14. TABLES

Table 14.1: Demographic data from 74 participants entering the study. All participants received their first vaccination at the age of 6 months. UTN, unique trial number; M, Male; F, Female

Vaccine	UTN	Sex	Remarks
IPV-MK	1	M	Withdrawn before third blood sample, cause often sick
IPV-Vero	2	F	
IPV-Vero	3	M	
IPV-Vero	4	F	
IPV-Vero	5	M	
IPV-Vero	6	F	Withdrawn before first blood sample, cause difficult blood sampling
IPV-MK	7	M	Withdrawn after third blood sample, cause often sick
IPV-Vero	8	M	
IPV-MK	9	M	
IPV-Vero	10	F	
IPV-MK	11	M	
IPV-Vero	12	F	
IPV-MK	13	M	
IPV-Vero	14	F	
IPV-Vero	15	F	
IPV-Vero	16	F	
IPV-Vero	17	F	
IPV-Vero	18	M	
IPV-MK	19	M	Withdrawn before first blood sample, cause often sick
IPV-Vero	20	F	
IPV-Vero	21	M	Withdrawn before first blood sample, cause very long way to laboratory
IPV-Vero	22	F	
IPV-MK	23	F	
IPV-MK	24	M	
IPV-Vero	25	M	Withdrawn before first vaccine dose, unknown reason
IPV-MK	26	M	
IPV-Vero	27	M	
IPV-Vero	28	M	Withdrawn before second vaccine dose, cause difficult blood sampling
IPV-Vero	29	F	
IPV-Vero	30	M	
IPV-Vero	31	F	
IPV-Vero	32	F	
IPV-MK	33	M	
IPV-Vero	34	F	
IPV-Vero	35	F	Withdrawn after third vaccine dose, cause painful blood sampling
IPV-MK	41	M	
IPV-MK	42	F	
IPV-Vero	43	M	
IPV-Vero	44	M	
IPV-Vero	45	M	

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Vaccine	UTN	Sex	Remarks
IPV-MK	46	M	Withdrawn before first dose, cause difficult blood sampling
IPV-Vero	47	F	Withdrawn before first dose, cause difficult blood sampling
IPV-Vero	48	F	Withdrawn before first dose, cause changed mind
IPV-Vero	49	M	
IPV-Vero	50	F	
IPV-Vero	51	F	
IPV-Vero	52	F	
IPV-MK	53	M	
IPV-Vero	54	M	Withdrawn before first blood sample, cause asthma treatment
IPV-MK	55	M	
IPV-Vero	56	M	
IPV-Vero	57	F	Excluded cause poor weight gain
IPV-Vero	58	M	Withdrawn before first blood sample, cause often sick
IPV-Vero	59	F	Withdrawn before second blood sample, cause often sick
IPV-MK	60	F	
IPV-MK	61	F	
IPV-Vero	62	M	
IPV-Vero	63	F	
IPV-Vero	64	F	
IPV-Vero	65	M	Withdrawn before first dose, cause difficult blood sampling
IPV-MK	66	M	
IPV-Vero	67	M	
IPV-MK	68	M	
IPV-Vero	69	M	
IPV-MK	71	M	Withdrawn after first vaccine dose, cause difficult blood sampling
IPV-Vero	72	M	Withdrawn before first blood sample, cause changed mind
IPV-Vero	73	M	
IPV-Vero	74	M	
IPV-MK	75	M	
IPV-Vero	81	M	
IPV-MK	82	M	
IPV-MK	83	F	
IPV-MK	84	F	
IPV-Vero	85	F	

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

Table 14.2.1: The serum neutralising antibody titres, expressed as ^{2}log reciprocal dilutions, are presented per individual participant. UTN, unique trial number; M, Male; F, Female; type 1,2,3, serum neutralising antibody titres of poliovirus type 1,2,3; ex, excluded for the analysis; -, not performed (no blood sample available, withdrawn or invalid test).

			blood sample 1			blood sample 2			blood sample 3			blood sample 4		
Vaccine	UTN	Sex	type 1	type 2	type 3	type 1	type 2	type 3	type 1	type 2	type 3	type 1	type 2	type 3
IPV-Vero	2	F	1	2	0	6	6	6	6	5	6	6	6	6
IPV-Vero	3	M	0	2	0	10	7	8	7	6	6	11	9	9
IPV-Vero	4	F	2	1	3	ex	ex	ex	ex	ex	ex	ex	ex	ex
IPV-Vero	5	M	2	1	2	10	8	9	-	4	4	9	7	7
IPV-Vero	8	M	2	3	1	8	4	8	6	4	5	11	9	11
IPV-Vero	10	F	3	2	0	3	5	5	4	4	6	9	7	9
IPV-Vero	12	F	1	2	1	7	5	4	4	3	3	9	8	7
IPV-Vero	14	F	1	0	1	-	-	-	ex	ex	ex	11	9	9
IPV-Vero	15	F	3	2	1	ex	ex	ex	ex	ex	ex	ex	ex	ex
IPV-Vero	16	F	-	-	-	7	6	6	6	5	6	8	8	7
IPV-Vero	17	F	3	3	2	ex	ex	ex	ex	ex	ex	ex	ex	ex
IPV-Vero	18	M	0	0	2	9	8	8	5	6	4	11	11	10
IPV-Vero	20	F	-	-	-	7	5	5	5	4	4	8	6	7
IPV-Vero	22	F	4	2	0	6	6	8	5	4	5	10	8	10
IPV-Vero	27	M	2	0	0	-	-	-	ex	ex	ex	8	6	8
IPV-Vero	29	F	0	0	0	9	8	9	8	6	7	10	10	9
IPV-Vero	30	M	4	3	4	6	2	5	4	2	1	10	8	10
IPV-Vero	31	F	-	-	-	ex	ex	ex	ex	ex	ex	9	8	9
IPV-Vero	32	F	3	2	2	7	6	7	5	5	5	7	6	7
IPV-Vero	34	F	0	0	0	6	4	4	6	4	0	6	8	3
IPV-Vero	35	F	2	3	3	9	4	7	6	4	4	-	-	-
IPV-Vero	43	M	2	3	2	10	8	10	7	4	6	8	7	10
IPV-Vero	44	M	4	2	1	6	5	7	6	5	7	9	8	8
IPV-Vero	45	M	3	0	0	8	8	9	5	4	5	11	10	11
IPV-Vero	49	M	1	1	0	7	6	6	8	5	4	9	6	7
IPV-Vero	50	F	3	4	0	5	6	5	2	2	4	9	8	8
IPV-Vero	51	F	1	1	0	9	9	8	7	5	6	9	11	9
IPV-Vero	52	F	3	1	4	9	7	5	5	4	2	10	9	9
IPV-Vero	56	M	0	2	1	8	6	7	7	5	7	10	9	9
IPV-Vero	62	M	3	2	2	8	5	7	5	4	5	11	9	9
IPV-Vero	63	F	1	2	0	10	6	9	7	6	7	8	7	8
IPV-Vero	64	F	-	-	-	9	6	7	6	5	6	7	7	7
IPV-Vero	67	M	ex	ex	ex	8	3	6	4	3	2	7	6	5
IPV-Vero	69	M	0	0	0	6	6	0	ex	ex	ex	10	9	3
IPV-Vero	73	M	0	2	1	8	7	8	7	5	6	10	7	11
IPV-Vero	74	M	1	1	0	9	6	4	7	6	0	10	7	9
IPV-Vero	81	M	-	-	-	-	-	-	5	4	3	10	8	9
IPV-Vero	85	F	2	3	2	8	6	6	6	5	6	10	9	9
IPV-MK	1	M	-	-	-	ex	ex	ex	-	-	-	-	-	-
IPV-MK	7	M	3	2	2	10	9	9	8	8	6	-	-	-
IPV-MK	9	M	0	0	0	7	7	5	6	7	4	11	9	10

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			blood sample 1			**blood sample 2**			**blood sample 3**			**blood sample 4**		
Vaccine	UTN	Sex	type 1	type 2	type 3	type 1	type 2	type 3	type 1	type 2	type 3	type 1	type 2	type 3
IPV-MK	11	M	2	0	0	-	-	-	5	7	9	10	10	11
IPV-MK	13	M	-	-	-	ex	ex	ex	6	5	1	7	7	5
IPV-MK	23	F	0	2	0	8	7	7	7	5	7	11	11	11
IPV-MK	24	M	-	-	-	-	-	-	4	3	5	8	7	8
IPV-MK	26	M	-	-	-	7	5	3	-	-	-	9	7	8
IPV-MK	33	M	2	3	2	9	5	8	5	4	5	10	7	10
IPV-MK	41	M	1	2	0	8	6	9	6	5	6	9	9	9
IPV-MK	42	F	3	3	1	7	5	6	ex	ex	ex	ex	ex	ex
IPV-MK	53	M	-	-	-	7	6	3	ex	ex	ex	7	6	3
IPV-MK	55	M	2	1	2	8	7	7	6	5	4	6	5	6
IPV-MK	60	F	-	-	-	ex	ex	ex	ex	ex	ex	ex	ex	ex
IPV-MK	61	F	-	-	-	-	-	-	5	3	4	10	10	10
IPV-MK	66	M	2	3	0	7	5	4	4	4	4	8	8	8
IPV-MK	68	M	1	0	0	7	6	7	5	3	3	9	8	7
IPV-MK	75	M	1	1	0	8	7	5	7	5	3	9	9	9
IPV-MK	82	M	2	4	0	ex	ex	ex	ex	ex	ex	ex	ex	ex
IPV-MK	83	F	1	0	0	-	-	-	6	5	4	9	8	10
IPV-MK	84	F	4	4	0	4	4	6	3	2	4	8	8	8

