, including monkey neurovirulence and tissue culture infectivity, but other lots similarly manufactured had failed. A requirement for serial lots to pass safety tests was then introduced at that time.

The Cutter incident was due to a lack of regulatory supervision of companies that had no experience in making IPVs, and serves as a lesson in vaccine safety.[253] Since the Cutter incident and the safety measures instituted as a result of that experience, there has been no evidence for defective manufacture of IPV. Several hundred million doses of IPV produced by the major manufacturers have been used without association with subsequent polio, or other serious reaction.[92,203,254] As mentioned previously, augmented use of IPV in routine vaccination in the US since 1997 and later in countries like the UK, Australia, Mexico, South Africa, and Turkey has permitted additional accumulation of data, again without indication of a causal relationship to serious adverse effects.

Recently, a retrospective safety issue has been raised. Like OPV, early versions of IPV contained simian virus 40 (SV40) derived from primary rhesus monkey kidney cells. Studies showed that SV40 transformed cells in culture and caused tumors in animals. After the discovery of the virus, SV40 was eliminated from IPV in 1963. Nevertheless, SV40 antigens have been discovered in mesothelial tumors, brain tumors, and non-Hodgkin's lymphomas, and even in individuals not exposed to polio vaccines before the vaccines were cleared of the virus.[255–257] The still unresolved issues are whether or not SV40 was successfully removed from the seed materials; whether SV40 infects humans from sources other than polio vaccines; whether if, having come from polio vaccines, it now has an independent human-to-human transmission; and whether or not it is a passenger virus in the tumors and not the causative agent. Although epidemiologic studies have been negative so far, the jury is still out.[258,259]

Flare-ups of disease were reported in approximately 6% of systemic lupus erythematosus patients who received IPV. However, about the same rate was seen in OPV recipients, and no control group was studied.[260]

Recommendations for IPV

Infants

IPV-containing vaccines are now recommended in routine public vaccination programs in many countries including in American infants and children.[261,262] In the United States, the routine schedule is a single dose at 2, 4, and 6 to 18 months followed by a fourth dose at 4 to 6 years of age (preschool entry). As of the end of 2011, IPV-containing vaccines are routinely recommended for infant vaccination against poliomyelitis in nearly 60 countries including Canada, almost all European countries including Eastern Europe, Australia, New Zealand, Mexico, Turkey, South Africa, Costa Rica, Taiwan, and Malaysia.[263]

Children

For children who need rapid protection because they are traveling to a zone where polio is endemic or epidemic, or for those who have not been vaccinated previously, the recommended schedule is two doses 1 month apart followed by a booster 6 months later (or, if pressed for time, at least 1 month later).

Adults, including travelers

Routine (re)vaccination of adults is not recommended in the United States,[265] but is recommended in some European countries.[266]

If adults need primary polio vaccination, they should always receive IPV, because VAPP after OPV appears to be more common after 18 years of age. IPV-containing combination vaccines made of low-dose diphtheria and tetanus toxoids plus IPV (some including also low-dose acellular pertussis antigens) have been developed and licensed in many countries.[121–125] In principle, vaccination of previously unvaccinated adults, to protect them from VAPP, is recommended when they are in contact with children excreting OPV. Adults traveling to polio-epidemic or polio-endemic areas should receive IPV as a booster before their first trip.[267] Laboratory personnel working with wild polioviruses should have previously completed vaccination. Health care workers should also be vaccinated because they may come into contact with wild poliovirus or reverted attenuated viruses excreted by vaccinees.

IPV is universally recommended for subjects with known congenital or acquired immunodeficiency, including HIV infection, in view of the VAPP risk in those patients after use of OPV.[268] Those receiving systemic steroid therapy or chemotherapy are included in this indication. In developing countries OPV is recommended for asymptomatic HIV-seropositive people, because the risk of polio from wild viruses is considered larger than the risk from VAPP. In industrialized countries where OPV is still routinely used but IPV is available for some indications, family contacts of immunocompromised people should receive IPV instead of OPV to avoid transmitting the vaccine viruses to the immunocompromised host.

Contraindications to IPV

Formal contraindications to IPV consist of previous severe reaction to IPV vaccine or known or documented allergy to streptomycin, neomycin, or polymyxin B. Neither pregnancy nor breastfeeding is a contraindication.

Simultaneous use with other vaccines

No clinically relevant interference effects have been described when IPV is used in association or in combination with licensed DTwP/DTaP, Hib, or hepatitis B vaccines. The largest experiences with IPV combinations have been between the mid-1980s and the mid-1990s with DTwP-IPV and DTwP-IPV/Hib in France and Canada, and since the mid-1990s with DTaP-IPV-backboned combinations including HepB and/or Hib in the United States, Canada, Europe, and elsewhere (see Chapter 40). In combination vaccines, IPV is compatible with DTaP, Hib, and hepatitis B, although generalization is difficult owing to the pharmaceutical specificities of all of these drug substances, which are the key driver of the mixability of these antigens. Extemporaneous mixing of two distinct liquid finished products should not be made by vaccinators.

Public health considerations

Results of vaccination programs with IPV

Experience with IPV in national programs has been longest in Europe and in Canada. Some countries have used IPV exclusively since the mid-1950s, and some as part of mixed or sequential schedules with OPV, as reviewed by Murdin,[203] Plotkin,[264] and Bonnet and Dutta.[94]

Table 27-14 lists the nearly 60 countries (2010) where IPV-containing vaccines are recommended for routine pediatric vaccination as IPV-only schedules or as part of sequential schemes with OPV or as IPV-only schedules supplemented by SIAs with OPV.[263] Some of these experiences are reviewed in the next section for several WHO regions.

Table 27-14 Countries where IPV is Recommended by Health Authorities or By Medical associations for Routine Pediatric Immunization (2010).*

IPV-only schedules	IPV/OPV sequential schedules
America Samoa	Bahamas
Andorra	Bahrain
Australia	Belarus
Austria	Bosnia-Herzegovina
Belgium	Costa Rica
Bulgaria	Jordan
Canada	Kuwait
Croatia	Lebanon
Cyprus	Malaysia
Czech Republic	Marshall Islands
Denmark	Mexico
Estonia	Montenegro
Finland	Palestine
France	Poland
Germany	Russian Federation
Greece	Saudi Arabia
Hong Kong	Syrian Arab Republic
Hungary	Ukraine
Iceland	United Arab Emirates
Ireland	Oman
Israel	**IPV/OPV combined schedules**
Italy	Turkey
Latvia	South Africa
Lithuania	Qatar
Luxembourg	
Malta	
Monaco	
Netherlands	
New Zealand	
Niue	
Norway	
Palau	
Portugal	
Romania	
San Marino	
Slovakia	
Slovenia	
South Korea	
Spain	
Sweden	
Switzerland	
Taiwan	
United Kingdom & Northern Ireland	
United States	

*Either as IPV-only schedules or as part of sequential IPV/OPV schedules or as part of IPV/OPV combined schedules.
IPV, inactivated polio vaccine; OPV, oral poliovirus vaccine.[269]

European region

Many countries of this region have been early adopters of IPV. Sweden has used IPV since 1957. In 1989, modern IPV replaced the original vaccine. Indigenous circulation of wild polioviruses was stopped by 1962,[269] although a subsequent outbreak occurred in an unvaccinated religious community without spread to the whole population.[270]

Similarly, IPV has been used in Finland for many years, starting with first-generation vaccine and changing to modern IPV in 1985. The only outbreak of polio reported since the introduction of IPV involved 10 cases in 1984 under the following circumstances.[271,272] The type 3 component of the first-generation IPV was of low potency, with a minority of vaccinees responding with antibodies and vaccination coverage had slipped to 80% before outbreak onset.[273] Investigations revealed that the type 3 wild-type virus was introduced, probably from Turkey, and was genetically distinct from the Saukett virus strain used to manufacture the vaccine[216] and, because of that it escaped neutralization.[273] A trypsin-treated vaccine was developed in an attempt to correct the specificity of the type 3 response,[274] but tests showed that it did not improve the immunogenicity.[274] OPV was brought in to stop the outbreak, after which the Finns returned to using IPV, but in the form of the modern vaccine. The modern IPV did induce neutralizing antibodies to the Finnish mutant virus, and no spread of polio virus to Sweden occurred during that outbreak.[269]

Denmark started with a mixed and sequential schedule in 1968. Starting in 1970, Danish infants received IPV at 5, 6, and 15 months of age, followed by OPV at 2, 3, and 4 years of age. Single polio cases were diagnosed in 1969, 1976, 1980, and 1986, and the last two were imported. No wild-type virus has been identified in sewage samples since 1968. Not surprisingly, seroimmunity has been virtually 100% at all ages of the Danish population.[203,275] No VAPP has occurred among 1.5 million Danes who have received two or more doses of IPV, and Denmark changed to an all-IPV schedule.

In the Netherlands where modern IPV had its roots in the late 1970s,[276] polio has been prevented in the general population by combining DTwP-IPV or, more recently, DTaP-IPV vaccine. In 2001, a survey of immunity in the general Dutch population revealed seropositivity rates of 97%, 93%, and 90%, respectively, for polioviruses types 1, 2, and 3.[277] As described earlier, however, two outbreaks have occurred in Protestant religious communities refusing vaccination without spread to others (see "Herd immunity").

