5.3.5.1 –Study Report of Controlled Clinical Study (Study 88A)

Name of sponsor/company: Rijksinstituut voor Volksgezondheid en Milieu (RIVM) Antonie van Leeuwenhoeklaan 11 3720 AL Bilthoven The Netherlands	*(For Authority use only)*
Name of finished product: IPV-Vero (lot E94-3-3B)	
Name of active ingredients: Formaldehyde-inactivated poliovirus produced with Vero-cells (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.	

incorrect intervals between the vaccination doses. From those 50 patients that completed the study correctly, 34 (17 males and 17 females) were randomised to receive IPV-Vero vaccine and the other 16 (11 males and 5 females) were randomised to receive the control vaccine, IPV-MK.

Inclusion criteria were defined as:

- infants with good health
- age 6 months ± 4 weeks
- born after ≥ 36 weeks pregnancy
- birth weight ≥ 2.5 kg
- parents able to communicate in Norwegian

Exclusion criteria were defined as follows:

- inadequate weight gain or suspected developmental delay
- previous immunisation with polio vaccine
- recruited in other clinical trial
- known allergy to any component of the vaccine
- expected to be lost to follow-up or to be unable to comply with the protocol

Test product, dose and mode of administration, batch number:
IPV-Vero (RIVM, lot E94-3-3B) contained per dose: formaldehyde-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 given by subcutaneous injection in thigh or upper arm at the age of 6, 7-8 and 16 months. The vaccine was similar to the control IPV-MK vaccine, with the only difference the cell source for virus propagation.

Duration of treatment:
Vaccination was given at the age of 6, 7-8 and 16 months.

Reference therapy:
This study was performed with IPV-MK from the RIVM as control vaccine, the vaccine used in the Norwegian child vaccination programme at that time. The vaccine contains per dose of 1 ml: formaldehyde-inactivated poliovirus type 1, 2 and 3: 40-8-32 D-antigen units and 2-phenoxyethanol: 5 mg and formaldehyde: 0.025 mg in phosphate buffer.

Criteria for evaluation:
Efficacy:
Neutralising antibody titres against poliovirus strain 1(Mahoney), 2 (MEF) and 3 (Saukett) were determined according to the micro-neutralisation assay in essence described by Albrecht et al (Albrecht, 1984). A neutralising titre of 8 and higher is considered protective (Galazka, 1993a; Galazka, 1993b;

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Labadie, 1996; Robertson, 1993). The efficacy results were considered satisfactory when all children in both vaccine groups had one month after the last vaccination antibody titres against all three poliovirus types above 8.

Safety:
After each vaccine dose the parents were requested to report adverse events by filling in a form. They were asked whether any of the following events appeared during the first three days after vaccination: fever, crying more than usually, redness and/or swelling at the injection site, pain at the injection site, rash, other events. They were also asked to report any event happening later than three days after vaccination if they suspected causal relationship to the vaccine. At the next visit at the child health clinic, the public health nurse asked for additional information if required. For analysis of adverse events, all available completed forms or equivalent reports by public health nurse are included.

SUMMARY-CONCLUSIONS

EFFICACY RESULTS:
For both vaccines, one month after the second as well as one month after the third vaccination, all children showed antibody titres above 8, the considered protective level, against all three types of poliovirus. No statistical significant differences in antibody titres per poliovirus type and per blood sampling between the two vaccine groups (IPV-Vero versus IPV-MK) were found utilising the Kruskall-Wallis test. In addition, the percentage of children that had high neutralising antibody titres was comparable between the two vaccine groups. In conclusion, this study indicates that IPV-Vero has potent immunogenic properties similar to IPV-MK.

SAFETY RESULTS:
Two SEAs were reported, both infants were in the group receiving IPV-Vero. Both participants were hospitalised, one admitted for contipation five days after the third vaccine dose and one admitted for febrile convulsions 12 weeks after the second vaccine dose. Both SAEs were considered unlikely related to the vaccine, since thy occurred more than three days after vaccination.
For both vaccines, the adverse events reported were generally mild. More adverse events were reported after the first dose of vaccination than after the second and third vaccination, which is in accordance with other findings on inactivated poliovirus vaccines. No significant differences in local and/or systemic reactions were found between the two vaccines. In conclusion, IPV-Vero is a safe and well-tolerated vaccine in immunologically naive children.

CONCLUSION:

5.3.5.1 –Study Report of Controlled Clinical Study (Study 88A)

Name of sponsor/company: Rijksinstituut voor Volksgezondheid en Milieu (RIVM) Antonie van Leeuwenhoeklaan 11 3720 AL Bilthoven The Netherlands	*(For Authority use only)*
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This study indicates that IPV-Vero has comparable potent immunogenic properties similar to IPV-MK. Both vaccines induced in all children, one month after the second as well as one month after the third vaccination, protective levels of antibodies against all three types of poliovirus. In addition, IPV-Vero showed to be a safe and well-tolerated vaccine. No differences in adverse events between IPV-Vero and IPV-MK were found. These findings are in accordance with results other clinical studies performed with IPV-Vero from other manufacturers. These studies showed consistently that IPV-Vero is a well-tolerated vaccine inducing high protective antibody titres comparable with IPV-MK (Drucker, 1986; Fillastre, 1989; Greiner, 1984; Haastrup, 2004).