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Table 14.2.2: Summary of serum neutralising antibody responses. Represented are the percentage of infants that had (protective) antibody levels (≥ 8). The geometric mean titre (GMT, the standard deviation (SD), as well as the number of participants (n) are presented per type of poliovirus 1, 2 or 3 (respectively PV1, 2, or 3). The first blood sample was taken 0-7 days before the first vaccination, the second blood sample was taken 4-8 weeks after the second dose, the third blood sample was taken 0-7 days before the third vaccination and the fourth blood sample was taken 4 weeks after the third vaccination.

		sample1		sample 2		sample 3		sample 4	
		Vero	*MK*	Vero	*MK*	Vero	*MK*	Vero	*MK*
PV1	% ≥ 3	34.4	*21.4*	100	*100*	96.8	*100*	100	*100*
	gmt	1.78	*1.71*	7.68	*7.46*	5.65	*5.53*	9.15	*8.81*
	sd	1.31	*1.14*	1.66	*1.39*	1.36	*1.30*	1.44	*1.42*
	n	32	*14*	31	*13*	31	*15*	34	*16*
PV2	% ≥ 3	21.9	*35.7*	97	*100*	93.8	*93.3*	100	*100*
	gmt	1.63	*1.79*	5.94	*6.08*	4.41	*4.73*	7.97	*8.06*
	sd	1.13	*1.48*	1.57	*1.32*	1.07	*1.67*	1.40	*1.57*
	n	32	*14*	31	*13*	32	*15*	34	*16*
PV3	% ≥ 3	12.5	*0*	96.8	*100*	81.3	*93.3*	100	*100*
	gmt	1.09	*0.5*	6.55	*6.08*	4.34	*4.60*	8.21	*8.31*
	sd	1.23	*0.86*	2.05	*2.02*	2.10	*1.88*	1.94	*2.21*
	n	32	*14*	31	*13*	32	*15*	34	*16*

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Table 14.3.1. The reported adverse events are listed per vaccine group and per vaccine dose 1, 2 or 3. Some participants had more than one symptom, therefore the number of events is higher than the number of persons with reported adverse events.

Adverse event	*1. dose Vero*	*1. dose MK*	*2. dose Vero*	*2. dose MK*	*3. dose Vero*	*3. dose MK*
n =	40	21	38	21	38	19
Redness, small	2 (5%)	2 (10%)		1 (5%)	3 (8%)	2 (11%)
Redness ≥ 2,5 cm + swelling		1 (5%)				
Tenderness	3 (8%)	1 (5%)	1 (3%)		3 (8%)	
Persons with local reaction	*5 (13%)*	*4 (19%)*	*1 (3%)*	*1 (5%)*	*4 (11%)*	*2 (11%)*
Fussiness, uneasiness etc.	13 (33%)	4 (19%)	7 (18%)	2 (10%)	5 (13%)	
Less active						
Eating less	1 (3%)					
Crying	3 (8%)	2 (10%)		1 (5%)		
Vomiting	1 (3%)				1 (3%)	
Diarrhoea	1 (3%)			1 (5%)		
Fever ≥38 °C	2 (5%)		1 (3%)	1 (5%)	2 (5%)	2 (11%)
Rash	1 (3%)				3 (8%)	
Persons with systemic adverse events	*14 35(%)*	*6 (29%)*	*8 (2%)*	*3 (14%)*	*7 (18%)*	*2 (11%)*
Persons without adverse event(s)	*21 (53%)*	*11 (52%)*	*29 (76%)*	*17(81%)*	*27 (71%)*	*15 (79%)*

Table 14.3.2. Presented are the number (and percentage) of participants with any reported adverse event after the first, second and third vaccine dose.

	After 1. dose		After 2. dose		After 3. dose	
Total	29/61	(47,5%)	13/59	(22%)	15/57	(26,3%)
IPV-Vero	19/40	(47,5%)	9/38	(23,7%)	11/38	(28,9%)
IPV-MK	10/21	(47,6%)	4/21	(19%)	4/19	(21,1%)

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16. APPENDICES

16.1.1 Clinical protocol

16.1.2 Sample Case Report Form (CRF)

16.1.3 Patient written information and informed consent

16.1.4 Curriculum vitae of principle investigator

Appendix 16.1.1 –Clinical protocol of Study 88A

CLINICAL TRIAL OF THE IMMUNOGENICITY OF A TRIVALENT INACTIVATED POLIOVACCINE GROWN ON VERO CELL CULTURE (IPV-VERO) GIVEN AT AGES 6, 7-8 AND 16 MONTHS AND OF ADVERSE EVENTS FOLLOWING IMMUNIZATION.

NIPH project no. 1.2.08 VAVA 96-01

Final version, 16. July 1996 with additions 13. november 1996.

Good clinical trial practice

This study will be done in conformity with current rules for Good clinical trial 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 utprøving av legemidler" (Ministry of Health and Social Affairs, Norway).

Confidentiality

The information contained in this document is the property of the sponsor of this study, the "Rijksinstituut voor Volksgezondheid en Milieu (RIVM)". The document is therefore provided in confidence to (potential) investigators, monitors, consultants or members of Review Boards for review. It is understood that this information will not be disclosed to others without written authorization from the RIVM, except to the extent necessary to obtain informed consent from those persons to whom the vaccine may be administered.

Appendix 16.1.1 –Clinical protocol of Study 88A

NIPH project no. 1.2.08 VAVA 96-01

Protocol additions 13. november 1996

4.6 Sample size

Both the study vaccine IPV-Vero and the presently used IPV probably are very immunogenic, and will both induce close to 100% seroconversion, with probably high titers. The background for including 120 children is determined by two aspects: (1) statistical power required for comparison (see also nomogram "Annex 1 to SOP 12N-GCP-12") and (2) operational possibilities to study the number of children required. Although the study proposal including 120 children may not be sufficient to investigate the equivalence between the two study products in this study alone, they will generate a first set of data enabling a reliable estimate of equivalence when combined with data from subsequent comparative trials. There is also cumulative evidence in the data of the study itself, as children are investigated at various occasions within the schedule.
(See also ref.: N.Begg & E.Miller: Role of epidemiology in vaccine policy. Vaccine 1990:8;180-89.)

4.7 Data handling, analyses and reporting

All clinical data on participants obtained from the handling, treatment, observation and laboratory analyses will be recorded. The investigator and sponsor assure that the anonymity of the participants is maintained. On case report forms (CRF) and other documents submitted to the sponsor, the participant should not be identified by name, but by initials and identification code. The investigator keeps a separate log of codes, names and addresses of participants.

Antibody titers will follow later, but are regarded as an integral part of the final CRF. Clinical and serological data will be entered in the LVO database.

The clinical and serological aspects of this study will be analyzed separately. They will be reported in English.

The final clinical report will contain:
- tabulation of drop-outs, and if available, the reason for withdrawal.
- full data and individual listings of all assessments of local symptoms, and other adverse events. They will be tabulated by type, severity, duration and outcome.
- structured summary with relevant data.

The final serological report will contain:
- comparison of antibody prevalence before and after vaccination(s), age, and sex of participants. A neutralizing titer of 1/8 and higher is considered to be protective.
As a secondary parameter differences in geometric mean titres before and after vaccination will be analyzed.
- titres of the antibody tests will be fully listed.
- structured summary with relevant data and figures.
- safety data; listing of results and Wilcoxon like analysis.
- immunogenicity data: listing of titers, frequency distribution, seroconversion Wilcoxon like methods, GMT differences by t-tests.

Appendix 16.1.1 –Clinical protocol of Study 88A

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Appendix 16.1.1 –Clinical protocol of Study 88A

ABBREVIATIONS

Ag	Antigen
IPV	Inactivated Poliovirus Vaccine
KRZ	Bureau for Quality and regulatory Affairs, RIVM
NIPH	National Institute of Public Health, Norway
LCB	Laboratory for the Control of Biologics, RIVM
LVO	Laboratory for Clinical Vaccine Research, RIVM
RIVM	Rijksinstituut voor Volksgezondheid en Milieu / National Institute of Public Health and the Environment
SLK	Norwegian Medicines Control Authority
SOP	Standard Operating Procedure
WHO	World Health Organization

Appendix 16.1.1 –Clinical protocol of Study 88A

SUMMARY OF CLINICAL PROTOCOL:

Title of the trial: Clinical trial of the immunogenicity of a trivalent inactivated poliovaccine grown on Vero cell culture (IPV-VERO) given at ages 6, 7-8 and 16 months and of adverse events following immunization.