Polio disappeared from Iceland in 1960 after the introduction of IPV vaccination in 1956.[269] Norway started vaccination with IPV in the late 1950s but switched to OPV in 1965. After that switch, there were six cases of VAPP, of which five were in unvaccinated people and the sixth in an individual given IPV 10 years earlier (L. Flagstrud and H. Nokleby, personal communication). Because most of the population had received IPV previously, it appears that VAPP had been almost completely prevented by prior IPV vaccination. Norway switched back to IPV in 1979, and since then the only reported poliomyelitis has been imported from abroad.[269]

France is a good example of a sizable country exposed to regular poliovirus importations that has kept the disease at bay with IPV vaccination only. France started vaccination with IPV in 1956, but in 1965 OPV became the recommended vaccine. Both OPV and IPV were in use until 1983, when modern IPV was recommended. VAPP occurred sporadically during the use of OPV but ceased to be seen after 1986.[278–280] The last wild poliovirus AFP case was reported in 1989, and attempts to find indigenous wild-type viruses in sewage have not been successful since 1989.[278–282]

In Germany, a switch from OPV to IPV was made in 1998, because in the prior decade there were 15 cases of VAPP compared to only 2 cases caused by imported wild viruses. Doses were recommended at 2, 4, and 11 to 14 months of age, with a booster in adolescence. However, because IPV-containing combination vaccines are in general use in Germany, most infants receive IPV doses at 2, 4, 6, and 11 to 14 months of age.

The United Kingdom switched from OPV use to an exclusive use of IPV in 2004 when a pentavalent aP-IPV combination became licensed and was then recommended. Many other European countries use all-IPV schedules. In addition, as the use of pentavalent and hexavalent combination vaccines containing IPV becomes more general, more countries are likely to switch.

Americas region

All Canadian provinces have used IPV, OPV, or a mixed sequential schedule since the inception of vaccination in 1955, and the experience has been particularly large in Ontario, Canada's most populous province. Since 1997, all provinces are using IPV through the use of IPV-containing acellular pertussis combinations. The last indigenous case of polio occurred in 1988, and was related to importation of the virus. Introductions of poliovirus from the Netherlands in 1979 and 1992 and from the Indian subcontinent in 1996 failed to spread to the general population.[109,212,283] Ontario, the largest province with the largest immigrant population, has had the most introductions, but provinces using OPV have also had wild poliovirus introduced. In every case, the wild virus was confined to unvaccinated immigrant groups or unvaccinated religious cults, while the general population was unscathed.

In the United States the early use of first-generation IPV was discussed previously (see "Herd immunity"). Despite incomplete application of the vaccine, polio incidence fell 95% between the introduction of the vaccine in 1955 and its abandonment in 1961 (see Figure 27-5). The remaining cases, many of them in IPV vaccinees, sapped confidence in the vaccine and caused its replacement by OPV.[203,263] The last cases of indigenously acquired wild-type paralytic poliomyelitis in the United States occurred in 1979 among unvaccinated Amish children in Pennsylvania, Missouri, Iowa, and Wisconsin. The evolution in polio vaccine policy in the United States is summarized in Table 27-15. Opinion gradually shifted away from OPV and toward IPV, but with the preference for a combination vaccine. Although a combination vaccine containing IPV was not licensed at that time, IPV was reintroduced into recommended use in the United States in its enhanced-potency form in 1997 as part of a sequential schedule consisting of two doses of IPV at 2 and 4 months of age, followed by two doses of OPV at 12 to 18 months and 4 to 6 years of age.[284] VAPP cases immediately decreased to three in 1997 and one in 1998. All of these cases occurred in children whose physicians had elected to start immunization with OPV rather than the recommended IPV. Three years later, in 2000, the United States chose four doses of IPV as the recommended regimen.[261,262] The primary reason for the reintroduction of IPV in the United States was the perception that polio was vanishing from the world, whereas paralysis associated with OPV was exacting an average yearly toll of 8 cases.[263,268,285,286] Before the switch occurred, concern was expressed that the use of stand-alone IPV vaccine might decrease immunization rates because of the necessity of additional injections. However, this was not the case, and immunization rates were unaffected by the change to partial and then complete IPV schedules.[59,287–289]

Mexico (since 2007) and Costa Rica (since 2010) have relied on the use of IPV, contained in a pentavalent aP-IPV combination vaccine, with continuation of SIAs with OPV twice a year in Mexico.

Table 27-15 Steps in US Decisions Regarding Polio Vaccination

1955	Historical IPV licensed
1961	Polio outbreak shows partial effectiveness of IPV; epidemiologic data show that IPV does not completely prevent poliovirus circulation
1963	tOPV licensed, replaces IPV as recommended vaccine
1964	Surgeon General's committee concludes that 57 cases of VAPP occurred between 1961 and 1964 (reversion to virulence first recognized in 1955)
1970s	Van Wezel and Cohen at RIVM improve manufacturing processes of IPV
1977	IOM report recommends OPV for children, IPV for adults
1978	Institut Mérieux develop technologies for manufacturing IPV in Vero cells; monkey cells no longer needed
1988	IOM report recommends staying with OPV until IPV combination available or 90% coverage reached
1995	IOM workshop recommends moving toward IPV
1997	Sequential schedule adopted by ACIP
1999	ACIP recommends sequential schedule or all IPV; OPV alone not recommended
2000	IPV only schedule recommended

ACIP, Advisory Committee on Immunization Practices; IOM, Institute of Medicine; IPV, inactivated poliovirus vaccine; OPV, oral poliovirus vaccine; RIVM, Rijksinstituut Voor Volksgezondheid en Milieu; VAPP, vaccine-associated paralytic poliomyelitis.

Eastern Mediterranean region

Israel has used both polio vaccines in an attempt to solve their particular epidemiologic situation in which two communities that live close together have different hygienic conditions and levels of vaccination coverage. After a brief experience with IPV, Israel started routine OPV vaccination in 1960. Vaccination coverage reached high levels among both Jewish and Arab children. Nevertheless, sporadic poliomyelitis continued among Jews, and small epidemics continued to occur in the West Bank and Gaza.[290–294] In view of the failure of OPV to control polio, in 1978 the Israelis introduced a combined mixed schedule: OPV was administered at 1, 2.5, 4, 5.5, and 12 months of age, and IPV (as a DTwP-IPV vaccine) was given at 2.5 and 4 months of age. For a time in the 1980s, there were no cases in Israel proper and only sporadic cases in the Palestinian areas.[290–292] All was well until 1988, when an epidemic of 15 cases of type 1 polio occurred in Israel[294] localized in one of two districts that had adopted IPV vaccination of infants. Although the analysis of this epidemic is controversial, it is clear that antibody responses to OPV were suboptimal among Israeli young adults, resulting in a low level of resistance. Conversely, the wild virus may have circulated among infants immunized with IPV only, allowing spread to their parents. The response to the epidemic included mass vaccination with OPV and the institution of three doses of DTP-IPV in the routine vaccination scheme together with four simultaneous doses of OPV.[294] Since 1988, no cases of polio have been reported in Israel or its territories, despite an outbreak in neighboring Jordan from 1991 to 1992 that caused wild virus circulation in Gaza.[293]

Western Pacific region

Since 2007, an IPV introduction program has been put in place in the entire Yogyakarta province of Indonesia, and IPV is the exclusive EPI vaccine used. Polioviruses were only isolated a few times in sewage samples after the switch to IPV, but some challenges in the environmental sampling occurred.[295] Seroprevalence/seroconversion surveys and vaccination coverage evaluations have not yet been reported.

Australia and New Zealand are now using IPV-containing acellular pertussis combinations based on a cost analysis showing that the introduction of IPV in a combination vaccine costing $10 or less is cost-effective.[296]

Rationale for the use of IPV

Since the early 1960s, the well-recorded vaccinology controversy is the choice of IPV or OPV for routine vaccination in infancy. Table 27-16 summarizes the advantages and disadvantages of IPV-only, OPV-only, or mixed and sequential IPV/OPV schedules.[264] In essence, the key arguments for IPV usage are safety (no VAPP and no induction of VDPVs), predictable and consistent immunogenicity, and the possibility of its inclusion in combination vaccines. The key arguments for OPV usage are induction of better mucosal intestinal immunity, ease of administration to large populations, and low cost. The argument for a mixed schedule is to fuse the immunogenicity advantages of each vaccine with less or null risk of VAPP when IPV is started first.

VAPP, which is discussed in detail in Chapter 28, is an inescapable phenomenon that has been consistently observed with OPV.[307,308] In our view, the following circumstances should lead to the choice of IPV for routine vaccination of infants in a particular country:

- Absence of paralytic polio and likelihood that wild polioviruses are no longer circulating. This criterion applies to countries where eradication of polio has been certified, even if importation is possible by migrants.
- High vaccination coverage with routine DTP, equivalent to 90% or better in infants and children, so that introduction of wild virus is unlikely to result in spread.
- Ability of the medical systems or of vaccinees to afford the costs of IPV-containing vaccines, although the cost issue is not straightforward, particularly when a full pharmacoeconomical cost-effectiveness analysis is made, including the cost of National Immunization Days with OPV.