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3. TABLE OF CONTENTS

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4. LIST OF ABBREVIATIONS AND DEFINITIONS

GCP	Good Clincial Practice
GMT	Geometric Mean Titre
IPV	Inactivated Poliomyelitis Vaccine
IPV-MK	IPV manufactured using subcultured monkey kidney cells for virus propagation
IPV-Vero	IPV manufactured using Vero cells as the cell source for virus propagation
LCB	Laboratory of Control of Biologicals
NIPH	National Institute of Public Health
PV 1,2,3	Poliomyelitits Virus type 1, 2, 3
RIVM	Rijksinstituut voor Volksgezondheid en Milieu
SD	Standard Deviation
SIS	Serological Information System
UTN	Unique Trial Number
WHO	World Health Organisation

5. ETHICS

5.1 INDEPENDENT ETHICS COMMITTEE

The study was approved by the Norwegian Medicines Control Authority and the Medical Ethical Committee of Region II, Norway.

5.2 ETHICAL CONDUCT OF THE STUDY

The study was done in conformity with current rules for Good Clinical Practice, as described by the Nordic Council on Medicines (NLN Publication No 28, 1989) and the ethical guidelines described in the "Declaration of Helsinki" and "Forskrifter av 21 august 1981 om klinisk utproving av legemidler" (Ministry of Health and Social Affairs, Norway).

5.3 PATIENT INFORMATION AND CONSENT

The participants were informed verbally and in writing about the purpose and design of the study and the possible risks of the investigation. The volunteers signed a written statement of consent that they will take part in the study and that they have been informed about relevant details of the study (see appendix 16.1.3). The statement was co-signed by the person providing the study information.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Principle investigator:	Sandbu S, MD, PhD (Pediatrician) National Institute of Public Health (NIPH) Dept Vaccinology Geitmyrsveien 75 N-0462 Oslo Norway
Coordinating investigator:	Rümke HC, MD, PhD Laboratory of Clinical Vaccine Research (LVO) Rijksinstituut voor Volksgezondheid en Milieu (RIVM) Antonie van Leeuwenhoeklaan 11 3720 AL BILTHOVEN The Netherlands
Author of the report(s)	Kaaijk P, PhD Rots NY, PhD
Monitoring	Sellaeg Helland O NIPH Dept Vaccinology
PV Antibody titrations	Birkeland Flugsrud L, PhD NIPH Dept Virology
Adverse events reporting	Nokleby H, PhD NIPH Dept Vaccinology
Institutions	Four well-babies' clinics of Ski municipality Helath Centre (at Ski, Siggerud, Langhus and Bolerasen) Ski Municipality Health Service Akershus County Norway
Advisory statistician	Nagelkerke N, PhD

7. INTRODUCTION

Inactivated poliovirus vaccine (IPV) has an excellent and long-standing record of safety and effectiveness. Its persistent immunogenicity correlates with excellent individual protection against poliomyelitis, as shown in several European countries, including The Netherlands. Endemic poliomyelitis disappeared after introduction of IPV in national immunisation programmes and more than 95% of the vaccinated population have persistently high levels of poliovirus neutralising antibodies (Bijkerk, 1984; Rümke, 1995; Böttiger, 1990). 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 vaccine failure (Oostvogel, 1994).

The optimal dose of IPV from three virulent poliovirus strains cultured on monkey kidney cells has been determined in extensive investigations in different countries, such as in Africa (Senegal, Burkina Faso, Kenya) and Thailand (Salk, 1978; Salk, 1982; Stoeckel, 1984; Cohen, 1984; Simasathien, 1994; Kok, 1992). In these studies in developing countries, the RIVM vaccine PU 78-02 was used, which was chosen later by the WHO as reference vaccine for potency of IPV. In man, the concentration of D-antigen in the vaccine has been shown to correlate with immunogenicity. Compared with toxoids, the amount of protein in IPV is much lower, and its purity is 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 in immunisation programs and during epidemics, e.g. in hospitals, both for personnel and polio-non-immune patients.

Currently, IPV is manufactured by the RIVM using monkey kidney cells as the cell source for virus propagation (IPV-MK). For this purpose, approximately 20 monkeys have to be sacrificed on a yearly basis. Therefore, alternative cell sources have been investigated in which the polioviruses can be propagated effectively at a large scale. Vero cells, a cell line derived from an African green monkey kidney, appeared to be an adequate alternative for subcultured monkey kidney cells. Vero cells have several advantages: it is a cheap alternative, it is safer with respect to viral contamination, Vero cells make further use of monkeys unnecessary and Vero cells are well-standardised and internationally accepted (Drucker, 1986; Fillastre, 1989; Grenier, 1984; Haastrup, 2004; Horie, 2001; Lang, 1997; Lang, 1999; Mallet, 1997; Montagnon, 1999; Netter, 1988; Vincet-Falquet, 1989).