Sponsor: Rijksinstituut voor Volksgezondheid en Milieu (National Institute of Public Health and the Environment) (RIVM)

Trial phase: Phase II study

Principal investigator: Synne Sandbu, M.D., Pediatrician, Department of Vaccinology, NIPH

Other investigators: Jan Ørnulf Melbostad, M.D., Chief medical officer, Ski municipality health services

Liv B. Flugsrud, M.D., Consultant, Department of Virology, NIPH

Hanne Nøkleby, M.D., Head, Department of Vaccinology, NIPH

Monitor: Oddveig Sellæg Helland, cand. pharm., Department of Vaccinology, NIPH

Trial centres: 3 well-babies' clinics i Ski municipality

Objectives:
- To study the immunogenicity of IPV-Vero when given to Norwegian infants at 6, 7-8 and 16 months of age.
- To study the safety of IPV-Vero when given to Norwegian infants at 6, 7-8 and 16 months of age.

Study design: Open, randomized, controlled study on immunogenicity and safety

Participants: Infants from age 6 months coming for polio vaccination

Sample size: 120 infants of whom 70% are allocated to receive IPV-Vero vaccine and 30% to receive the control vaccine.

Inclusion criteria:
- age 6 months (± 4 weeks)
- born after ≥ 36 weeks pregnancy
- birth weight ≥ 2,5 kg
- parent's written informed consent

Exclusion criteria:
- 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

Vaccine doses: 3 injections with IPV-VERO vaccine (40-8-32 D-Ag units per 0,5 ml dose; lot no 94-3-3B) at ages 6, 7-8 and 16 months.

Control: 3 injections with the presently used polio vaccine (Poliovaksine "RIVM" inaktivert - trivalent) (40 - 8 - 32 Ag units per 1 ml dose) at ages 6, 7-8 and 16 months.

Appendix 16.1.1 –Clinical protocol of Study 88A

Administration: Subcutanous injection in thigh or upper arm.

Main parameters of immune response:
Determination of type-specific neutralizing antibodies

Main parameters of safety:
Registration of local and systemic symptoms

Statistical analysis of immunogenicity data:
Listing of titres of the type-specific neutralizing antibodies before and after vaccination, frequency distribution, seroconversion Wilcoxon like methods, GMT differences by t-tests.

Statistical analysis of safety data:
Listing of all adverse events and Wilcoxon like analysis.

Planned trial period: 1996 to 1998

Appendix 16.1.1 –Clinical protocol of Study 88A

FLOW CHART

Infants' age (months)	5	6	7-8	9-10	16	18
		±4 weeks	±4 weeks		±4 weeks	
Visits	V0	V1	V2	V3	V4	V5
Information to parents	x	x				
Informed consent signature		x				
Medical history		x	x	x	x	x
Incl and excl criteria review		x				
Infant's inclusion		x				
Review contra-indications			x		x	
Serum sample		x		x	x	x
Vaccination		x	x		x	
Parental monitoring form		x	x		x	
Review of parental monitoring form			x	x		x

Appendix 16.1.1 –Clinical protocol of Study 88A

1. BACKGROUND AND OBJECTIVES OF THE PRESENT STUDY

1.1 Introduction

Inactivated poliovirus vaccine (IPV) has a long standing record of safety and high immunogenicity. A major factor limiting large scale production is the source of suitable cells for virus propagation. Up to now RIVM has used monkey kidney cells. At present, about 20 monkeys each year have to be sacrificed. Therefore, alternative cell sources have been investigated on which poliovirus can be multiplied effectively at a large scale. The use of Vero cells for this purpose is a reliable and cheap alternative, with the following advantages over the currently used monkey kidney cells:
- The Vero cell is a continuous cell line, making further use of animals for virus propagation unneccessary.
- Vero cells are better standardized than monkey kidney cells
- Vero cells have lower chance of being infected than the monkeys and their kidney cells. For regular IPV production, RIVM breeds their monkeys in a closed colony, with a minimal chance of extraneous infection.

Vero cells are derived from monkey kidneys. These cells are widely used for production of vaccines (IPV and rabies virus vaccine). Such vaccines are considered safe and potent. The American Food and Drug Administration has licensed an IPV based on Vero cells for unrestricted use in the United States. After a phase of preclinical testing of IPV derived from polioviruses grown in Vero cells, the RIVM conducted a phase I-II trial on safety and immunogenicity of the vaccine in adults. Now the RIVM proposes to initiate clinical studies with this vaccine in infants. The virus strains used for the new vaccine are the same as for the vaccine in present use.

1.2 Vaccination and immunity

It has been proven that IPV induces excellent individual protection against poliomyelitis. The evidence comes from the epidemiological experience in many European countries, including the Netherlands and Scandinavian countries, in which endemic poliomyelitis disappeared after introduction of IPV in national immunization programmes. Also in developing countries the protective efficacy has been proven. The recent few epidemics in the Netherlands are attributed to failure to vaccinate rather than vaccine failure.

The optimal dose of IPV derived from virulent poliovirus strains cultured on monkey kidney cells has been determined in extensive investigations in Mali, Burkina Faso, Israel, Finland and Sweden. These studies were done with the RIVM vaccine PU 78-02, which later was chosen by the WHO as a reference vaccine for the potency of IPV. It has been clearly demonstrated that immunogenicity in man correlates with the concentration of D-antigen in the vaccine.

1.3 The use of Vero cells for the cultivation of vaccine virus

Vero cells have been accepted for use as substrates for the propagation of vaccine viruses for human use. In France, Sweden and the United States of America inactivated poliovirus vaccine propagated on Vero cells has been licensed for unrestricted human use. Also a rabies vaccine cultured on Vero cells is widely used.

1.4 Anticipated benefits of new IPV-VERO

As compared to the current use of tertiary monkey kidney cells the benefits of the use of Vero cells for vaccine virus production are the following:
1. monkeys do not have to be killed for vaccine production
2. production of vaccine is less dependent on external influences
3. quality control of Vero cells for virus culture is better maintained and validated, using a seed lot system, and fewer safety tests have to be done

once the cell seed lot is approved.
4. the maintenance of a costly colony of monkeys is no longer necessary.
5. opposition against the use and sacrification of primates as laboratory animals might endanger the availability of vaccines.

The choice of Vero cells for vaccine production thus warrants the availability of a safer product at lower costs.

1.5 Overall strategy for clinical development of IPV-VERO

The present study is the second in a series of clinical trials with IPV-VERO, either as a single product, or in combination with other antigens. The single product is used in the Netherlands only at a small scale, but it is exported to several European countries.
The next vaccine to be tested is IPV-VERO, combined with new formulations of diphtheria and tetanus toxoids, for use in older children and adults. Next, this new DT-IPV will be the basis for a new vaccine for primary infant immunizations, after (a-cellular) pertussis-, and possibly also Haemophilus influenzae type b vaccine antigens are included.

1.6 Objectives of the present study

1. To study the antibody response to IPV-VERO vaccine in infants.
2. To study adverse events following immunizations with IPV-VERO vaccine in infants.

In adults, only booster reactions and not primary immune reactions can be assessed. Data on primary immune reactions can only be obtained in children, as they are immunogenically naive. In the Netherlands, children are vaccinated with combined DTP-IPV and DT-IPV. Therefore it is more difficult to study immunogenicity in children there, as it would involve several changes from the normal vaccination program.

2. VACCINE

Inactivated poliovaccines are in general use since the nineteen fifties. The vaccine produced and used in the Netherlands has a long standing record of safety and efficacy. The vaccine contains the three types of poliovirus: type 1, 2 and 3.

2.1 Production of the vaccine

The production of the vaccine proceeds in five steps. These steps are (i) cell and virus cultivations, (ii) downstream processing, (iii) inactivation, (iv) mixing of the three monovalent virus pools and subsequent (v) final filling with the other compounds mentioned under 2.2.

(i) The cultivations are performed in homogeneous cultivation systems. In these systems Vero cells are cultivated. They are used as a substrate for the cultivation of the three virus suspensions. Both cell and virus cultures are done according to the seed lot principle. The seed lots are stored in a large number of frozen aliquots. They are thoroughly tested for their safety and fitness for use. In this respect, the Vero cells may be a safer substrate than the tertiary monkey kidney cells which are used in the routine production of IPV in RIVM. The virus seeds are derived from the same strains as those for the routine product (type 1, 2 and 3 poliovirus: Mahoney, MEF 1 and Saukett strains). The seed lot system warrants optimal reproducibility. Cells are cultured in Eagle's Minimum Essential Medium, containing bovine serum and lactalbumin hydrolysate. Virus cultures are done in Medium 199.

(ii) The virus harvest is clarified by filtration, concentrated by

ultrafiltration, and purified using two column chromatographic steps (with different column materials for each filtration run).

(iii) The concentrated and purified virus suspension is diluted to the desired D-antigen concentration with medium 199, and inactivated by the addition of formaldehyde. The virus inactivation is done with the utmost care, by an extensively validated procedure, followed by virulence tests to ascertain the complete inactivation of the virus. Henceforth, IPV does not contain any living virulent poliovirus, and is furthermore tested for any other living organisms. Hazards as occurred in the so called "Cutter incident" in the fifties in the USA with incompletely inactivated virus can be ruled out.