A dose of OPV costs $0.13 to $0.14 for UNICEF or for other types of public markets, whereas a dose of IPV stand-alone costs €2.5, but this price may be unduly high because volume orders are low. In private markets, the price of stand-alone IPV vaccines and IPV-containing combination vaccines vary widely, depending on the type of markets and the type of vaccine used (the IPV-containing combinations representing the vast majority of volumes distributed), and prices start at several US dollars. Public sector prices also vary considerably depending on the type of market, volume purchased, and contract conditions. However, given the right conditions, the prices of IPV-containing combination vaccines (today

Table 27-16 Advantages and Disadvantages of All-OPV, All-IPV, or IPV/OPV Mixed Vaccination Schedules

Feature	All OPV	All IPV	IPV/OPV
VAPP	1 case per 250,000 to 800,000 following first vaccinations*	No cases	Estimated reduction of 50-100% in VAPP cases
Safety (other than VAPP and VDPV)	Excellent	Excellent	Excellent
Systemic immunity	Good	Good	Good
Intestinal immunity	Excellent	Shorter excretion and reduced titers in excreta after challenge Transmission impact variable	Excellent
Oropharyngeal immunity	Excellent	Excellent	Excellent
Efficacy	Excellent	Excellent	Excellent
Transmission to contacts and secondary vaccination	Yes	No	Some
Extra injections	No	Yes if standalone No if part of combination vaccine	Same as for all IPV
Reduced compliance	No	Possible if stand-alone vaccine	Possible if stand-alone vaccine
Availability of combinations	None	Yes	Yes
Cost	Low	Higher, although price difference depends on volume, use of combinations	Intermediate

*WHO estimate is between 1/250,000 and 1/800,000 first OPV doses. From WHO. Wkly Epidemiol Rec 86:205-220, 2011.
IPV, inactivated polio vaccine; OPV, oral poliovirus vaccine; VAPP, vaccine-associated paralytic polio; VDPV, vaccine-derived polioviruses.

all of them are acellular pertussis combination vaccines) could be in the $5 to $8 per dose range. If the IPV-containing combinations were based on whole-cell pertussis rather than acellular pertussis vaccines and ideally manufactured from non-Western manufacturing units with lower manufacturing cost structures, the prices would be lower. Although these prices per dose are greater than the price of OPV, the human and financial costs of VAPP and VDPV, the high amount of wastage of OPV, and the cost of keeping the oral vaccine frozen must be taken into account. An analysis commissioned by the Bill and Melinda Gates Foundation[297] concluded that if requested, current manufacturers could supply IPV for all the world's children, although several years would be required for ramping up. The report also estimated that this level of production could lower the price per dose to between $0.50 and $2.00. However, the price of IPV in combination vaccines was not calculated. These prices are still substantially higher than the cost of OPV and WHO is undertaking efforts to bring them down to those of a course of OPV (see the following section). Khan[298] concluded that if the risk of recrudescence of wild or vaccine strain polio is taken into account, the cost of IPV replacement of OPV would be less than continued use of OPV.

In the scope of its Global Polio Eradication Initiative Strategic Plan 2010-2012, WHO has actively engaged in promoting research and development activities toward the emergence of affordable IPV solutions. The major focus for IPV research has been on its use post wild poliovirus circulation eradication when OPV use must stop because of the potential for cVDPVs, although research on possible pre-eradication IPV vaccination has also been conducted. The hope for post-eradication IPV use is to minimize the risks of reintroduction and spread of polioviruses as cVDPVs, or through laboratory containment breaks, spread from chronic immune-deficient poliovirus shedders, and even the potential for reintroduction of polioviruses as part of bioterrorism. By assuring continuing population immunity through IPV, those risks could be markedly reduced. The Polio Research Committee,[301] the polio working group of the WHO Strategic Advisory Group of Experts,[299] and the Independent Monitoring Board[302] are regularly reviewing progress made from a multipronged approach. This approach includes developing a better understanding of the role that can be played by IPV in boosting immune responses, particularly intestinal immunity in populations shown to be poorly responsive to OPV, to the development of new IPV vaccines, or to new ways of using existing vaccines. The "low-dose" option consisting of the use of the ID intradermal route (described above), or of one-dose IPV regimen followed by one or more OPV ("light" mixed sequential schedule), or of two-dose IPV-only regimen is being explored (see "Immune responses"). The use of classical (aluminum salts) or new (squalene-based emulsions or other) adjuvants aimed at reducing the amount of antigen is also under active investigation. The most advanced option is the use of the Sabin strains allowing potential new manufacturers, particularly those in the developing world who may be able to produce vaccine more cheaply, to play a role in IPV supply (see "IPV manufactured from Sabin strains"). Finally, the development of new and alternate poliovirus seed strains usable for IPV manufacturing based on stabilized Sabin-like strains or on more innovative options based on the use of noninfectious genetic material transfected in expression systems is under investigation.

The most recent position of WHO[300] is that "The national choice of vaccines and vaccination schedules during the pre-eradication period must include OPV or IPV, or a combination of both, and should be based on assessments of the probabilities and consequences of wild poliovirus importation". However, WHO notes that after eradication, use of OPV will have to stop and the vaccine may become unavailable.

The criteria for adopting mixed sequential schedules beginning with IPV and ending with OPV are the same, but with the addition of a public health policy factor: the desire to prevent polio by all possible means, taking advantage of both vaccines but also eliminating VAPP.[309,310]

Role of IPV in poliomyelitis eradication

The role of IPV in facilitating eradication and its verification is much disputed, ranging from no role at all[304,321] to complete substitution of IPV for OPV.[322]

Continuous wild poliovirus circulation has been eradicated from several of the WHO regions, but isolated importations of polioviruses have occurred in some of them, such as in Russia[323] recently and may continue to occur.

The principal weapon in the eradication efforts has been OPV, given in national campaigns, although the same goal was achieved in many European countries using IPV. OPV campaigns are also having a marked impact on the incidence of polio in traditionally endemic areas, such as the Indian subcontinent and Africa.[311] However, confidence in the feasibility of eradication has wavered.[312] First, because in 2003 false journalistic rumors concerning HIV and estrogen contamination of OPV caused cessation of vaccination in Nigeria, which subsequently led to poliovirus circulation and spread to 18 countries;[313] second, because the phenomenon of epidemics due to VDPV attributable to extensive mutation and recombination after circulation was recognized;[314] and third, because the costs of the program began to cause donor fatigue. Although successful elimination of wild polio in India has been made with a never before attained low level of polio incidence at the end of 2011,[306] some Indian scientists have been particularly vociferous in calling for greater use of IPV.[315-317] The viewpoint of the WHO is that only OPV should be used as the principal tool for eradicating polio in developing countries.[303,304] However, John,[305] working in Southern India, showed that IPV can be highly effective in preventing polio without the problems of OPV (VAPP and the need for repeated administration to obtain uniform seroconversion). Nevertheless, India may have eradicated polio using an OPV-only approach. As of May 2012, only one case of acute flaccid paralysis due to wild poliovirus had been reported in India during 2011, a case in West Bengal, with onset in January.[306] The WHO recognizes that there may be as many as 500 VAPP cases per year throughout the world,[318] that VDPV has become a real threat to eradication,[319] and that monovalent and bivalent OPVs are needed to increase efficacy.[320]

Various strategies for the "endgame" have been suggested. The stated strategy of WHO is to stop using OPV once eradication has been certified.[313] WHO advisory groups are now deliberating on what the role of IPV should be post-eradication. It is likely that at a minimum, IPV will be used in all countries that manufacture IPV, and it is also likely that IPV will be made available to other countries that wish to use it. What is more controversial is whether IPV will be recommended for all countries or if it will be left to individual countries to make their own choices. The risk for countries that do not use IPV is the potential for late recognition of a return of polioviruses. Since so many infections are subclinical, by the time cases would be recognized, it could be very difficult to contain, particularly if underlying population immunity is 0% among cohorts born since the stoppage of OPV. This strategy involves simply observing for poliovirus circulation and for cases of poliovirus-induced paralysis in the absence of vaccination and then reintroducing monovalent OPV to contain any outbreaks that are detected.[324,325] Moreover, reports of immunosuppressed individuals who excrete poliovirus for long periods of time[328] raise the specter of reintroduction of the virus.

A second strategy would be to continue OPV vaccination while attempting to detect circulating wild poliovirus, but today the difficulty would be in detecting the wild virus in a sea of excreted attenuated viruses, some mutated toward virulence and some recombinants with other polioviruses.[326,327] VAPP would continue to occur, so paralysis caused by polioviruses would not be truly eradicated. Even more concern has been generated by the realization that revertants of Sabin strains became epidemic in Egypt, Haiti, the Dominican Republic, Madagascar, China, and the Philippines, although with the exception of Nigeria recently, most of these outbreaks were quite small regarding the number of cases they caused.[314,320,329,330] On the other hand, the Nigerian outbreak of cVDPVs indicates the potential these viruses have for regaining the full neurovirulence and transmissibility characteristics of wild viruses.

A third strategy could be proposed, consisting of a gradual switch from OPV to combined pediatric vaccines containing IPV (eg, DTP/Hib/hepatitis B/IPV) as wild poliovirus disappears from more and more countries. Vaccination with IPV would facilitate the search for polioviruses in the environment, because screening would not be obscured by OPV vaccine strains and yet protection against polio would be maintained. Such a strategy may be all the more valuable because it has been calculated that, even after a 5-year period without polio cases, there is still a 0.1% to 1.0% probability of silent transmission.[331]

Also, under active consideration, is simultaneous OPV/IPV use in mass vaccination campaigns in high risk areas to maximize immunity induction per child contact. The issue is whether coverage with an injectable vaccine used under a campaign mode can be high enough to get the improved population immunity or whether decrease in coverage would outweigh any benefits of increased immunity of using both vaccines simultaneously. The potential role of IPV in the tOPV-to-bOPV switch under active consideration, because WPV2 seems to have been eradicated, is worth mentioning. An advantage of IPV would be providing continuing type 2 immunity to prevent re-emergence of type 2 wild viruses or cVDPVs and in boosting immunity against types 1 and 3, which could hasten eradication of those two types.

The results of the IPV introduction program in the Yogyakarta province in the Philippines in place since 2007 illustrates the impact of an OPV-to-IPV switch strategy. Since the adoption of an IPV stand-alone vaccine (with a 3+1 regimen) in September 2007 in a population of 3,571,865 with an annual birth cohort of 52,723, no drop in vaccination coverage rates during 4 consecutive years of follow up (remained > 95%) has been observed. Environmental sampling (inlet sewage) confirmed the maintenance of absence of WPV circulation, and a very rapid decrease of isolated polioviruses with only 5 samples with Sabin-like and no VDPVs (with the caveat that 24 months out of the 55 month period of follow up were missed). Finally, seroprevalence and dose 3-to-dose 4 seroconversion survey done on 188 infants revealed 100% seroprotection post-dose 3 and increase in GMT from dose 3 to dose 4.