The RIVM manufactured an IPV vaccine containing polioviruses grown on Vero cells, further termed IPV-Vero. The poliovirus strains used for this new vaccine are similar to the vaccine that is presently used in the National Immunisation Programm (IPV-MK), the Salk virus Mahoney (type 1), MEF-1 (type 2) and Saukett (type 3). The only difference is the cell substrate for virus propagation.

A phase I-II trial on safety and immunogenicity of IPV-Vero in healthy adult volunteers has already been performed in 1994-1995 (Rümke, 1998). However, in that study only booster reactions and not primary immune reactions could be assessed in the primed adults. Therefore, the present study was conducted to obtain data on primary immune reactions in immunogenically naive children. It was convenient to do this study in Norway, which probably is the only European country where IPV was not given simultanously with other vaccines until 1998.

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8. STUDY OBJECTIVES

The study was conducted to compare the safety and immunogenicity of IPV-Vero with the standard IV-MK in immunologically naive children in order to obtain data on primary immune reactions.

9. INVESTIGATIONAL PLAN

9.1 OVERALL STUDY PLAN AND DESIGN

The present clinical trial is a randomised, controlled, prospective study on immunogenicity and safety of IPV-Vero compared to the control IPV vaccine manufactured using monkey kidney cells (IPV-MK). It was planned to include 120 infants. Seventy percent of the participants will be randomised to receive IPV-Vero and 30% to receive IPV-MK by subcutaneous injections in thigh or upper arm at ages 6, 7-8 or 16 months. Four venous blood samples were taken. Blood sample 1 was taken 0-7 days before the first vaccination, sample 2 was taken 4-8 weeks after the second dose, sample 3 was taken 0-7 days before the third vaccination and sample was taken 4 weeks after the third vaccination. Serum neutralising antibodies were determined with Vero cells as indicator cells and wild poliovirus strains for challenge. The parents gave completed diaries on local and systemic symptoms occurring the first 3 days after vaccination by filling in a form with specific questions for symptoms and grading, and symptoms occurring later if suspected to be related to the vaccine. The form was provided at the time of vaccination. At next visit to the child health clinic the form was returned to the public health nurse.

Infants'age (mths)	5	6 ± 4 weeks	7-8 ± 4 weeks	9-10	16 ± 4 weeks	18
Visits	v0	v1	v2	v3	v4	v5
Information to parents	x	x				
Informed consent signature		x				
Medical history		x				
Inclusion/exclusion criteria review		x				
Infants'inclusion		x				
Review contra-indications			x		x	
Blood sample		x		x	x	x
Vaccination		x	x		x	
Diary		x	x		x	
Review parental monitoring form			x	x		

9.2 DISCUSSION OF STUDY DESIGN

The present study was conducted to compare the safety and immunogenicity of IPV-Vero with IPV-MK in immunologically naive children. In this study, data on primary immune reactions of IPV-Vero could be obtained and compared with the presently used IPV-MK vaccine. The study was conducted in Norway, since this is the only European country where IPV was not given simultaneously with other vaccines until 1998. The vaccine was injected subcutaneously according to the Norwegian immunisation program. It was chosen to perform the clinical study in (naive) infants, which are the target population for the Norwegian (and Netherlands) Immunisation Program. It was decided to omit the preservative agent, 2-

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phenoxyethanol, from the formulation. This was done, because the intention was to leave this preservative from IPV-Vero for marketing.

9.3 SELECTION OF STUDY POPULATION

9.3.1 Inclusion criteria

Inclusion criteria were defined as follows:
- infants with good health
- age 6 months ± 4 weeks
- born after ≥ 36 weeks pregnancy
- birth weight ≥ 2.5 kg
- parents able to communicate in Norwegian

9.3.2 Exclusion criteria

Exclusion criteria were defined as follows:
- inadequate weight gain or suspected developmental delay
- previous immunisation with polio vaccine
- recruited in other clinical trial
- known allergy to any component of the vaccine
- expected to be lost to follow-up or to be unable to comply with the protocol

9.3.3 Removal of patients

A total of 74 children were enrolled in the study, 56 out of these 74 children completed the study and 18 were withdrawn. However, 50 out of the 56 children completed the study according to the protocol with correct intervals between the vaccinations and blood sampling.

9.4 TREATMENT

9.4.1 Treatment administered

IPV-Vero (lot E94-3-3B), the tested vaccine (0.5 ml), given subcutaneously in thigh or upper arm at ages 6, 7-8 and 16 months.

IPV-MK (lots used were 751J, 752C, 752G and 753A), the control vaccine (1 ml).

9.4.2 Identity of investigational product

IPV-Vero (lot E94-3-3B), the tested vaccine, contained per dose: formaldehyde-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.

IPV-MK (lots used were 751J, 752C, 752G and 753A), the control vaccine, this vaccine was used in the Norwegian child vaccination programme at that time. The vaccine contained per dose of 1 ml: formaldehyde-inactivated poliovirus type 1, 2 and 3: 40-8-32 D-antigen units and 2-phenoxyethanol: 5 mg and formaldehyde: 0.025 mg in phosphate buffer.