(iv) The monovalent virus pools are mixed to concentrated trivalent bulk based upon D-antigen concentration in these three pools, in a ratio of 40:8:32 for the types 1, 2 and 3 poliovirus, respectively.

(v) The trivalent bulk is diluted with phosphate buffer with the addition of formaldehyde to the composition described in 2.2.

2.2 Description of vaccine

Aspect, formulation and labelling
The product under study is a clear orange-red to orange-yellow suspension with pH 7,0, filled in 3 ml glass vials with rubber stopper, sealed with an aluminium capsule.
The vaccine (lot E94-3-3B, use before March 1, 1997 and new lot thereafter) contains per dose of 0.5 ml:
formalin-inactivated poliovirus type 1, 2 and 3: 40-8-32 D-antigen units and formaldehyde: 0.025 mg in phosphate buffer.
The color is due to fenol red.
The filling volume is 0.7 ml.

The vaccine is to be injected intramuscularly or subcutanously.
The vaccines will be labeled as shown on the release certificate.

2.3 Quality control

The control testing is done as below, according to WHO requirements for IPV and Vero cells.

Vero cell seed
- identity
- absence of adventitious agents in guinea-pigs, mice, rabbits and in vitro; absence of tumorogenicity in rats and in vitro cell cultures

Virus seed strains used for vaccine production
- identity,
- sterility

Monovalent, trivalent or final bulk or final lot
- safety; sterility; abnormal toxicity in guinea-pigs and mice; local toxicity in rats; LAL test for endotoxin; safety for cell cultures (absence of residual live poliovirus).
- immunogenicity; D-antigen content; potency testing in rats.
- other tests; protein content; bovine serum proteins; pH; concentration of formaldehyde.

The new element in this vaccine is the use of Vero cells for vaccine virus cultivation. The Vero cells are tested both in vitro and in experimental animals for absence of contaminating microorganisms, residual DNA and oncogenic properties. The DNA content in the final product is below the maximal allowed concentration of 100 pg per dose, to eliminate potential oncogenic properties.

The certificates for release of the seeds of Vero cells and virus strains for vaccine production, as well as the certificate for release for human use of the final product under study are included in appendix 1.

2.4 Vaccine supply and storage

The vials of the trial vaccine will be distributed to the study centre by the manufacturer without breaking the cold chain. The investigator takes responsibility for the vaccines by signing a receipt form. The vaccine shall be stored at +2 to +8 °C. At the end of the study each vial of the vaccine that has not been used for vaccinating a participant must be handed over to the study coordination center, maintaining the cold chain.

2.5 Rationale for doses selection

Derived from the same poliovirus strains, the vaccine under study will be filled with similar D-antigen concentrations as IPV based on monkey kidney cells. The vaccine under study is biochemically equivalent to the IPV in current use, the only difference being the cell substrate for virus propagation. Henceforth, the current 40-8-32 D-Ag content per dose is also appropriate for the new IPV-VERO, produced by RIVM. In addition, all laboratory parameters indicate similar immunogenic properties as the classical monkey kidney cells IPV.
An IPV with similar D-antigen concentrations derived from virulent strains grown on Vero cells produced by Institute Mérieux, induced similar levels of antibodies as the vaccines containing inactivated virus strains grown on monkey kidney cells.
The schedule for single IPV is 3 doses, the third given at least 6 months after the second dose.

2.6 Results of phase I-II study

An open phase I-II trial has been conducted in 48 adults to study the safety and immunogenicity of the IPV-VERO. The participants were given 2 intramuscular injections with 4 weeks interval.

The occurence of (one or more) general symptoms was reported by 5 out of 47 volunteers. 42 out of 47 volunteers reported local symptoms (muscle stiffness, redness, pain, swelling, itching). All the reported reactions were of mild intensity, with the exception of one incidence of moderate headeche.

Following vaccination with IPV-Vero, strong antibody responses with at least 8-fold titer rise against all three types of poliovirus was detected in all the participants one week after vaccination, indicating a strong secondary response in previously primed individuals. The second vaccination after four weeks did not further increase the magnitude of antibody formation, which suggests that an immune plateau had been achieved after one vaccination.

2.7 Vaccine for comparison

The presently used "Trivalent poliovaksine RIVM". Tertiary monkey kidney cells are used as substrate for the cultivation of the three virus suspensions. In the same way as described for IPV-Vero the suspensions are purified and inactivated by the addition of formaldehyde. The vaccine does not contain antibiotics or adjuvants.
The vaccine contains per dose of 1 ml:
formalin-inactivated poliovirus type 1, 2 and 3: 40-8-32 D-antigen units and 2-fenoxyetanol: 5 mg and formaldehyde: 0.025 mg in phosphate buffer.
The color is due to fenol red.

3. PARTICIPANTS

3.1 Study population

120 well babies coming for their routine immunization in Ski municipality.

3.2 Inclusion criteria:
- age 6 months (± 4 weeks)
- born after ≥ 36 weeks pregnancy
- birth weight ≥ 2,5 kg
- parent's written informed consent

3.3 Exclusion criteria:
- inadequate weight gain or suspected developmental delay
- previous immunisation with poliovaccine
- recruited in other clinical trial
- known allergy to any component of the vaccine
- the administration of plasma products (including immunoglobulins) ≤3 months prior to the study
- expected to be lost to follow-up or to be unable to comply with the protocol

3.4 Potential risks and safety measures

The vaccine will be administered by a qualified public health nurse who will observe the participant for 20 minutes after the vaccination, according to general guidelines for injections. All equipment and medication for handling acute and severe allergic reactions will be available in the unit where the vaccine will be given. In case of a delayed reaction to the vaccine, the investigator can be contacted.

The trial vaccine has been released by RIVM for clinical testing and has met all the requirements necessary to administer this vaccine to human volunteers (see appendix 1).

Mild adverse reactions to the vaccine may occur. They are expected to be mainly local and transient.

3.5 Benefits

The major potential benefit of this study is for the community. The participants will get a vaccine which, according to other studies, is equivalent to the presently used IPV in effect and side effects. When antibody titrations are completed, any participants with antibody titer below protective level will be informed, and additional vaccine doses will be offered.

3.6 Discomfort to participants

Local and systemic reactions may occur. The risk to the individual participant is not believed to be greater than if following the ordinary child vaccination program.

The participant will have to make ekstra visits to laboratory for blood sampling. The participants will have 4 venipunctures, approximately 5 ml blood being drawn each time.

3.7 Insurance

The parties are insured by NIPHs membership in the Norwegian Drug Liability Committee.

3.8 Informed consent

The parents are given written information at previous visit at well babies' clinic. Written informed consent is given before inclusion in the study. (Copy of written information enclosed.)

3.9 Withdrawal of participants

Participants have the right to withdraw from the study at any time and for any reason. The investigator also has the right to withdraw participants from the study in the event of intercurrent illness or other condition specified as exclusion criterium, adverse event, protocol violation, or other reasons. An excessive rate of withdrawals may render the study uninterpretable, and should be avoided. Should the parents decide to withdraw a participant, all efforts will be made to complete and report the observations as thoroughly as possible. A complete final evaluation at the time of withdrawal should be made, and the reason for withdrawal should be recorded, if known.

4. STUDY DESIGN AND STUDY PROCEDURES

4.1 Methodology

Open clinical study with a control group receiving trivalent inactivated poliovaccine "RIVM", which is the vaccine presently used in Norway.

For each block of 10 infants included in the study, 7 will be vaccinated with the IPV-Vero and 3 will be vaccinated with the presently used IPV. Within each block of 10 participants computerised randomization will be done using the random function in the program Microsoft Excel 5.0.

The vaccine will be given in accordance to the Norwegian child immunization program at ages 6, 7-8 and 16 months.

Venous blood samples will be drawn before first vaccine dose, after dose 2 and before and after dose 3.

The two vaccine products are delivered in vials looking different, so the vaccinators can not be blinded for the product. The parents will not be told which vaccine is given. The personnell doing the laboratory analyses will be blinded for the vaccine product.

As the vaccine is part of the childhood immunization program, every infant should be offered vaccination and it will not be possible to have an unimmunized control group.

In addition there are historical controls, a study of 103 infants who were immunized 1992-93 with trivalent inactivated poliovaccine "RIVM" and bled twice.

4.2 Vaccination

Basic immunization consists of 3 doses à 0,5 ml test vaccine (1 ml control vaccine) given as s.c. injection. Interval between 1. and 2. dose is 6 weeks (4-10 weeks). Interval between 2. and 3. dose is 9 months (6-12 months). Usually vaccine is given at ages 6, 7-8 og 16 months.

Public health nurses do the vaccination.
Medically responsible for vaccination is the physician in charge of the well babies' clinic.