It is evident that high-income and many middle-income countries are already using or will soon switch to IPV, principally to avoid sporadic or epidemic VAPP associated with the use of OPV. Some of the more affluent developing countries will also avail themselves of IPV. In view of the possible use of poliovirus as a biologic warfare weapon, many countries will continue to use IPV even if eradication of wild virus circulation is achieved.[332] Developing countries may also be loathe to risk resurgence of polio if OPV immunization is stopped as a result of uncertainties concerning persistent circulation of wild or revertant vaccine viruses in normal and immunosuppressed individuals.[333,334]

The principal arguments offered against conversion from OPV to IPV in many low-income developing countries are cost, origin of vaccine supply, and decreased intestinal immunity.[335] To some extent the first two points are related because large production volumes reduce costs of manufacturing and of quality controls and allow better planning, but put all the cards in the hands of a limited number of players. So far, companies had no incentive to produce more IPV. However, the more cogent response to cost is that IPV should not be used as a stand-alone vaccine with the attendant expenses of separate administration, but as part of a combination vaccine instead.[336] Combinations containing IPV based on diphtheria-tetanus-acellular pertussis vaccines are readily available, but the key missing product is a

truly affordable pentavalent or hexavalent combination probably made on a whole-cell pertussis DTP backbone (assuming that the pharmaceutical technical challenges around the effect of preservatives in multidose presentations are solved). If there were a demand (remember the oft-stated desire to bring new vaccines to the EPI schedule), the cost of IPV would be negligible as part of such affordable DTP-based combinations. But in this context, the key driver for future IPV performance will be the coverage rate achieved through routine immunization. The question of the value of the community protection induced by IPV in a context of vaccination coverage rates ranging from 50% to 80% still needs to be clarified. If the only way to raise this vaccination coverage would be through National Immunization Days with OPV, then the added value of IPV usage might be more difficult to prove.

An annual production of between 200 and 300 million doses of IPV is feasible in the immediate future. To reduce the need for a larger supply, the use of IPV in developing countries could be targeted to countries or regions of countries surrounding areas where poliovirus is supposedly eliminated; thus the appearance of the virus could be recognized by isolation from excreta rather than by outbreaks of paralysis.

Although OPV vaccination must be continued in countries where wild-type polioviruses still circulate or in countries at substantial risk of suffering from reintroduction of wild-type polioviruses, other countries with high vaccination coverage and where there is an absent wild-type poliovirus circulation or moderate reintroduction risks should consider switching to sequential IPV/OPV schedules or to IPV alone. Moreover, countries that discontinue OPV after putative eradication of wild poliovirus should consider adding IPV to their vaccination schedules to protect their populations against reintroduction of polioviruses.

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SHORT COMMUNICATION

IPV-Vero Vaccine Induces a Strong Booster Reaction and is Well Tolerated in Adults

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A phase 1–2 trial was conducted in 48 adults to study safety and immunogenicity of an inactivated poliovirus vaccine produced using Vero cells (IPV-Vero). Participants received 2 intramuscular injections with IPV-Vero (40-8-32 D-Ag units) 4 weeks apart. IPV-Vero was well tolerated, and induced strong antibody responses in all participants. At least an 8-fold titre rise against all 3 types of poliovirus was found within 1 week of the first vaccination, indicating a strong secondary response in primed individuals. Two days after the first vaccination, there was no indication for such a booster reaction. The second vaccination 4 weeks after the first dose did not further increase antibody levels, indicating that an immune plateau had been achieved after the first vaccination. The second vaccination was not reactogenic despite the presence of these high pre-vaccination antibody levels. We conclude that IPV-Vero is well tolerated and strongly immunogenic in adults. In pre-immune adults 1 dose is enough to induce an impressive booster reaction.

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INTRODUCTION

Inactivated poliovirus vaccine (IPV) has an excellent and long-standing record of safety and efficacy. Its persistent immunogenicity correlates with excellent individual protection against poliomyelitis, as shown in several European countries, including The Netherlands and Sweden. Endemic poliomyelitis disappeared after introduction of trivalent IPV in national immunization programmes and more than 95% of the vaccinated population have high and persistent levels of poliovirus (PV) neutralizing antibodies (1–3). In The Netherlands, the most recent epidemics (in 1978 and 1992–93) occurred in small communities of people who had rejected vaccinations for religious reasons and are attributed to their choice not to vaccinate rather than to vaccine failure (4).

For the Netherlands vaccination programme, our institute (RIVM) supplies quadruple DPT-IPV and triple DT-IPV vaccine. Currently, the IPV component is produced using monkey kidney (MK) cells for virus culture (5). RIVM explored another cell substrate in which PV can be propagated effectively on a large scale. Vero cells, also derived from monkey kidneys, have advantages over MK cells. They are reliable and cheap, better standardized, have a smaller risk of being contaminated than monkeys and their kidney cells and further use of primates for virus propagation is unnecessary. Vero cells are widely used by others for production of live and killed viral vaccines (OPV, IPV and rabies) (6). IPV produced on Vero cells (IPV-Vero) is considered safe and potent, as reviewed by Vidor et al. (7).

The present study in adults was the first in a series to investigate the safety and antibody response to IPV-Vero. Further studies in infants to compare the immunogenicity of IPV-Vero and IPV-MK are ongoing.

MATERIALS AND METHODS

Vaccine

IPV-Vero (lot E9433B) was produced using standard methods (5), and contained per dose of 0.5 ml: formalin-inactivated poliovirus (strains Mahoney, MEF-1 and Saukett), type 1, 2 and 3: 40-8-32 D-antigen units respectively, and formaldehyde: 0.025 mg in phosphate buffer. The vaccine was injected in the deltoid or triceps muscle.

Study

This combined phase 1–2 study was descriptive and without control vaccine. The study has been approved by the Medical Ethical Review Board of the University Hospital Utrecht, and was performed between November 1994 and February 1995, at the Department of Intensive Care and Clinical Toxicology of the University Hospital Utrecht, The Netherlands.

Volunteers were recruited by advertisements in the "Utrecht University Weekly" magazine on University bulletin boards and by mailing volunteers from former clinical trials. Thus, most volunteers were students. After screening for inclusion and exclusion criteria, participants gave written informed consent.

Vaccinations were given at day 0 and 28. Venous blood samples for antibody determinations were taken at day 0, 2, 7, 28 and 56 from the first vaccination. Reactogenicity was assessed at days 0, 2, 7, 28, 30 and 56.

Antibody response

Serum neutralizing (SN) antibody levels were determined with Vero cells as indicator cells, and wild PV strains for challenge (8), the same strains as used for vaccine production. After inactivation, sera were investigated in a 2-fold dilution series up to 17 dilution steps. SN activity is expressed as 2 log reciprocal titres (e.g. 5 means $1/32 = 2^{-5}$). For statistical comparison of antibody levels the Kruskall-Wallis test was used, with EpiInfo (9).

Adverse events

After vaccination, volunteers were observed for 1 h for heart rate, blood pressure and temperature. Temperatures were measured orally at days 0, 2, 28, and 30. Local and systemic symptoms were studied by observation and questionnaires. The injection site was examined for inflammatory symptoms.

Participants kept a diary about their well-being and possible adverse experiences, for discussion at subsequent visits, at which the participant was asked for general well-being, inability to perform normal daily activities, headache, gastrointestinal complaints, joint complaints and skin abnormalities.

Reactions were graded according to severity. A mild reaction was perceived by the participant but was easily tolerated. A moderate reaction was giving enough discomfort to interfere with normal daily activities.

RESULTS

Study population

A total of 48 volunteers were enrolled and 47 completed the study (18 males and 30 females; mean age 23.5 y, range 18–39 y). One participant was excluded during the study due to protocol violation, from another the 2 last blood samples were excluded due to an insufficient interval between vaccinations.

Antibody response

The results of immunogenicity are summarised in Table I. Cumulative distributions of SN titres are shown in Fig. 1. Not unexpectedly, all participants had detectable antibodies before vaccination. A titre of ≥ 3 (1/8 or higher) is considered to be protective. To PV type 3 (PV3) an SN titre below 3 was found in only 3 individuals and to PV1 and PV2 all had initial titres ≥ 3.

Two days after the first vaccination there was little difference from pre-vaccination titres. However, after 7

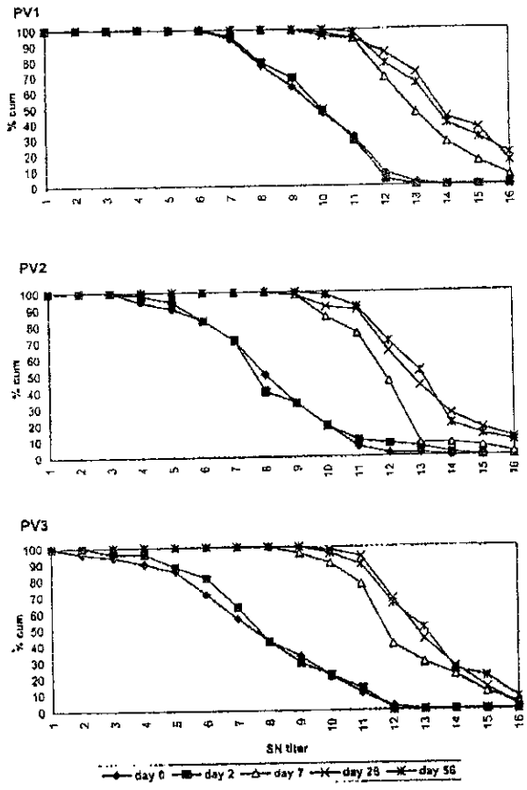

Fig. 1. Poliovirus neutralizing antibody response to IPV-Vero vaccine. The percentage reverse cumulative frequency of serum neutralizing titres is given per poliovirus serotype. Vaccinations were given on days 0 and 28 and blood samples were taken on days 0, 2, 7, 28 and 56.