Both vaccines were produced by RIVM with same production process with the exception of the cell substrates used for virus propagation.

9.4.3 Method of assigning patients for treatment groups

Randomisation in blocks of ten children (seven on tested vaccine and three on control vaccine) was done using the random function of the program Microsoft Excel. Because inclusion was done at four different well-babies' clinics, four of the blocks were not filled up. Of nine blocks used, 16 participant numbers were not filled.

9.4.4 Selection of doses in the study

Three doses (0.5 ml) of IPV-Vero or three doses (1 ml) of the control vaccine (IPV-MK) were given according to the standard treatment schedule of the Norwegian child vaccination programme at the time of the study. It was chosen to present the new vaccine, IPV-Vero, in a volume of 0.5 ml, because it is less painful.

9.4.5 Selection of timing of dose for each patient

Three doses of IPV-Vero or the control vaccine, IPV-MK, were given at the age of 6, 7-8 and 9 months according to the standard treatment schedule of the Norwegian child vaccination programme used at the time of the study.

9.4.6 Blinding

The IPV-Vero and IPV-MK vaccine were supplied in different (identifiable) packages and the person performing the vaccination could not be blinded for randomisation. However, the parents were not informed which vaccine was given to their child, so the evaluation of safety and imunogenicity were done blinded.

9.4.7 Prior and concomitant therapy

Previous immunisation with an IPV vaccine was forbidden.

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9.4.8 Treatment compliance

The administration of the vaccine as well as blood sampling were performed by trained medical staff.

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 Efficacy measurements assessed

Efficacy assessment:
Venous blood samples for antibody determinations were taken at 0 to 7 days before the first vaccination, 4 to 8 weeks after the second vaccination, 0 to7 days before the third vaccination and the last blood sample was taken at least 4 weeks after the third vaccination and at the maximum age of 2 years. Serum neutralising antibodies were determined with Vero cells as indicator cells and wild poliovirus strains for challenge. After inactivation, sera were investigated in two-fold dilution series. The starting dilution was 1:2 and the highest dilution was 1: 2048. Antibody determinations were performed at the Department of Virology of the National Institute of Public Helath in Oslo.

Safety assessment:
The parents gave written reports of local and systemic symptoms occurring the first three days after vaccination by filling in a form with specific questions for symptoms and grading, and symptoms occurring later if suspected to be related to the vaccine. The form was provided at the time of vaccination. At next visit to the child health clinic the form was returned to the public health nurse.

9.5.2 Appropriateness of measurements

Determination of serum neutralising antibody levels is a standard method to reveal the immunogenicity (efficacy) of IPV vaccines. Based on other studies, a serum neutralising titer of 8 or higher is considered to be protective for IPV vaccines by WHO (Galazka, 1992; Galazka, 1993; Labadie, 1996; Robertson, 1993). Epidemiologic studies to investigate the potency of IPV-Vero for protection against poliomyelitis are practically impossible because the risk for acquiring poliomyelitis in the Netherlands is minimal. For safety measurement of the vaccine all standard study parameters to detect any related adverse event were assessed.

9.5.3 Primary efficacy variable(s)

Antibody titres against poliovirus type 1,2 and 3 presented in tables and figures are expressed as ^{2}log reciprocal titres of the highest final dilution of serum resulting in neutralisation. A neutralising titre of 8 and higher against type 1, 2 and 3 PV is considered protective according to WHO (Galazka, 1992; Galazka, 1993; Labadie, 1996; Robertson, 1993).

9.5.4 Drug concentration measurements

No drug concentration measurements were performed.

9.6 DATA QUALITY ASSURANCE

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The clinical phase of the study was performed in accordance with the recommended principles of Good Clinical Practice for studies with medicine in the European Community (CPMP/ICH/135/95) as described by the Nordic Council on Medicines (NLN Publication no 28, 1989) and with Norwegian regulatory requirements.

9.7 STATISTICAL METHODS PLANNED AND DETERMINATION OF SAMPLE SIZE

9.7.1 Statistical and analytical plans

Differences in the geometric mean antibody titres per blood sample and per serotype between the two vaccine groups will be evaluated for statistical significance using the Kruskall-Wallis test.
Full data and individual listings of all assessments of local and systemic adverse events, tabulated by type, severity, duration and outcome, will be made.

9.7.2 Determination of sample size

The objective of this open randomised controlled prospective study was to investigate the safety and immunogenicity to IPV-Vero compared to the control vaccine, IPV-MK. The intention was to include 120 infants and allocate 70% to receive IPV-Vero vaccine and 30% to receive the control vaccine.
This number of participants should be enough to show that three times of vaccination with IPV-Vero will result in a protective neutralising antibody titre comparable to IPV-MK. In addition, this number of participants was expected to be enough to study the safety of the vaccine. No serious adverse reactions and only mild (local) symptoms were expected from (recent) clinical studies with IPV-MKC and IPV-Vero.