4.3 Blood samples

Venous blood specimens will be collected before 1. dose, 1 month after 2. dose, before 3. dose and 1 month after 3. dose.
Venous blood samples :

1. 1. blood sample within 1 week before 1. dose polio vaccine.
2. 2. blood sample at least 4 weeks and maximun 8 weeks after 2. dose polio vaccine.
3. 3. blood sample within 1 week before 3. dose polio vaccine.
4. 4. blood sample at least 4 weeks after 3. dose polio vaccine, and latest at next ordanary visit at age 2 years.

The separated serum samples are sent as A-post to Department of Vaccinology, NIPH. The samples are frozen at -20°C until testing at Department of Virology, NIPH.

4.4 Other vaccines given simultanously

Other vaccines can be given simultanously. In that case, the concomitant vaccine should be recorded with type and lot number, injection site and adverse reaction at this site.

4.5 Protocol deviations

The protocol is written to ensure that participants are treated correctly, and that useful, reliable and homogeneous data are collected. The dates, times and dosages specified in this protocol should be adhered to as much as possible. However, to comply with irregularities due to vacation, disease, etcetera, deviations will be tolerated to some extent .

- The inclusion period will not exceed approximately 6 months, and study population should not exceed 120 infants.

- Regarding age at first vaccine dose, a deviation of 1 month is acceptable.
- As to the interval between the first and second doses, a minimum of four weeks and a maximum of 10 weeks is acceptable.
- As to the interval between second and third doses, a minimum of 6 months and a maximum of 12 months is acceptable.
- The blood samples before 1. and 3. vaccine doses should be taken within 8 days before vaccination.
- Interval from 2. vaccine dose to 2. blood sample should be minimum 4 weeks and maximum 8 weeks.
- The 4. blood sample should be taken within 1 year after 3. vaccine dose.

Any faulty administration of the vaccine under study (e.g. overdose) or any other violation of the protocol leads to the situation described in 5.1.3.

4.6 Data handling, analyses and reporting

All clinical data on participants obtained from the handling, treatment, observation and laboratory analyses will be recorded. The investigator and sponsor assure that the anonymity of the participants is maintained. On case report forms (CRF) and other documents submitted to the sponsor, the participant should not be identified by name, but by initials and identification code. The investigator keeps a separate log of codes, names and addresses of participants.

Antibody titers will follow later, but are regarded as an integral part of the final CRF. Clinical and serological data will be entered in the LVO database.

The clinical and serological aspects of this study will be analyzed separately. They will be reported in English.

The final clinical report will contain:
- tabulation of drop-outs, and if available, the reason for withdrawal.

- full data and individual listings of all assessments of local symptoms, and other adverse events. They will be tabulated by type, severity, duration and outcome.
- structured summary with relevant data.

The final serological report will contain:
- comparison of antibody prevalence before and after vaccination(s), age, and sex of participants. A neutralizing titer of 1/8 and higher is considered to be protective.
As a secondary parameter differences in geometric mean titres before and after vaccination will be analyzed.
- titres of the antibody tests will be fully listed.
- structured summary with relevant data and figures.

5. STUDY PARAMETERS

5.1 ADVERSE REACTIONS

Clinical adverse events will be graded on a four point scale, according to the guidelines given below:
1. *Mild*: awareness of a sign or symptom but easily tolerated.
2. *Moderate*: discomfort enough to interfere with normal daily activities.
3. *Severe*: incapacitating with inability to do normal activity.
4. *Life threatening*: presents a hazard with a potential for causing death.

5.1.1 Local symptoms

The parents will be requested to examine the site of injection for aspects, related to a possible inflammatory reaction, such as
- redness and swelling: scored as diameter of largest possible circle (in millimeters)
- warmth, itching, and pain: scored by intensity, using the above mentioned four point scale.

These items are recorded on a registration form.
Any action taken will also be registered by the investigator.

5.1.2 General symptoms

During the study the parents of the participants are asked to make notes on the registration form about possible adverse experiences.

5.1.3 Notification of adverse events / adverse reactions

The parents will register adverse events during the first three days in a special form given them at the time of immunization. On the next clinic visit they will be asked about any serious unexpected events at any time, whether or not they are believed to be vaccine related.
Reactions that have resulted in contact with a doctor, will as soon as possible be notified from the well babies' clinic by letter or telephone to the responsible persons at Department of Vaccinology. Such reactions shall also be notified to the official Norwegian register of vaccine adverse events.
Severe reactions should be notified within 24 hours.

The sponsor is entitled to terminate the study at any time for reason of:
- monitoring data, showing that the investigator violates the study protocol or performs unacceptable otherwise.
- new data on the safety or efficacy of the product under study that makes continuation unsafe or useless.
Should premature termination be necessary, procedures and further treatment of participants will be arranged on an individual basis.

5.2 Immunogenicity

The pre- and post immunization sera will be analyzed for neutralizing antibodies against poliovirus. The analyses are done at Department of Virology, NIPH.

The assay of poliovirus neutralizing antibodies is done as microneutralization test with Vero cells as substrate and Sabin-strains of the three poliovirus types as challenge using the final pH of the medium in the wells as indicator of presence or absence of virus (metabolic inhibition test). Serum is set up in two-fold dilution series in micro trays, two rows for each virus. The starting dilution is 1:5 and the highest dilution is 1:640. To each dilution is added an equal volume of the Sabin strains of poliovirus 1, 2 and 3 respectively in a dilution presumed to give a final amount of 100 $TCID_{50}$ in the serum-virus mixture. The actual dose of virus in each run will be estimated by a back-titration, using Karber's method. After incubation for 3 hours at 37°C and over night at 4°C, Vero cells are added. The trays are further incubated for 7 days at 37°C. Then the pH in the media, which contains phenol red, is registered. A yellow colour indicates virus neutralization or normal cell growth, red indicates virus growth or cell toxicity.

Antibody titer is the inverse value of the highest dilution with virus neutralization in both rows. Titer $\geq$10 is regarded by WHO as protective and is registered as positive.

The results will be evaluated both as the fraction of serum samples considered positive at each step as well as by comparing the geometric mean titres at each step. The evaluation may also include the number of children exhibiting a fourfold or higher rise in titre after a vaccine dose.

All individual primary results for each child will be sent to the sponsor.

6. ETHICAL CONSIDERATIONS

The trial is to be conducted in accordance with the ethical guidelines described in the latest revision of the "Declaration of Helsinki", with current rules for Good clinical trial practice, as described by the Nordic Council on Medicines (NLN Publication No 28, 1989) and with Norwegian regulatory requirements. The protocol will be approved by the Norwegian Medicines Control Authority and the Medical Ethical Committee of Region II, Norway, before the start of the trial.

Vaccination against poliomyelitis is part of the Norwegian child immunization program. From studies in adults there are reasons to believe that IPV-Vero is at least as good as the vaccine in current use. As the IPV-Vero vaccine shall be used in infants, trials in infants are necessary. The added inconvenience consists of 4 blood samples drawn. The risk connected to drawing blood samples is considered negligible.

7. TIME FRAMES

Start: 1996
Inclusion period: 6 months.
Total duration of the study: approx. 2 years.

8. ORGANISATION AND RESPONSIBILITY

The study will be organised by Department of Vaccinology, NIPH.
Clinical trial coordinator is Synne Sandbu.
Tel no: +47 22042356
Fax no: +47 22042301

The trial centre will be Ski municipality health services, 3 well babies' clinics.
Medically responsible is Jan Ørnulf Melbostad, Chief medical officer of Ski municipality health services.

The polio antibody titrations will be done at Department of Virology, NIPH.
Responsible is Liv Birkeland Flugsrud.

Monitor is Oddveig Sellæg Helland, Department of Vaccinology, NIPH.

Sponsor is RIVM.

Organization of Sponsor:

Rijksinstituut voor Volksgezondheid en Milieu (RIVM)
Antonie van Leeuwenhoeklaan 9, 3721 MA Bilthoven
PO Box 1, 3720 BA Bilthoven, The Netherlands

Acting on behalf of RIVM:
Trial and vaccine related questions:
Dr. H.C. Rümke MD PhD, Laboratory for Clinical Vaccine Research (LVO)
Tel no: +31 30 274 2202
Fax no: +31 30 274 4430

Finance, contract, insurance:
Anne-Marie Kuipers-Bakker MBA

Vaccine regulatory questions:
Herman Dirksen, Bureau KRZ

Appendix 16.1.1 –Clinical protocol of Study 88A

Appendix 1:
THE CERTIFICATES FOR RELEASE OF THE SEEDS OF VERO CELLS AND VIRUS STRAINS FOR VACCINE PRODUCTION AND THE CERTIFICATE FOR RELEASE FOR HUMAN USE OF THE FINAL PRODUCT IPV-VERO.