Table I. *Summary of serum neutralizing antibody response to IPV-Vero in adults, vaccinated on day 0 and day 28*

		Day 0		Day 2		Day 7		Day 28		Day 56
PV1										
	% ≥1/8	100		100		100		100		100
	gmt	9.3	ns	9.3	*	12.5	ns	13.4	ns	13.3
	SD	1.8		1.7		1.7		1.9		1.8
PV2										
	% ≥1/8	100		100		100		100		100
	gmt	7.5	ns	7.6	*	11.6	ns	12.4	ns	12.5
	SD	2.2		2.4		1.8		2.0		1.7
PV3										
	% ≥1/8	93.8		95.8		100		100		100
	gmt	7.0	ns	7.3	*	11.7	ns	12.4	ns	12.5
	SD	2.7		2.3		2.0		1.6		1.8
	n =	48		48		48		47		46

gmt, geometrical mean titre and SD, standard deviation are expressed as a 2 log reciprocal titre (e.g. 5 means $1/32 = 2^{-5}$). Titre differences for successive examination days (day 2 vs day 0, etc.) were evaluated for statistical significance using the Kruskall-Wallis test.

* $p < 0.000001$.

ns, $p > 0.01$.

Table II. *Adverse events after IPV-Vero at day 0 and day 28 in adults (n = 47)*

(a) General symptoms	#1			#2		
Day of examination	0	2	7	28	30	56
General well-being	0	0	0	0	0	0
Normal daily activities	0	1	0	0	0	0
Headache	0	1	0	1	1	0
Gastrointestinal complaints	1[a]	1[a]	1[a]	1[a]	2[a]	0
Joint complaints	0	0	0	0	0	0
Skin abnormalities	0	1	0	0	1	0
Any general symptom	1	4	1	1	4	0
(b) Local symptoms	#1			#2		
Day of examination	0	2	7	28	30	56
Redness	5	0	0	10	0	0
Swelling	1	0	0	0	0	0
Itching	0	0	0	0	1	0
Warmth	0	0	0	0	0	0
Pain	0	2	0	0	5	1
Muscle stiffness	1	35	0	1	14	0
Any local symptom[b]	6	36	0	11	18	1

All local symptoms were of mild intensity. All general symptoms were mild except in one participant (underlined) who had a moderate headache.

[a] All occurring in one volunteer, and regarded as not causally related to vaccination.

[b] Some participants had more than one symptom.

days all participants showed at least an 8-fold (3 titre steps) increase for PV1 antibodies, and a more than 16-fold (> 4 titre steps) increase for PV 2 and 3. This was also found in the 3 individuals with 'non-protective' pre-titres: they showed in 7 days strong booster reactions, from 1–10, 2–13 and 1–14, respectively. Apparently, these individuals had excellent immunological memory.

The second vaccination added little to the SN titres which had been reinforced by the first vaccination in these pre-immune participants. Maximal immunity has already been achieved within 1 week of the first vaccination.

Adverse events

The results regarding safety are summarised in Table II. Severe and acute reactions did not occur. The highest recorded temperature was 37.6°C, recorded twice out of 564 measurements. General symptoms were reported by 5 subjects (11%) and local reactions (mainly muscle stiffness) by 42 (89%). The reactions encountered were mild in intensity. Only 1 participant complained of headache with moderate intensity.

Notably, reactions were also very mild after the second vaccination, if they occurred at all, even while all participants had high antibody titres at that time. Arthus reactions did not occur.

DISCUSSION

In this evaluation of the effects of IPV-Vero vaccination very strong antibody responses were observed in all participants. At least 8-fold titre rises against all 3 types of poliovirus occurred within 1 week of the first vaccination, indicating a strong secondary response in already primed individuals. Two days after the first vaccination there was not yet any indication of the booster reaction. The second vaccination after 4 weeks did not further increase the level of antibodies, indicating that an immune plateau had been reached already after the first dose. The strong antibody reaction is not surprising because participants were from the generation of the Dutch population in which more than 90% have received at least 3 childhood vaccinations against poliomyelitis, which is reflected by a high antibody prevalence in this age group (2) and high prevaccination antibody levels among the participants. Therefore, adults are not suitable to investigate a primary antibody response; studies in infants are ongoing.

The vaccine under study is very similar to the IPV-MK currently used in the Netherlands. The only difference is the cell substrate for virus propagation. Biochemical and immunochemical parameters, and *in vivo* potency in rats indicate immunogenic properties equivalent to IPV-MK. It has been clearly demonstrated that immunogenicity in humans correlates with the concentration of D-antigen in the vaccine (10, 11). The optimal dose of trivalent IPV contains 40-8-32 D-Ag units of the 3 types of poliovirus, respectively, which has been determined with IPV-MK in extensive investigations in several countries, both as IPV and as combined DPT-IPV (10–16). The serological response to IPV-Vero was expected to be similar. In this study, the current 40-8-32 D-Ag content per dose appeared very strong indeed. Although a formal comparison with immunogenicity

of RIVM IPV-MK was not done, we regard the 40-8-32 D-Ag content, similar to Vero-produced IPV from another manufacturer (7), appropriate for use in adults. Studies comparing IPV-Vero and IPV-MK are ongoing.

The 2-dose schedule used here is mainly chosen to study safety aspects. The presence of high pre-vaccination antibody titres did not augment the prevalence of adverse reactions after the second dose. Arthus reactions may occur in hyper-immune persons after vaccination with diphtheria and or tetanus toxoids, but may be also associated with impurities of such vaccines given repeatedly (17). Such reactions are caused by immune-complex formation between the vaccine antigen and high levels of the corresponding antibodies, but we did not encounter them. Compared with toxoids, the amount of protein in IPV is much lower, and its purity better. The vaccine is therefore useful for the rapid induction of immunity, with a low occurrence of side-effects and without the possibility of spreading vaccine virus (as oral polio vaccine does). This makes IPV suitable for use during epidemics, e.g. in hospitals, both for personnel and polio-non-immune patients.

We conclude that IPV-Vero is a well-tolerated and potent immunogenic vaccine in adults. In pre-immune adults 1 dose is enough to induce an impressive booster reaction.

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ANTIGEN CONTENT OF INACTIVATED POLIOVIRUS VACCINE FOR USE IN A ONE- OR TWO-DOSE REGIMEN *

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ABSTRACT

The immunologic response to inactivated poliovirus vaccine following one and two doses has been studied in infants in developing and developed countries using vaccine prepared at the Rijks Instituut voor de Volksgezondheit, The Netherlands. Virus was grown in microcarrier cultures of monkey kidney cells, purified, concentrated, and inactivated with formalin. The vaccines used contained different quantities of D-antigen units for each of the three types. The data reveal that both antibody and immunologic memory (booster-type responsiveness) were induced in virtually all individuals following a single dose of a sufficient quantity of antigen. Immunologic memory was readily revealed by the booster-type response following a second dose given six months after the first. The degree of booster-type response to a second dose is linked primarily to the quantity of antigen used for primary immunization, and secondarily to the quantity of antigen used for the booster dose.

The data base is presented for formulating the antigen content of an inactivated poliovirus vaccine that can be relied upon to be protective after the first dose when given alone or when incorporated with combinations of other antigens (diphtheria-pertussis-tetanus) that may require two or more doses.

KEY WORDS: INACTIVATED POLIOVIRUS VACCINE; ANTIGEN CONTENT

There is a need, especially in developing countries, for a vaccine against poliomyelitis that can be relied upon to be protective after the first dose, either when given alone or when combined with other antigens (e.g., DPT) that may require two or more doses (1). For the purpose of establishing the quantity of inactivated poliovirus antigens for a trivalent vaccine that would produce such an effect, a series of serological studies in infants was initiated in 1977 in developing and developed countries (2).

Experimental inactivated poliovirus vaccines (IPV) for this purpose containing different quantities of poliovirus D-antigen units for each of the three types, were prepared at the Rijks Instituut voor de Volksgezondheid (RIV), The Netherlands, using virus propagated in microcarrier cultures of monkey kidney cells, purified, concentrated, and inactivated with formalin (3). In some of the studies vaccines prepared in other laboratories were included for comparison.

A summary of the results of the first study (2), which was carried out in Mali in 1977—78, is shown in Fig. 1. This figure reveals the percent of infants (4—7 months of age, in groups of 25—34), with antibody titers of 1 : 4 or greater one month following a single dose of vaccines containing the different quantities of D-antigen units indicated on the abcissa, graded in four-fold steps (i.e., 320 to 5

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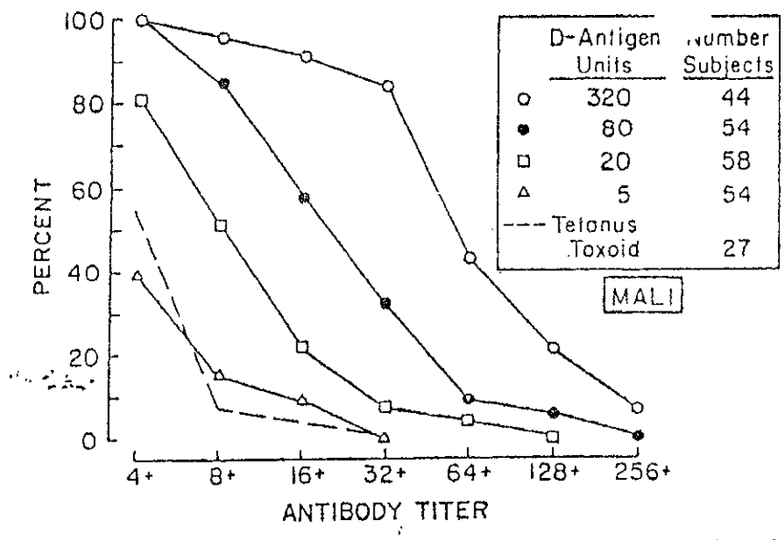

Fig. 2. Mali inactivated poliovirus vaccine study. Cumulative percent distribution of type 1 poliovirus antibody titers one month after one dose of vaccines with different D-antigen unit content per dose. Vaccines prepared by Rijks Instituut voor de Volksgezondheid. (Reprinted courtesy of S. Karger, Basel) (4).