9.8 CHANGES IN STUDY CONDUCT

Only 74 children were include in the study, instead of the intended 120, because inclusion was more difficult than presumed. Many parents had a feeling against their offspring taking part in a clinical study. There also appeared to be a certain scepticism against vaccination in the population in Ski municipality at that time. Therefore the planned 6 months inclusion period was extended to 11 months. A total of 74 infants (32 females (43%) and 42 males) were included in the study, being 61,6% of the intended number. Finally, fifty infants completed the study according to the protocol.

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10. STUDY PATIENTS

10.1 DISPOSITION OF PATIENTS

Seventy-four infants fulfilled all in- and exclusion criteria and were randomised for the study.

- One child was excluded from the study, because of poor weight gain.
- Eighteen children were withdrawn from the study, thirteen from the IPV-Vero group (UTN 6, 21, 25, 28, 35, 47, 48, 54, 57, 58, 59, 65, 72) and five of the IPV-MK group (UTN 1, 7, 19, 46, 71). Fifteen children were withdrawn immediately after randomisation (UTN 6, 19, 21, 25, 28, 46, 47, 48, 54, 57, 58, 59, 65, 71, 72). The other three children (UTN 1, 7, 35) were withdrawn as indicated in Figure 2. Seven children were withdrawn because of difficult blood sampling (UTN 6, 28, 35, 46, 47, 65, and 71). Five children were withdrawn, because they were often sick (UTN 1, 7, 19, 58, 59). Two children were withdrawn, because the parents changed their mind (UTN 48, 72). One child was withdrawn for unknown reason (UTN 25), one child was withdrawn, because of the long distance to the laboratory. One child was withdrawn, because of asthma treatment.
- Six participants (3 IPV-Vero and 3 IPV-MK) were excluded from efficacy analysis due to incorrect interval (71-87 days) between the first and second vaccine dose (protocol 28-70 days) (UTN 1, 4, 15, 17, 60 and 82). Data from these children were not excluded from per intention to treat analysis.

See also figure 2.

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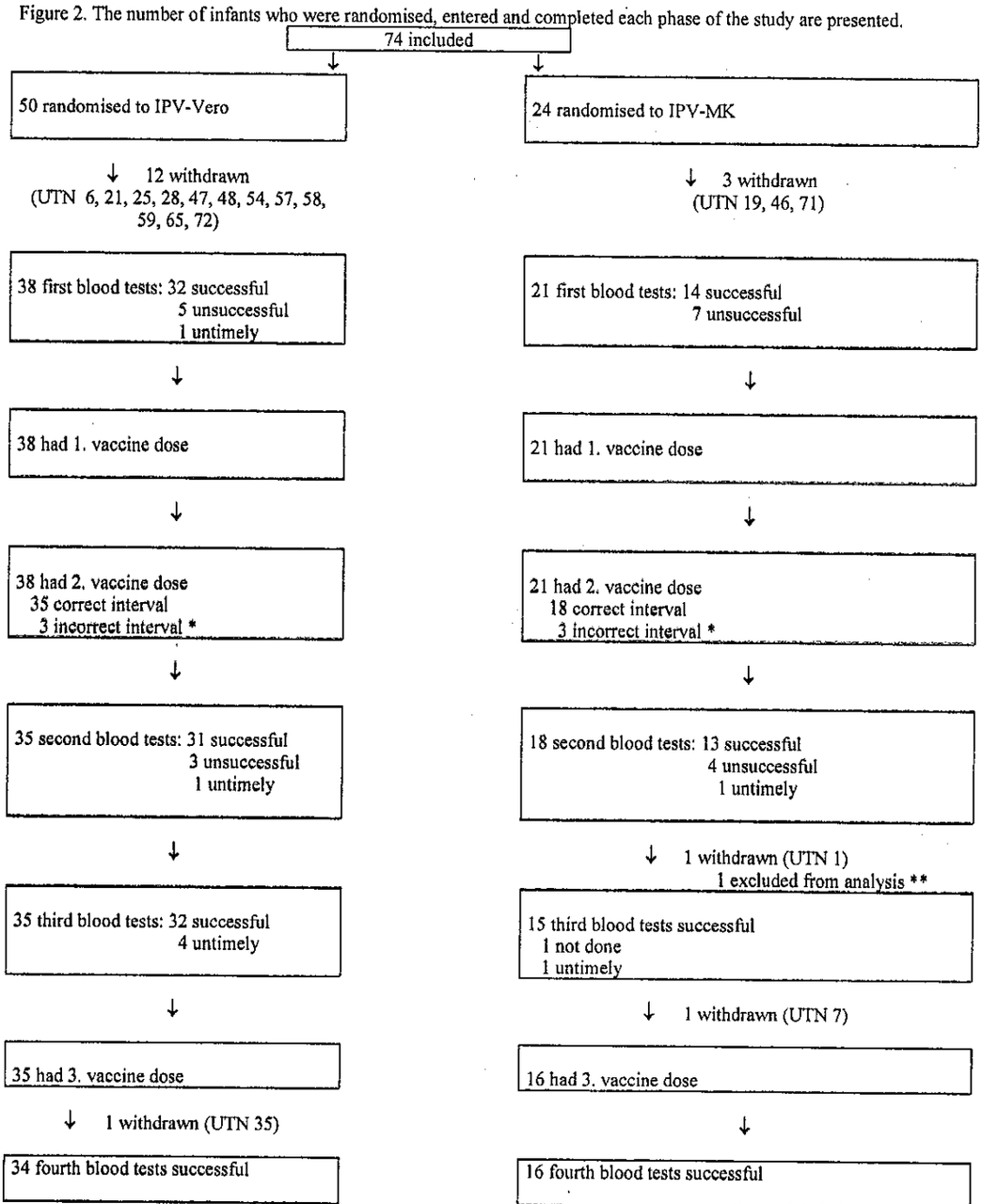
Figure 2. The number of infants who were randomised, entered and completed each phase of the study are presented.