Appendix 2:
THE USE OF VERO CELLS FOR THE CULTIVATION OF VACCINE VIRUS

Appendix 3:
- FORELDREINFORMASJON OM KLINISK STUDIE AV POLIOVAKSINE IPV-VERO
- KLINISK STUDIE AV POLIOVAKSINE IPV-VERO: SAMTYKKESKJEMA

Appendix 4:
- POLIOVAKSINASJON I STUDIEN VAVA 96-01: OPPSUMMERINGSSKJEMA
- POLIOVAKSINASJON I STUDIEN VAVA 96-01: INNTAKSSKJEMA
- POLIOVAKSINASJON I STUDIEN VAVA 96-01, FORELDRESKJEMA: REGISTRERING ETTER 1. DOSE POLIOVAKSINE
- POLIOVAKSINASJON I STUDIEN VAVA 96-01, FORELDRESKJEMA: REGISTRERING ETTER 2. DOSE POLIOVAKSINE
- POLIOVAKSINASJON I STUDIEN VAVA 96-01, FORELDRESKJEMA: REGISTRERING ETTER 3. DOSE POLIOVAKSINE
- 1. DOSE POLIOVAKSINE I STUDIEN VAVA 96-01
- 2. DOSE POLIOVAKSINE I STUDIEN VAVA 96-01
- POLIOVAKSINASJON I STUDIEN VAVA 96-01: HELSESTASJONSBESØK ETTER 2. VAKSINEDOSE
- 3. DOSE POLIOVAKSINE I STUDIEN VAVA 96-01
- POLIOVAKSINASJON I STUDIEN VAVA 96-01: HELSESTASJONSBESØK ETTER 3. VAKSINEDOSE
- LABORATORIESKJEMA NR. 1-4 I STUDIEN VAVA 96-01

Appendix 5:
ANTISTOFFRESPONS ETTER VAKSINASJON MOT POLIOMYELITT MED IPV-VERO
PROTOKOLL VAVA 96-01: ARBEIDSRUTINER:

FOLIO 1181

Appendix 16.1.2 –Sample Case report Form of Study 88A

Form 0

FOLKEHELSA
Statens institutt for folkehelse
National Institute of Public Health

FORMS IN CONNECTION WITH THE VAVA 96-01 STUDY

PERSONAL DETAILS
Vaccination no.: Initials:
Name:
Date of birth:
Sex: M ☐ F ☐

FORM NO.	TITLE	FILLED IN BY	ENTERED IN STUDY BOOK	
			Date	Sign.
1	Parental information + consent	Parents		
2	Admission form	Health visitor + doctor		
3 *	Laboratory form no. 1	Health visitor + lab		
4	1st dose of polio vaccine	Vaccinator		
5	Parents' form: Registration after 1st dose of polio vaccine	Parents		
6	2nd dose of polio vaccine	Vaccinator		
7	Parents' form: Registration after 2nd dose of polio vaccine	Parents		
8 *	Laboratory form no. 2	Health visitor + lab		
9	Paediatric health centre visit after 2nd dose of polio vaccine	Health visitor		
10	Paediatric health centre visit before 3rd dose of polio vaccine	Health visitor		
11 *	Laboratory form no. 3	Health visitor + lab		
12	3rd dose of polio vaccine	Vaccinator		
13	Parents' form: Registration after 3rd dose of polio vaccine	Parents		
14 *	Laboratory form no. 4	Health visitor + lab		
15	Paediatric health centre visit after 3rd dose of polio vaccine	Health visitor		
16 **	Discontinued participation in the VAVA 96-01 study	Health visitor + doctor		

*) The laboratory forms must be **partly filled in by the health visitor**, taken to the laboratory and sent from there to the coordinator.
) This form is only to be filled in if the vaccinated child is excluded or withdraws **during the study.

These are the forms in **white** fields that are included in the study binder by the health visitor / vaccinator. The forms in shaded fields will be dealt with by the coordinator / monitor.

CAIF S.A.
María Bernarda Belay
Farmacéutica
Co - Directora Técnica
M.P. 15.148

Appendix 16.1.2 –Sample Case report Form of Study 88A

Form 1

FOLKEHELSA
Statens institutt for folkehelse
National Institute of Public Health

POLIO VACCINATION IN THE VAVA 96-01 STUDY:
INFORMATION FOR PARENTS ABOUT A CLINICAL STUDY OF POLIO VACCINE IPV-VERO

The polio vaccine offered to Norwegian infants as part of the infant vaccination programme is produced in the Netherlands. The vaccine is safe and only rarely causes any side effects worth mentioning. It provides good protection against all three types of polio virus. In order to produce vaccine, polio virus is cultured on cells taken from the kidneys of apes. The manufacturer now wishes to change over to growing the virus on cells that grow in a culture (Vero cells). This will result in more standardised cells that are always identical, and the use of apes can be avoided. In every other respect the new vaccine is produced in precisely the same way as the vaccine that is currently in use.

The new vaccine has been tried out as a booster dose for previously vaccinated adults. It resulted in antibody formation that was just as good as with the vaccine that is currently in use, and there were just as few side effects. However, the vaccine cannot be used in the vaccination programme until it has been shown to also provide adequate protection in infants. The vaccine should in that case be given by itself, as is the case in the Norwegian infant vaccination programme.

The aims of the study are as follows:

1. *The children are vaccinated according to the usual programme. 70% of the children are given the Verocelle vaccine and 30% are given the usual polio vaccine.*

2. *The parents fill in the form with reports of any unusual events in the children in the first 3 days following vaccination, regardless of whether they believe these have anything to do with the vaccination. This is done in order to compare the incidence of side effects for the two types of vaccine.*

3. *Four blood samples are taken from the arm: one sample before the first vaccine dose, one sample at least four weeks after the second dose, one sample before the third dose and one at least four weeks after the third dose.*

Polio vaccine causes few side effects. Children might be bad-tempered, distressed and screaming, or more sleepy than usual during the first few days. There may be short-lasting fever in rare cases. Soreness and swelling at the injection site are also rare. We do not anticipate any side effects after taking blood samples.

If any unexpected/serious side effects occur in conjunction with vaccination or taking samples, you must contact a doctor immediately. Please also contact the paediatric health centre so that they can report the event to the study director at the Norwegian Institute of Public Health's Department of Vaccines.

Parents may take their children out of the study at any time without having to give a reason. If they do, their child will continue to be vaccinated entirely as normal.

Department of Vaccines, the Norwegian Institute of Public Health,
1996

Appendix 16.1.2 –Sample Case report Form of Study 88A

Form 1

FOLKEHELSA
Statens institutt for folkehelse
National Institute of Public Health

POLIO VACCINATION IN THE VAVA 96-01 STUDY:
CONSENT FORM
(To be completed in duplicate. This is the paediatric health centre's copy)

I/we have been provided with information about the aims of the study and consent to my/our child

Name:

date of birth:

taking part in the IPV-Vero polio vaccine study. I/we understand that I/we are free to take my/our child out of the study at any time.

Date

Signature

Appendix 16.1.2 –Sample Case report Form of Study 88A

Form 2

FOLKEHELSA
Statens institutt for folkehelse
National Institute of Public Health

POLIO VACCINATION IN THE VAVA 96-01 STUDY: ADMISSION FORM

(Keep the form at the paediatric health centre. Send a copy to the Norwegian Institute of Public Health. Copy sent (date):)

PERSONAL DETAILS

Name:
Initials: Date of birth: Sex: M ☐ F ☐
Postal address:
Birth weight:
Place of birth:
Number of children in the household:
Parents' homeland: ☐ Norway, both parents ☐ Other, specify:
Ethnic background:
Informed consent signed (date):

INCLUSION CRITERIA:

	Yes	No
Generally good health	☐	☐
Born after a pregnancy lasting ≥36 weeks	☐	☐
Birth weight ≥2.5 kg	☐	☐
Parents have given written consent	☐	☐
Parents understand Norwegian	☐	☐

EXCLUSION CRITERIA:

	Yes	No
Bad weight increase	☐	☐
Suspected delayed development	☐	☐
Previously given polio vaccine	☐	☐
Given blood products ≤ 3 months before start	☐	☐
Taking part in another clinical study	☐	☐
Known allergy to component of the vaccine	☐	☐
Planning to move from the area	☐	☐
Anticipated problems with follow-up	☐	☐

CONCLUSION:

	Yes	No	
Can take part in the study	☐	☐	Included as vaccinated child no.:
Admission carried out by (sign.):			Date:
Approval by doctor (sign.):			Date:

Laboratory form no. 1 (form 3) issued to the parents (date and sign.):
1st blood sample to be taken on (date):

APPROVED:

Study coordinator (sign.): Date:
Monitor (sign.): Date:

Appendix 16.1.2 –Sample Case report Form of Study 88A

Form 3

FOLKEHELSA
Statens institutt for folkehelse
National Institute of Public Health

LABORATORY FORM NO. 1 IN THE VAVA 96-01 STUDY

(The form is given to the parents, who take it with them to the laboratory. The laboratory then sends it to the Norwegian Institute of Public Health together with the blood sample)

PERSONAL DETAILS
Vaccinated child no.: Initials:
Name:
Date of birth:

1st DOSE OF POLIO VACCINE
To be given (date):

APPOINTMENT
Fürst Medisinske Laboratorium, Ski Storsenter (3rd floor, 5th elevator stop. Entrance from Jernbanevn. or via the centre). Tel.: +47 22 90 95 00.
day date time

Emla plasters
number issued ☐

BLOOD SAMPLE (7-0 days before 1st vaccine dose)
Date taken:
Total volume of blood: ml
Laboratory:
Signature:

For the laboratory:
Send serum together with this request to VAVA, Folkehelsa, Postboks 4404 Torshov, NO-0403 Oslo. On the same day, fax a copy of this form to Folkehelsa at +47 22 04 23 01. Keep the copy at the laboratory.