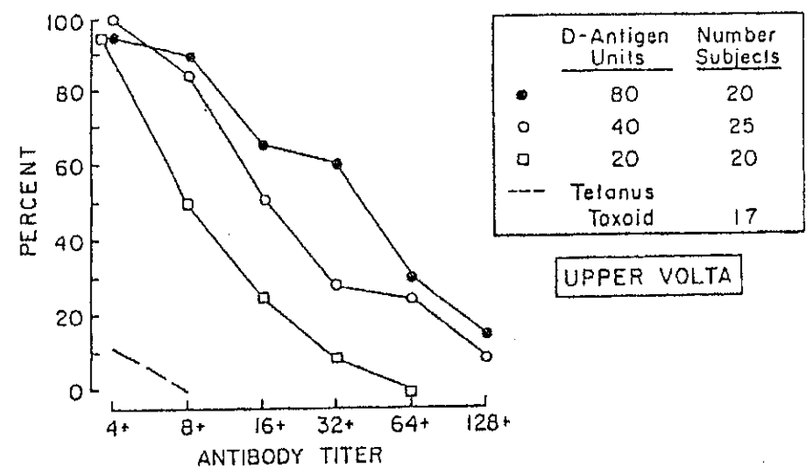

Fig. 3. Upper Volta inactivated poliovirus vaccine study. Cumulative percent distribution of type 1 poliovirus antibody titers one month after one dose of vaccines with different D-antigen unit content per dose. Vaccines prepared by Rijks Instituut voor de Volksgezondheid. (Reprinted courtesy of S. Karger, Basel) (4).

group was divided into two parts. The first (approximately 50—60 %) received a uniform dose of the RIV vaccine containing 40-4-16 D-antigen units for types 1, 2, and 3, respectively. The second group received the same vaccine for the second dose as for the first. In all groups a blood sample was collected one month after the second dose.

Fig. 4a shows the distribution of type 1 antibody prevaccination, one month post first, and one month post the second dose in the groups given the three different RIV vaccines containing 80, 40, and 20 D-antigen units, respectively, for both the first and the second doses.

It is clear that more than 90 % have detectable antibody to type 1 after the first dose and the levels of antibody attained are in proportion to the D-antigen content of the vaccines. It is also clear that after the second dose a striking booster effect is observed. The same pattern is seen for type 2 in Fig. 4b

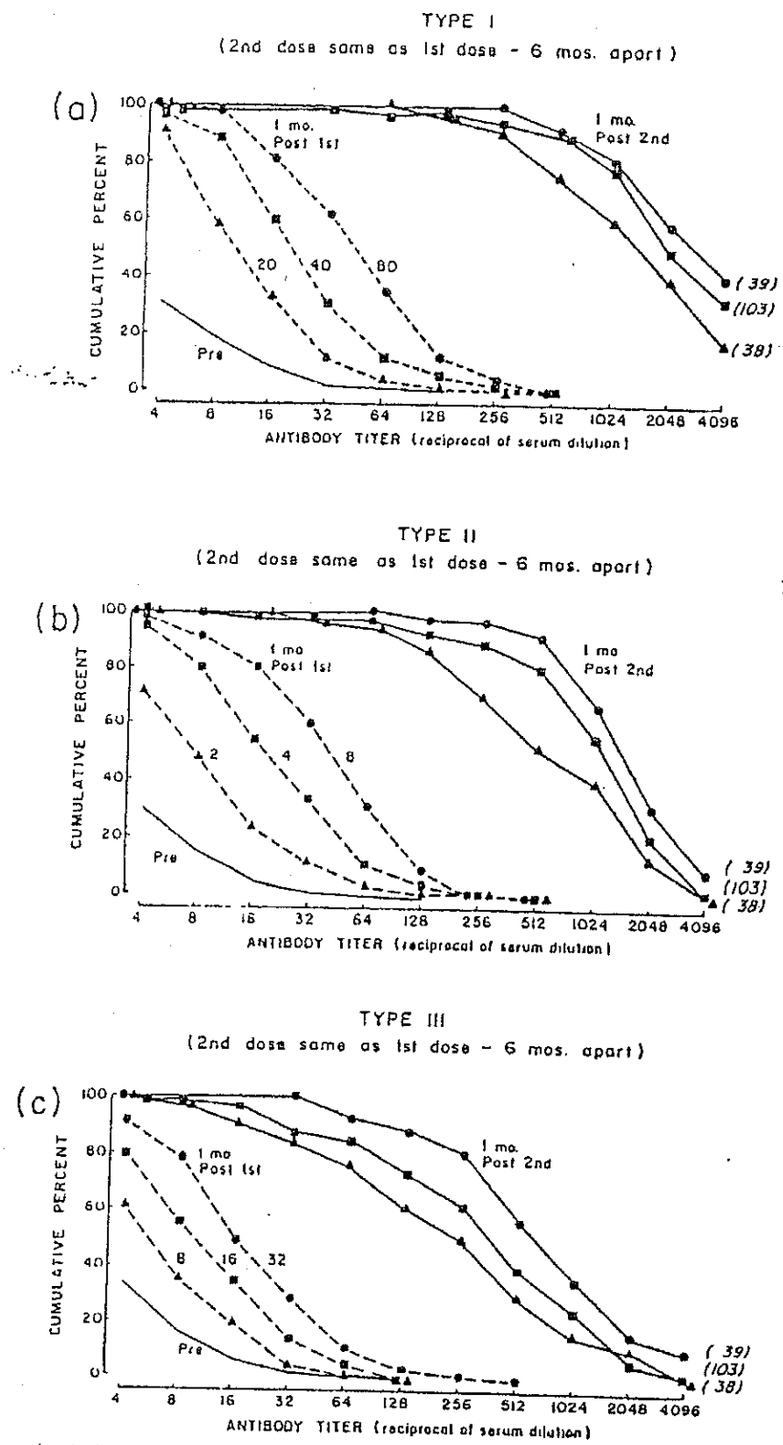

Fig. 4. Finland inactivated poliovirus vaccine study. Cumulative distribution of polio antibody titers one month after a first dose and one month after a second dose (administered six months after the first dose) of vaccines containing: (a), 20, 40, or 80 D-antigen units for type 1; (b) 2, 4, or 8 D-antigen units for type 2; and (c) 8, 16, or 32 D-antigen units for type 3. Vaccines prepared by Rijks Instituut voor de Volksgezondheid.

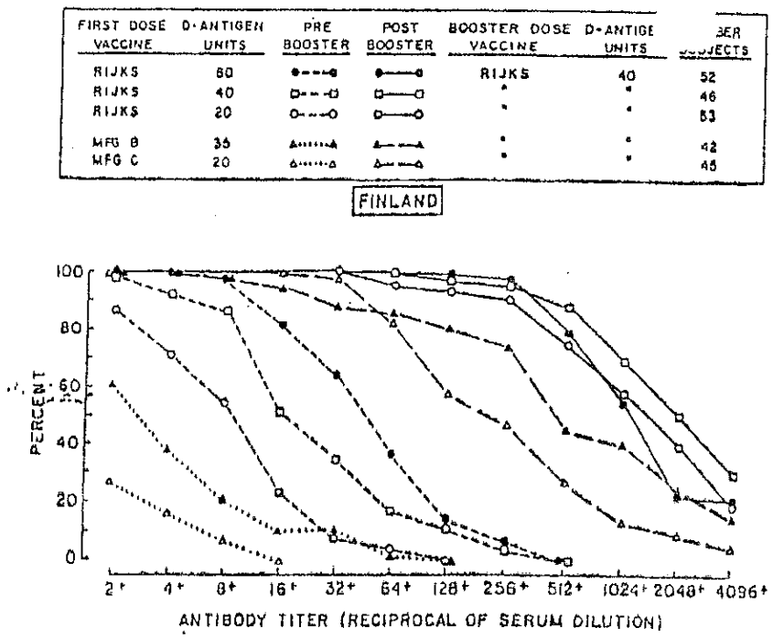

Fig. 6. Finland inactivated poliovirus vaccine study. Cumulative percent distribution of type 1 poliovirus antibody titers before and after a booster dose administered six months after a first dose of Rijks Instituut voor de Volksgezondheid (RIJKS) vaccines and manufacturers (MFG) B and C vaccines. (Reprinted courtesy of S. Karger, Basel) (4)

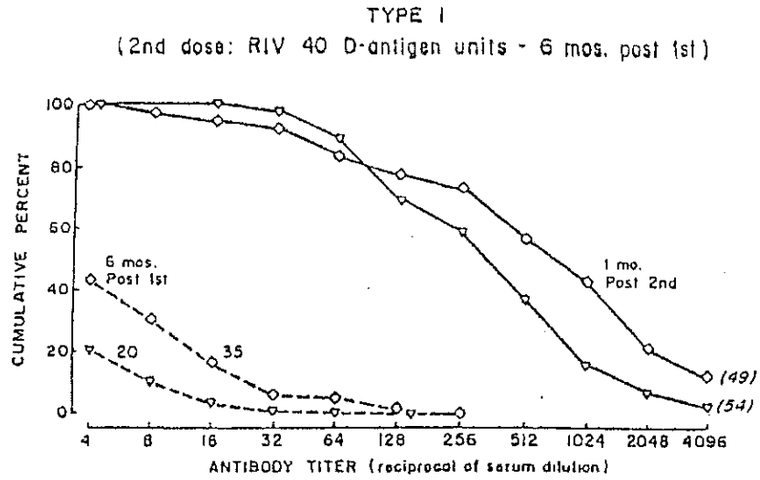

Fig. 7. Finland inactivated poliovirus vaccine study. Cumulative percent distribution of type 1 poliovirus antibody titers six months after a first dose of two conventional vaccines (containing 20 and 35 D-antigen units per dose) currently used in Finland, and one month after a second dose of Rijks Instituut voor de Volksgezondheid (RIV) vaccine (administered six months after the first dose) containing 40 D-antigen units ped dose. Numbers in parentheses = number of subjects per group.