6 participants (3 IPV-Vero and 3 IPV-MK) were excluded from analysis due to incorrect interval (71-87 days) between the first and second vaccine dose (protocol 28-70 days) (UTN 1, 4, 15, 17, 60 and 82). Data from these children were not excluded from per intention to treat analysis.

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** 1 participant (IPV-MK) had 372 days between second and third dose (protocol 183-365 days), therefore blood sample three and four were excluded from analysis (UTN 42).

10.2 PROTOCOL DEVIATIONS

One participant (IPV-MK) had 372 days between 2nd and 3rd vaccine dose (protocol defines 183-365 days). From this participant the third and fourth blood samples were excluded for analysis (UTN 42).

Seven participants had an incorrect interval between vaccination and blood sampling:
One participant (IPV-Vero) had 1st blood sample 8 days before 1st vaccine dose (protocol defines 0-7 days) (UTN 67). Two participants (1 IPV-Vero, 1 IPV-MK) had taken 2nd blood sample resp. 58 and 57 days after 2nd vaccine dose (protocol defines 28-56 days) (UTN 13 and 31). Five participants (4 IPV-Vero and 1 IPV-MK) had 3rd blood sample 8-12 days before 3rd vaccine dose (protocol defines 0-7 days) (UTN 14, 27, 31, 53 and 69). Data from these blood samples were excluded for efficacy analysis.

11. EFFICACY EVALUATION

11.1 DATA SETS ANALYSED

A total of 74 children enrolled the study, 56 out of these 74 children completed the study. However, 50 out of the 56 children completed the study according to the protocol. The remaining six children did not receive all vaccination doses at the correct interval. Data from 50 children were used for immunogenicity analysis. The immunogenicity of the 56 children that completed the study was analysed as well, but only the summary results and not the details will be presented in this report.
Safety data from all children receiving at least one vaccination (n=61) were analysed.

11.2 DEMOGRAPHIC CHARACTERISTICS

Baseline characteristics of the individual patients are presented in Table 14.1.
Forty-two males and thirty-two females entered the study. Fifty-six children completed the study according to the protocol from which 30 were male and 26 were female. From the 50 children that completed the study according to the protocol, 28 were male and 22 female.

11.3 MEASUREMENT OF TREATMENT COMPLIANCE

All medication was administered by medical staff and controlled by investigators.

11.4 EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL PATIENT DATA

11.4.1 Analysis of efficacy data

All participants in both vaccine groups had (protective) antibody titres of 8 or higher against all three types of poliovirus after the third vaccination dose (blood sample 4). Also four weeks after the second vaccination (blood sample 2), the antibody titres were 8 or higher (see Figure 3). Four to eight weeks after the second vaccination, only one child had an antibody titre below 8 for the poliovirus type 2 and one other child had an antibody titre below 8 for poliovirus type 3, both children were from the IPV-Vero group. All the others showed antibody titres above 8 in both vaccine groups. See also Table 14.2.2.

In none of the four blood samples, differences in serum-neutralising antibody titres were found between the two vaccine groups (IPV-Vero versus IPV-MK).