CAIF S.A.
María Bernarda Belay
Farmacéutica
Co - Directora Técnica
M.P. 15.148

Appendix 16.1.2 –Sample Case report Form of Study 88A

Form 4

FOLKEHELSA
Statens institutt for folkehelse
National Institute of Public Health

1st DOSE OF POLIO VACCINE IN THE VAVA 96-01 STUDY

(Usually at 6 months old. Keep the form at the paediatric health centre. Send a copy to the Norwegian Institute of Public Health.
Copy sent (date):)

PERSONAL DETAILS

Vaccinated child no.: Initials: Date of birth:
Name:

Consent form signed Yes ☐ No ☐

Inclusion and exclusion criteria (see form 2) have been gone through today Yes ☐ No ☐

Were any exclusion criteria found (see form 2)? Yes ☐ No ☐

1st BLOOD SAMPLE:

Date taken:

Travel expenses received (date):

POLIO VACCINE DOSE NO. 1:

Batch no. (starting with E 94 or higher/starting with 750 or higher):
Dose size:
Injection site:
Other simultaneously administered
vaccines: No ☐ Yes ☐
If yes, give details (type, batch no, and injection site):
Paediatric health centre:

Date: Vaccinator's signature:

FORM

Parents' form: Registration after 1st dose of polio vaccine (form 5) issued

(date and sign.):

Appendix 16.1.2 –Sample Case report Form of Study 88A

Form 5

FOLKEHELSA
Statens institutt for folkehelse
National Institute of Public Health

POLIO VACCINATION IN THE VAVA 96-01 STUDY, PARENTS' FORM: REGISTRATION AFTER 1st DOSE OF POLIO VACCINE

(Give the filled-in form to the health visitor at your next visit to the paediatric health centre. The health visitor keeps the original and sends a copy to the Norwegian Institute of Public Health. Copy sent (date):)

Vaccinated child no.: Name: Date of birth:
Polio vaccine dose no. given (date) Paediatric health centre:

Did anything out of the ordinary happen with your child during the first 3 days after vaccination? If YES, give a description on the reverse if necessary

FEVER No ☐ Yes ☐

When: How high:
For how long:

SCREAMING MORE THAN USUAL No ☐ Yes ☐

When: For how long:
How:

REDNESS/INFLAMMATION AT THE INJECTION SITE No ☐ Yes ☐

When: For how long:
Area of redness larger than a one-krone coin (2.5 cm) No ☐ Yes ☐
Area of inflammation larger than a one-krone coin (2.5 cm) No ☐ Yes ☐

PAIN AT THE INJECTION SITE No ☐ Yes ☐

When: For how long:
Describe your child's behaviour:

RASH: No ☐ Yes ☐

When: For how long:
How:

OTHER: No ☐ Yes ☐

Give a description:

Did anything happen with your child later on which you suspect may be connected with the vaccination?
No ☐ Yes ☐ If YES, give a description on the reverse of this sheet

Appendix 16.1.2 –Sample Case report Form of Study 88A

Form 6

FOLKEHELSA
Statens institutt for folkehelse
National Institute of Public Health

2nd DOSE OF POLIO VACCINE IN THE VAVA 96-01 STUDY

(Usually at 8 months old. Keep the form at the paediatric health centre. Send a copy to the Norwegian Institute of Public Health.
Copy sent (date):)

PERSONAL DETAILS
Vaccinated child no. Initials: Date of birth:
Name:

SIDE EFFECTS AFTER 1st DOSE OF POLIO VACCINE
Did anything out of the ordinary happen with your child after the 1st dose of polio vaccine? Yes ☐ No ☐
If yes, give details:
Health visitor's assessment of the side effects:

	1	2	3	4	(1 = very mild, 4 = very severe)
Pain:	☐	☐	☐	☐	
Screaming:	☐	☐	☐	☐	

Parents' form: Registration after 1st dose (form 5) received (date):

Consent form signed Yes ☐ No ☐
Inclusion and exclusion criteria (see form 2) have been gone through today Yes ☐ No ☐
Were any exclusion criteria found (see form 2)? Yes ☐ No ☐

POLIO VACCINE DOSE NO. 2:
Batch no. (starting with E 94 or higher/starting with 750 or higher):
Dose size:
Injection site:
Other simultaneously administered vaccines: No ☐ Yes ☐
If yes, give details (type, batch no. and injection site):
Paediatric health centre:
Date: Vaccinator's signature:

2ND BLOOD SAMPLE: To be taken (date):

FORMS
Parents' form: Registration after 2nd dose of polio vaccine (form 7) issued (date and sign.):
Laboratory form no. 2 (form 8) issued (date and sign.):

Appendix 16.1.2 –Sample Case report Form of Study 88A

Form 7

FOLKEHELSA
Statens institutt for folkehelse
National Institute of Public Health

POLIO VACCINATION IN THE VAVA 96-01 STUDY, PARENTS' FORM: REGISTRATION AFTER 2nd DOSE OF POLIO VACCINE

(Give the filled-in form to the health visitor at your next visit to the paediatric health centre. The health visitor keeps the original and sends a copy to the Norwegian Institute of Public Health. Copy sent (date):)

Vaccinated child no.: Name: Date of birth:
Polio vaccine dose no. given (date): Paediatric health centre:

Did anything out of the ordinary happen with your child during the first 3 days after vaccination? If YES, give a description on the reverse if necessary

FEVER No ☐ Yes ☐

When: How high:
For how long:

SCREAMING MORE THAN USUAL No ☐ Yes ☐

When: For how long:
How:

REDNESS/INFLAMATION AT THE INJECTION SITE No ☐ Yes ☐

When: For how long:
Area of redness larger than a one-krone coin (2.5 cm) No ☐ Yes ☐
Area of inflammation larger than a one-krone coin (2.5 cm) No ☐ Yes ☐

PAIN AT THE INJECTION SITE No ☐ Yes ☐

When: For how long:
Describe your child's behaviour:

RASH: No ☐ Yes ☐

When: For how long:
How:

OTHER: No ☐ Yes ☐

Give a description:

Did anything happen with your child later on which you suspect may be connected with the vaccination?
No ☐ Yes ☐ If YES, give a description on the reverse of this sheet

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M.P. 15.148

Appendix 16.1.2 –Sample Case report Form of Study 88A

Form 8

FOLKEHELSA
Statens institutt for folkehelse
National Institute of Public Health

LABORATORY FORM NO. 2 IN THE VAVA 96-01 STUDY

(The form is given to the parents, who take it with them to the laboratory. The laboratory then sends it to the Norwegian Institute of Public Health together with the blood sample)

PERSONAL DETAILS

Vaccinated child no.: Initials:
Name:
Date of birth:

1st DOSE OF POLIO VACCINE

Date administered:

APPOINTMENT

Først Medisinske Laboratorium, Ski Storsenter (3rd floor, 5th elevator stop. Entrance from Jernbanevn. or via the centre). Tel.: +47 22 90 95 00.
day date time

Emla plasters
number issued ☐

BLOOD SAMPLE (4-8 days after 2nd vaccine dose)
Date taken:
Total volume of blood: ml
Laboratory:
Signature:

For the laboratory:
Send serum together with this request to VAVA, Folkehelsa, Postboks 4404 Torshov, NO-0403 Oslo. On the same day, fax a copy of this form to Folkehelsa at +47 22 04 23 01. Keep the copy at the laboratory.

Appendix 16.1.2 –Sample Case report Form of Study 88A

Form 9

FOLKEHELSA
Statens institutt for folkehelse
National Institute of Public Health

PAEDIATRIC HEALTH CENTRE VISIT AFTER 2nd DOSE OF POLIO VACCINE IN THE VAVA 96-01 STUDY

(Usually at 10-month check-up. Keep the form at the paediatric health centre. Send a copy to the Norwegian Institute of Public Health. Copy sent (date):)

PERSONAL DETAILS
Vaccinated child no. Initials: Date of birth:
Name:

SIDE EFFECTS AFTER 2nd DOSE OF POLIO VACCINE
Parents' form: Registration after 2nd dose (form 7) received (date):
Did anything out of the ordinary happen with your child after the 2nd dose of polio vaccine? Yes ☐ No ☐
If yes, give details:

Health visitor's assessment of the side effects:

	1	2	3	4	(1 = very mild, 4 = very severe)
Pain:	☐	☐	☐	☐	
Screaming:	☐	☐	☐	☐	

2. BLOOD SAMPLE:
Date taken:
Travel expenses received (date):

Appendix 16.1.2 –Sample Case report Form of Study 88A

Form 10

FOLKEHELSA
Statens institutt for folkehelse
National Institute of Public Health

THE VAVA 96-01 STUDY: PAEDIATRIC HEALTH CENTRE VISIT BEFORE 3rd DOSE OF POLIO VACCINE

(Usually at 15 months old. Keep the form at the paediatric health centre. Send a copy to the Norwegian Institute of Public Health. Copy sent (date):)