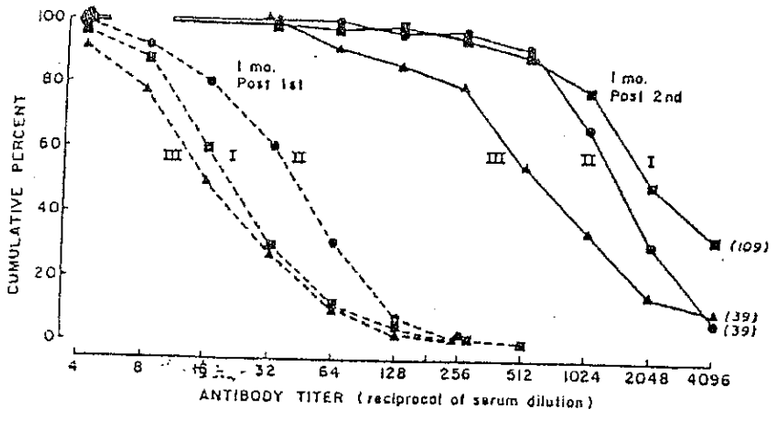

Fig. 10. Finland inactivated poliovirus vaccine (IPV) study: types 1, 2, and 3 antibody levels after a first and second dose (administered six months apart) of proposed IPV for general use (40-8-32 D-antigen units per dose for types 1-2-3, respectively). Vaccine prepared by Rijks Instituut voor de Volksgezondheid. Numbers in parentheses = number of subjects per group. (Reprinted courtesy of Behring Institute Mitteilung, Marburg) (5)

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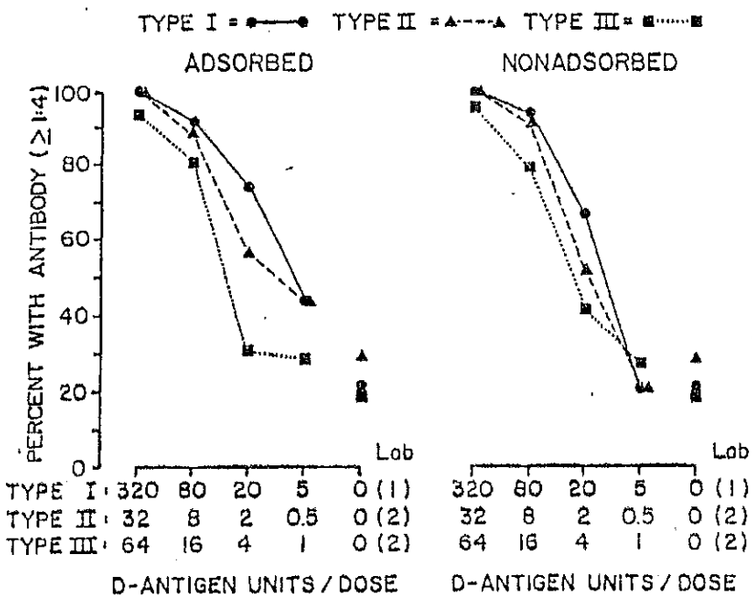

Fig. 1. Relationship between D-antigen units and antibody response to a single dose of inactivated poliovirus vaccine: composite of selected results from two laboratories. (Reprinted courtesy of S. Karger, Basel) (2).

type 1 D-antigen units per dose, 32 to 0.5 type 2, and 64 to 1 type 3). The data reveal an essentially linear relationship between the amount of antigen contained in the vaccine and percent seropositivity following a single dose. The frequency with which residual maternal antibody or antibody acquired by natural infection was observed is indicated by the points for the control group shown on the right of the chart.

Fig. 2 reveals the percent distribution of type 1 poliovirus antibody titers one month following a single dose of the vaccines used in the Mali study. By comparison with a group given tetanus toxoid for control, the dosage response effect is revealed by the relative positions of the distribution curves in the groups given 320, 80, 20, and 5 D-antigen units for type 1, respectively.

In view of these results a further study was carried out in Upper Volta in 1978—79 (4) using two-fold differences in antigen concentration over the midportion of the range studied in Mali. Fig. 3 shows the response to the type 1 component after a single dose of 80, 40, and 20 D-antigen units. These data reveal the presence, one month later, of antibody titers of 1 : 4 or greater in more than 90 % of vaccinees, as compared to about 10 % in the control group given tetanus toxoid; the differences seen in the relative position of the antibody titer distribution curves reflect the differences in the quantity of antigen contained in each of the three vaccines tested in this study.

A second dose was given six months later in accordance with the protocol for this study. While persistence of antibody was demonstrated after six months and a sharp booster response observed, the prevalence of natural infections in Mali and Upper Volta interfered with the interpretation of the data on dose response effects and antibody persistence. To avoid this complication a further investigation was carried out in Finland and in Sweden, since both are free of naturally occurring poliomyelitis virus infections and in both only IPVs have been in continuous use. The data to be reported at this time are only from the Finland study (4).

The basic design of the Finland study is shown in Table 1. Five vaccine preparations were used. Three were prepared at the RIV; and one each was from two different manufacturers of IPV, one of these (manufacturer C) is the vaccine in general use in Finland. Approximately 100 infants were in each group and received their first dose at five months of age. A blood sample was collected by venipuncture prior to the first dose, one month later, and again six months later just prior to a booster dose. For the booster the

T. ; 1

Poliovirus vaccines studied in Finland (2 doses at 6-month interval).

D-antigen units for types 1-2-3		
Part 1		Part 2
First dose	Booster dose	First and booster doses
Rijks Institute:	Rijks Institute:	Rijks Institute:
80-8-32	40-4-16	80-8-32
40-4-16	40-4-16	40-4-16
20-2- 8	40-4-16	20-2- 8
Manufacturer B:		Manufacturer B:
35-1.5-7	40-4-16	35-1.5-7
Manufacturer C:		Manufacturer C:
20-2.2-4	40-4-16	20-2.2-4

and for type 3 in Fig. 4c. Although the antibody response to the first dose is not as uniformly as high as for types 1 and 2, nevertheless, after the second dose all responded with antibody levels of 1 : 4 or greater and more than 90 % with antibody levels of 1 : 64 or greater.

The degree of persistence of type 2 antibody six months after the first dose is indicated in Fig. 5a. This figure also reveals antibody levels one month after the second dose following a uniform second dose consisting of 40 D-antigen units of the RIV vaccine. Similar persistence was observed for type 2 antibody as seen in Fig. 5b. Fig. 5c indicates a distinct decline in type 3 antibody levels in the six months post first dose in contrast to the constancy observed for types 1 and 2. For all three types there is a tendency for the differences observed post first dose to be reduced after the second dose.

Fig. 6 shows the antibody distribution pre and post booster dose comparing the RIV vaccines and those of manufacturers B and C; the type 1 D-antigen components of the latter correspond to that of the RIV 40 and 20 D-antigen unit vaccines. However the type 1 primary antibody response to the manufacturers' vaccines was distinctly less than to the RIV vaccines; there was also a lesser response to a uniform booster dose. An explanation is proposed below for the dissociation seen here between D-antigen unit content and antigenic potency in the RIV and the other vaccines. This figure also reveals that the antigenic potency of the vaccine used for the primary dose influences the degree of antibody response to a booster dose.

Fig. 7 shows the superior ef. of higher potency vaccine used for the booster dose when low potency vaccine is used for primary immunization, as compared to Fig. 8 which shows the inferior effect when the same low potency vaccine is used for both booster and primary doses.

Fig. 9 shows more clearly the dissociation between D-antigen unit measurement and antibody response in humans for the type I component of the commercial vaccines when compared with the performance of the vaccines prepared by the RIV methods. It is believed that these differences are attributable to technical factors. The RIV vaccines are made from virus purified and concentrated before inactivation with formalin; however, vaccines prepared by manufacturers B and C are inactivated with formalin and either not further treated or are purified and concentrated thereafter. This question is currently under investigation. The shaded area of Fig. 9 shows the geometric mean antibody response to a single dose of IPV containing the 40-8-32 D-antigen unit formula which is now under study in several countries.

Fig. 10 shows the antibody distribution curves post first and post second dose for types 1, 2, and 3 of the RIV 40-8-32 D-antigen unit vaccine. It is to be noted that the IPV used in The Netherlands for many years has contained the 20-2-7.5 D-antigen units, respectively, in association with diphteria-pertussis-tetanus antigens (DPT).

By comparison with the vaccines currently used in Finland (Fig. 8), where poliomyelitis has been brought under complete control and where virus has been eliminated from circulation, the more potent vaccine referred to in Fig. 10 can be expected to be protective after one or two doses.

A detailed report will be made at a later time of early favorable observations in progressively expanding field studies in endemic areas in West Africa where such poliovirus vaccines compined with DPT are being used in routine immunization programs — which also include immunization against BCG, measles and yellow fever (6).