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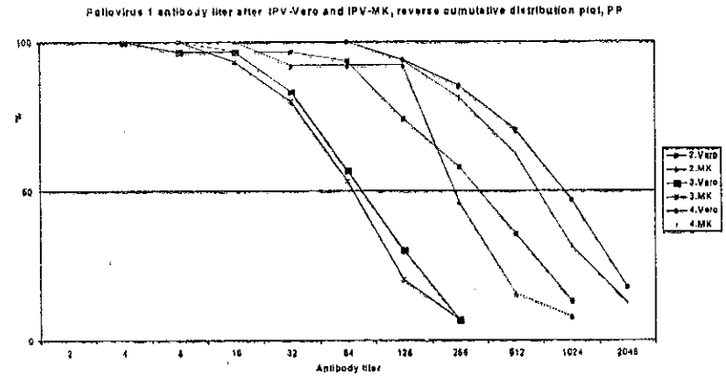
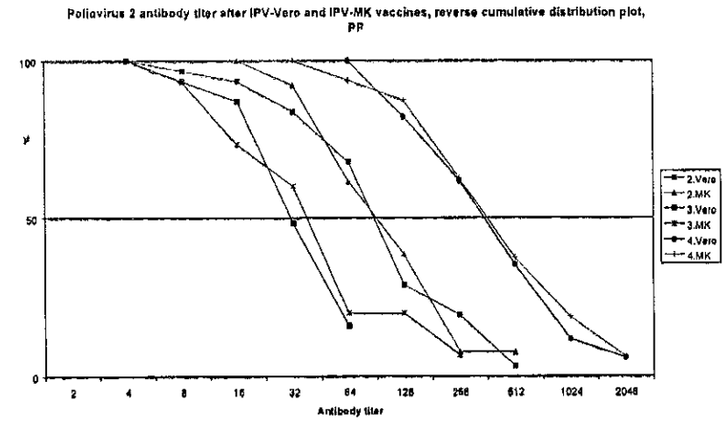
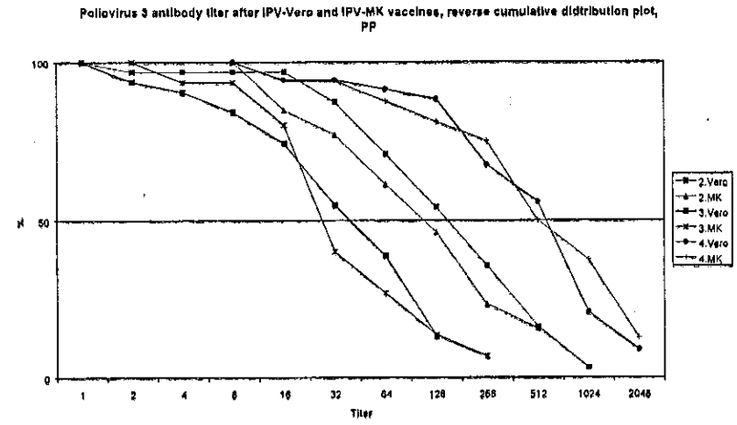
Figure 3. The percentage reverse cumulative frequency of serum neutralising titres is given per poliovirus type 1, 2 and 3. Titres are expressed as ^{2}log reciprocal dilutions. Vero, IPV-Vero; MK, IPV-MK; 2. 3. and 4.; blood sample 2, 3 and 4.







11.4.2 Statistical/analytical issues

The Kruskall-Wallis test was performed to compare the immunogenicity data between the two groups. In the per protocol analysis as well as in the per intension to treat analyses, no statistically significant differences were found in antibody titres between the two vaccine groups in the four blood samples. All p-values were above 0.1.

11.4.3 Tabulation of individual response data

The pre- and post-vaccination antibody titres of the individual participants are represented in Table 14.2.1. The immunogenicity data are summarised in Table 14.2.2.

11.4.4 Drug dose, drug concentration and relationship to response

In the present study, each participant received the same dose of the vaccine, and therefore no dose/response relationship could be determined.

11.4.5 Drug-drug and drug-disease interactions

Not applicable.

11.4.6 By-patient displays

Individual patient data are listed in Table 14.2.1.

11.4.7 Efficacy conclusion

For both vaccine groups, all participants that received the three vaccinations according to the protocol had (protective) antibody titres ≥ 8 against all three types of poliovirus. Also, when the six participants that received the three vaccinations with incorrect intervals were taken along, all participants had protective levels of antibodies against all three types of poliovirus. It is concluded that IPV-Vero is a potent immunogenic vaccine in immunologically naive children. In the present study, three doses of both IPV vaccines appeared to induce protective antibody levels in all children.

12. SAFETY EVALUATION

12.1 EXTENT OF EXPOSURE

All participants were vaccinated three times by subcutaneous injection in thigh or upper arm at ages 6, 7-8 and 16 months. Thirty-four children received three doses of IPV-Vero (lot E94-3-3B), the other 14 children received IPV-MK (lots used were 751J, 752C, 752G and 753A). For IPV-Vero, each dose contained: formaldehyde-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. For the IPV-MK, the control vaccine, each dose contained: formaldehyde-inactivated poliovirus type 1, 2 and 3: 40-8-32 D-antigen units and 2-phenoxyethanol: 5 mg and formaldehyde: 0.025 mg in phosphate buffer.

12.2 ADVERSE EVENTS

Safety analysis was performed on the 61 children receiving one vaccination, 59 children receiving two vaccinations and 57 receiving all three vaccinations (including one child that was excluded from the study because of poor weight gain.

12.2.1 Brief summary of adverse events

The reported adverse events were mostly considered mild. No participant was withdrawn because of adverse events. More adverse events were reported after the first dose than after the second or third vaccine dose. Two serious adverse events were reported in two participants, both from the IPV-group. These two participants were hospitalised during the study, one admitted for constipation five days after the third vaccine dose, and one admitted for febrile convulsions 12 weeks after the second vaccine dose. These two reported serious adverse events were unlikely related to the vaccine since they occurred more than three days after vaccination.