Further and more extensive studies are now being planned using IPV of the potency here proposed, prepared according to the RIV methods. In a more recent development, the use of an approved continuously propagating cell line has eliminated the need for monkeys

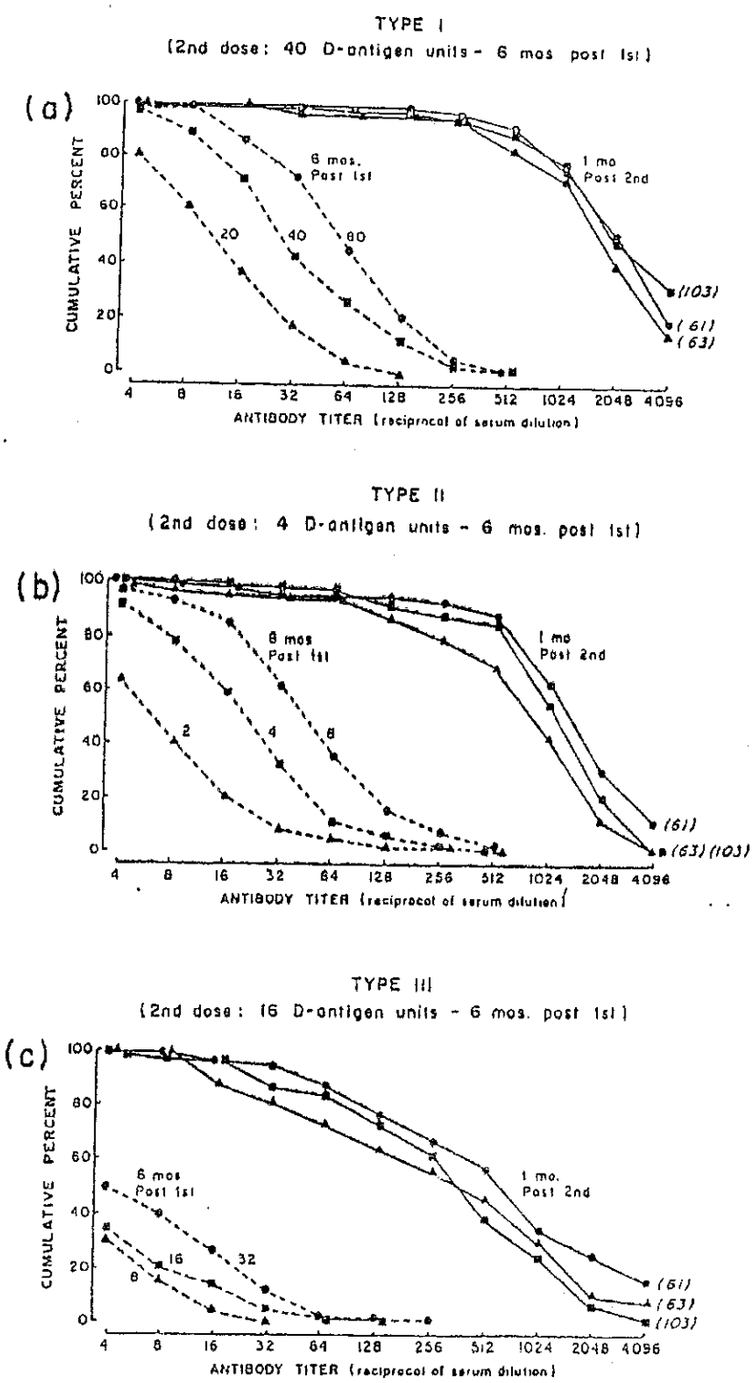

Fig. 5. Finland inactivated poliovirus vaccine study. Cumulative percent distribution of poliovirus antibody titers six months after a first dose and one month after a second dose (administered six months after the first dose) of vaccines containing: (a) type 1 — 20, 40, or 80 D-antigen units for the first dose, and 40 D-antigen units for the second dose; (b) type 2 — 2, 4, or 8 D-antigen units for the first dose, and 4 D-antigen units for the second dose (c) type 3 — 8, 16, or 32 D-antigen units for the first dose, and 16 D-antigen units for the second dose. Vaccines prepared by Rijks Instituut voor de Volksgezondheid. Numbers in parentheses = number of subjects per group.

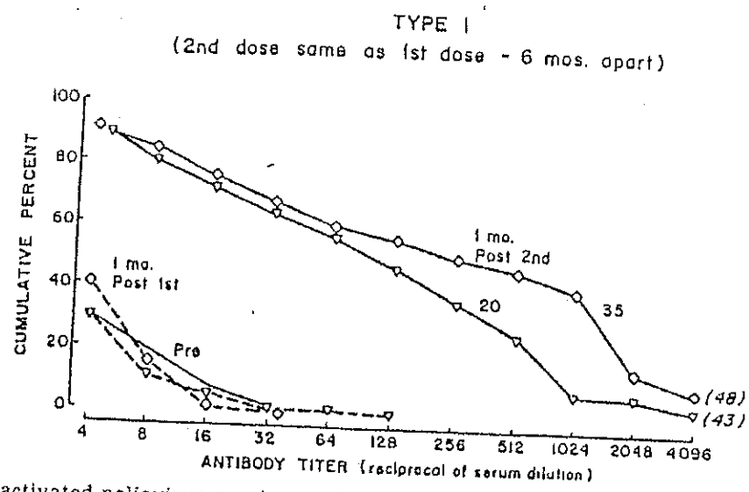

Fig. 8. Finland inactivated poliovirus vaccine study. Cumulative percent distribution of Type 1 poliovirus antibody titers one month after a first dose and one month after a second dose (administered six months after the first dose) of two conventional vaccines (containing 20 and 35 D-antigen units per dose) currently used in Finland. Numbers in parentheses = number of subjects per group.

to provide cells as substrate for producing virus (7). This now permits production of IPV on a very large scale thereby sharply reducing cost per dose to a level accessible to developing countries (8).

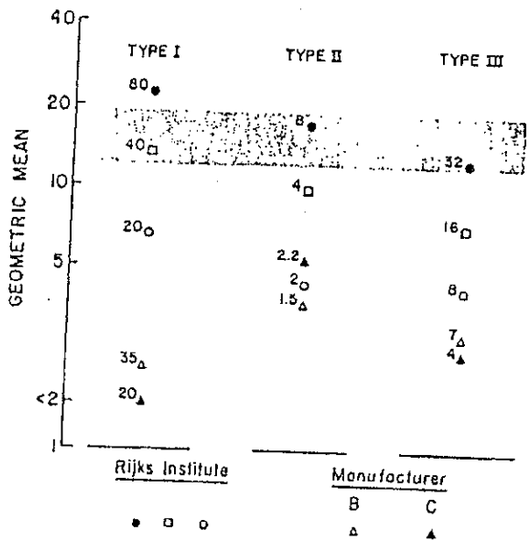

Fig. 9. Finland inactivated poliovirus vaccine study. Geometric mean antibody titers induced by a first dose of vaccines of different D-antigen unit content: comparison of vaccines prepared by Rijks Instituut voor de Volksgezondheid and by manufacturers B and C. (Reprinted courtesy of S. Karger, Basel) (4)

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Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Poliomyelitis vaccine, suspension for injection 0.5 mL
Poliomyelitis vaccine multidose, suspension for injection 2.5 mL

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose of 0,5 ml poliomyelitisvaccine contains the following active components:
Inactivated poliomyelitis virus type 1 (Mahoney)* 40 D-antigen units
Inactivated poliomyelitis virus type 2 (MEF 1)* 8 D-antigen units
Inactivated poliomyelitis virus type 3 (Saukett)* 32 D-antigen units
For the full list of excipients, see section 6.1.

*) Cultivated on Vero-cells.

3 PHARMACEUTICAL FORM

Suspension for injection. The product is a suspension of formaldehyde inactivated and purified virus filled in ampoules or vials.
The vaccine colour varies from orange-yellow to orange-red.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Active immunisation against poliomyelitis.

4.2 Posology and method of administration

Posology
One dose consists of 0.5 ml for both children and adults. The vaccine is given subcutaneously or intramuscularly.
Primary immunization consists of three vaccinations, administered with a minimum interval of 4 weeks.

Persons fully immunized against poliomyelitis and leaving to areas with a high incidence of poliomyelitis, are advised to re-vaccinate with a single-dose of polio vaccine approx. 1 month before departure, particularly when their last immunization was more than 15 years ago.

Paediatric population
Children should receive the primary series within the first 6 months after birth.

After completion of the first series of vaccinations, a booster dose can be administered after an interval of at least six months. If local authorities recommend a vaccination schedule that starts before the age of 2 months and/or if the interval between doses is less than 8 weeks, a booster dose should be administered, however not before the age of 9 months.

In the Netherlands children are preferable vaccinated with the combination vaccine Diphtheria (Pertussis) Tetanus Poliomyelitis vaccine in line with the National Vaccination Program.

Method of administration
The vaccine is administered subcutaneously or intramuscularly.

4.3 Contra-indications

The general contra-indications that apply for every vaccine:
- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

The vaccine colour may range from orange-yellow to orange-red. Vaccine with a clearly yellow or violet colour cannot be used.

Since every dose can contain trace amounts of neomycin, streptomycin and polymyxin B, you should be careful giving this vaccine to persons who are sensitive to one of these antibiotics.

Do not admininister if the vaccinee is suffering from a severe infection, with fever.

Older children and adults can faint after vaccination. This generally occurs shortly after vaccination and can occur simultaneously with nausea and vomiting. If fainting at earlier vaccinations has occurred or symptoms indicating fainting have been observed the person should be vaccinated when sitting or lying.

Under no circumstances administer Poliomyelitis vaccine intravascular.

As for any injectable vaccine, adequate treatment provisions need to be present, in case any anaphylactic reactions should occur following vaccination. If required, injections of epinephrine or corticosteroids can be given, dosed according to age and or body weight.