12.2.2 Display of adverse events

The local and systemic adverse events are presented in Table 14.3.1. Some participants had more than one symptom. All reported events were listed regardless of causal relationship to the vaccine. More adverse events were reported after the first dose than after the second or third vaccine dose (see Table 14.3.2). All local symptoms were generally of mild intensity. Only one child in the IPV-MK group had local swelling and redness > 2.5 cm after the first vaccination. One child in the IPV-Vero group avoided using the vaccinated arm the first day after the first vaccine dose. However, none of the local reactions lasted for more than two days. Some of the children with slight redness and/or tenderness to touch were reported to be uneasy or fretful or have periods of crying. One child in the IPV-Vero group had tenderness at injection site after all three doses, but no visible local reaction. Most of the infants with systemic adverse events were described as fussy, restless, silent, fretful, more or less sleepy than usual. A few infants had short periods of crying. One infant had diarrhoea six weeks after the first vaccine dose, two had fever lasting for three days and one had periods of restlessness for four days. All other systemic events occurred for a short period of time (< 1 hour – 2 days). All subjects recovered completely. In a total of seven cases the parents reported other reasons for fever (a cold, teething, other family members had same symptoms),

from which five out of the IPV-Vero group and two out of the IPV-MK group. Events that occurred later than three days after vaccination were considered unlikely to have causal relationship to the vaccination. Four children from the IPV-Vero group were reported to have fever or a cold later than three days after the first vaccine dose. Two children from the IPV-MK group were reported to have otitis starting four days and fever starting three weeks after the second dose and one had rash starting four days after the third vaccine dose during three days. Two of the infants, both had received IPV-Vero, were hospitalised during the study, one admitted for constipation five days after the third vaccine dose (UTN 10), and one admitted for febrile convulsions 12 weeks after the second vaccine dose (UTN 49). Both cases were considered unlikely to have a causal relationship with the vaccine, since they occurred more than three days after vaccination.

12.2.3 Analysis of adverse events

The number of adverse events reported from the infants receiving IPV-Vero were compared with those from IPV-MK group for each type of adverse event and for all local and all systemic events. This was performed for all vaccine doses separately and taking all doses together. No differences between the two vaccines could be found.

12.2.4 Listing of adverse events by patients

The adverse events are listed per study group and per vaccination in Table 14.3.1.

12.3 DEATHS AND OTHER SERIOUS EVENTS

Two of the participants, both had received IPV-Vero, were hospitalised during the study (one admitted for constipation five days after the third vaccine dose (UTN 10), one admitted for febrile convulsions 12 weeks after the second vaccine dose (UTN 49). Both cases were considered unlikely to have a causal relationship with the vaccine, since they occurred more than three days after vaccination.

12.4 CLINICAL LABORATORY EVALUATION

No laboratory parameters were analysed for safety evaluation.

12.4.1 Listing of individual laboratory measurements by patient and each abnormal laboratory value

No laboratory measurements, apart from the analysis of serum neutralising antibody titres, were performed.

12.4.2 Evaluation of each laboratory parameter

No laboratory measurements, apart from the analysis of serum neutralising antibody titres, were performed.

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12.5 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY

No other physical abnormalities or other observations, apart from the reported adverse events, were described.

12.6 SAFETY CONCLUSIONS

The adverse events were mostly mild. No participant was withdrawn because of adverse events. More adverse were reported after the first dose than after the second or third vaccine dose. Two SAEs were reported, however they were unlikely related to the vaccine since they occurred more than three days after vaccination.

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13. DISCUSSION AND OVERALL CONCLUSIONS

The vaccine under study, IPV-Vero, is immunochemically equivalent to the IPV-MK currently in use in the Netherlands Immunisation Programm. The only difference is the cell substrate for virus propagation. In vitro biochemical and immunochemical parameters, and in vivo potency in rats indicate immunogenic properties of IPV-Vero equivalent to the classical IPV-MK. This clinical study was conducted to compare the immunogenicity and safety of IPV-Vero with IPV-MK in unprimed infants. The infants were vaccinated at the age of 6, 7-8 and 16 months. Our group and others have already shown that two doses of IPV-MK induced neutralising antibodies against the three types of the poliovirus in over 95% of the infants (Salk, 1978; Salk, 1982; Stoeckel, 1984; Cohen, 1984; Simasathien, 1994; Kok, 1992). It was, however, recommended to give a third dose at least six months after the second dose.
All participants in both vaccine groups had (protective) antibody titres ≥ 8 (or ≥ 3 when expressed ^{2}log reciprocal) against all three types of poliovirus after the last (third) vaccination dose.

Two SAEs were reported, however they were unlikely related to the vaccine since they occurred more than three days after vaccination. The reported adverse events were generally mild. No participant was withdrawn because of adverse events. More adverse events were reported after the first dose than after the second or third vaccine dose. No differences in rate or intensity of adverse events were found between the IPV-Vero versus the IPV-MK group.

IPV-Vero appeared to be an immunogenic and well-tolerated vaccine in immunologically naive infants. Three doses of both IPV vaccines at the age of 6, 7-8 and 16 months appeared to be enough to induce protective antibody levels in all children.