PERSONAL DETAILS

Vaccinated child no.: Initials: Date of birth:
Name:

3rd BLOOD SAMPLE:

To be taken (date):

FORM

Laboratory form no. 3 (form 11) issued (date and sign.):

Appendix 16.1.2 –Sample Case report Form of Study 88A

Form 11

FOLKEHELSA
Statens institutt for folkehelse
National Institute of Public Health

LABORATORY FORM NO. 3 IN THE VAVA 96-01 STUDY

(The form is given to the parents, who take it with them to the laboratory. The laboratory then sends it to the Norwegian Institute of Public Health together with the blood sample)

PERSONAL DETAILS
Vaccinated child no.: Initials:
Name:
Date of birth:

3rd DOSE OF POLIO VACCINE
To be given (date):

APPOINTMENT
Fürst Medisinske Laboratorium, Ski Storsenter (3rd floor, 5th elevator stop. Entrance from Jernbanevn. or via the centre). Tel.: +47 22 90 95 00.
day date time

Emla plasters
number issued ☐

BLOOD SAMPLE (7-0 days after 3rd vaccine dose)
Date taken:
Total volume of blood: ml
Laboratory:
Signature:

For the laboratory:
Send serum together with this request to VAVA, Folkehelsa, Postboks 4404 Torshov, NO-0403 Oslo. On the same day, fax a copy of this form to Folkehelsa at +47 22 04 23 01. Keep the copy at the laboratory.

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Appendix 16.1.2 –Sample Case report Form of Study 88A

Form 12

FOLKEHELSA
Statens institutt for folkehelse
National Institute of Public Health

3rd DOSE OF POLIO VACCINE IN THE VAVA 96-01 STUDY

(Keep the form at the paediatric health centre. Send a copy to the Norwegian Institute of Public Health,
Copy sent (date):)

PERSONAL DETAILS

Vaccinated child no.: Initials: Date of birth:
Name:

3rd BLOOD SAMPLE:

Date taken:
Travel expenses received (date):

Consent form signed	Yes ☐ No ☐
Inclusion and exclusion criteria (see form 2) have been gone through today	Yes ☐ No ☐
Were any exclusion criteria found (see form 2)?	Yes ☐ No ☐

POLIO VACCINE DOSE NO. 3:

Batch no. (starting with E 94 or higher/starting with 750 or higher):
Dose size:
Injection site;
Other simultaneously administered
vaccines: No ☐ Yes ☐
If yes, give details (type, batch no. and injection site):
Paediatric health centre:
Date: Vaccinator's signature:

4th BLOOD SAMPLE:

To be taken (date):

FORMS

Parents' form; Registration after 3rd dose of polio vaccine (form 13) issued (date and sign.);
Laboratory form no. 4 (form 14) issued (date and sign.);

1188

Appendix 16.1.2 –Sample Case report Form of Study 88A

Form 13

FOLKEHELSA
Statens institutt for folkehelse
National Institute of Public Health

POLIO VACCINATION IN THE VAVA 96-01 STUDY, PARENTS' FORM: REGISTRATION AFTER 3rd DOSE OF POLIO VACCINE

(Give the filled-in form to the health visitor at your next visit to the paediatric health centre. The health visitor keeps the original and sends a copy to the Norwegian Institute of Public Health. Copy sent (date):)

Vaccinated child no.: Name: Date of birth:
Polio vaccine dose no. given (date) Paediatric health centre:

Did anything out of the ordinary happen with your child during the first 3 days after vaccination? If YES, give a description on the reverse if necessary

FEVER No ☐ Yes ☐

When: How high:
For how long:

SCREAMING MORE THAN USUAL No ☐ Yes ☐

When: For how long:
How:

REDNESS/INFLAMATION AT THE INJECTION SITE No ☐ Yes ☐

When: For how long:
Area of redness larger than a one-krone coin (2.5 cm) No ☐ Yes ☐
Area of inflammation larger than a one-krone coin (2.5 cm) No ☐ Yes ☐

PAIN AT THE INJECTION SITE No ☐ Yes ☐

When: For how long:
Describe your child's behaviour:

RASH: No ☐ Yes ☐

When: For how long:
How:

OTHER: No ☐ Yes ☐

Give a description:

Did anything happen with your child later on which you suspect may be connected with the vaccination?
No ☐ Yes ☐ If YES, give a description on the reverse of this sheet

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Appendix 16.1.2 –Sample Case report Form of Study 88A

Form 14

FOLKEHELSA
Statens institutt for folkehelse
National Institute of Public Health

LABORATORY FORM NO. 4 IN THE VAVA 96-01 STUDY

(The form is given to the parents, who take it with them to the laboratory. The laboratory then sends it to the Norwegian Institute of Public Health together with the blood sample)

PERSONAL DETAILS

Vaccinated child no.: Initials:
Name:
Date of birth:

3rd DOSE OF POLIO VACCINE

Date administered:

APPOINTMENT

Fürst Medisinske Laboratorium, Ski Storsenter (3rd floor), 5th elevator stop. Entrance from Jernbanevn. or via the centre). Tel.: +47 22 90 95 00.
day date time

Emla plasters
number issued ☐

BLOOD SAMPLE (At least 4 weeks after the 3rd vaccine dose)
Date taken:
Total volume of blood: ml
Laboratory:
Signature:

For the laboratory:
Send serum together with this request to VAVA, Folkehelsa, Postboks 4404 Torshov, NO-0403 Oslo. On the same day, fax a copy of this form to Folkehelsa at +47 22 04 23 01. Keep the copy at the laboratory.

Appendix 16.1.2 –Sample Case report Form of Study 88A

Form 15

FOLKEHELSA
Statens institutt for folkehelse
National Institute of Public Health

PAEDIATRIC HEALTH CENTRE VISIT AFTER 3rd DOSE OF POLIO VACCINE IN THE VAVA 96-01 STUDY

(Keep the form at the paediatric health centre. Send a copy to the Norwegian Institute of Public Health.
Copy sent (date):)

PERSONAL DETAILS

Vaccinated child no. Initials: Date of birth:
Name:

SIDE EFFECTS AFTER 3rd DOSE OF POLIO VACCINE

Registration of side effects after 3rd dose supplied (date):
Did anything out of the ordinary happen with your child after the 3rd dose of polio vaccine? Yes ☐ No ☐
If yes, give details:

Health visitor's assessment of the side effects:

	1	2	3	4	(1 = very mild, 4 = very severe)
Pain:	☐	☐	☐	☐	
Screaming:	☐	☐	☐	☐	

4th BLOOD SAMPLE:

Date taken:
Travel expenses received (date):

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Appendix 16.1.2 –Sample Case report Form of Study 88A

Form 16

FOLKEHELSA
Statens institutt for folkehelse
National Institute of Public Health

DISCONTINUED PARTICIPATION IN THE VAVA 96-01 STUDY

(Only fill this form in if the vaccinated child is excluded or withdraws during the study. Keep the form in the binder at the paediatric health centre)

PERSONAL DETAILS
Vaccinated child no.: Initials:
Name:
Date of birth:
Sex: M ☐ F ☐

EXCLUDED FOR MEDICAL REASONS ☐ Yes ☐ No

Date: Doctor (sign.):
Reason(s):

WITHDREW FROM THE STUDY ☐ Yes ☐ No

Date: Health visitor (sign.):
Reason(s):

APPROVED
Study coordinator (sign.): Date:
Monitor (sign.): Date:

Appendix 16.1.2 –Sample Case report Form of Study 88A

POLIO VACCINATION IN THE VAVA 96-01 STUDY: SUMMARY FORM

1+2: **PERSONAL DETAILS**
Vaccinated child no.: Initials: Date of birth: Sex: M ☐ F ☐

Name:
Postal address:
Birth weight: Number of children in the family:
Ethnic background: Consent form signed (date):
Admission date: Done by: Paediatric health centre:

3: **1st BLOOD SAMPLE** taken (date):

4: **POLIO VACCINE DOSE NO. 1:** Batch no. Date given:
Other vaccines taken at the same time: No ☐ Yes ☐ Give details

Paediatric health centre: Vaccinator:

5: **REGISTERING SIDE EFFECTS AFTER 1ST DOSE** supplied (date):

6: **POLIO VACCINE DOSE NO. 2:** Batch no. Date given:
Other vaccines taken at the same time: No ☐ Yes ☐ Give details

Paediatric health centre: Vaccinator:

7: **REGISTERING SIDE EFFECTS AFTER 2ND DOSE** supplied (date):
8: **2nd BLOOD SAMPLE** taken (date):

9: **PAEDIATRIC HEALTH CENTRE VISIT AFTER 2ND VACCINE DOSE** form issued (date):

10 + 11: **3rd BLOOD SAMPLE** taken (date):

12: **POLIO VACCINE DOSE NO. 2:** Batch no. Date given:
Other vaccines taken at the same time: No ☐ Yes ☐ Give details

Paediatric health centre: Vaccinator:

13: **REGISTERING SIDE EFFECTS AFTER 3rd DOSE** supplied (date):
14: **4TH BLOOD SAMPLE** taken (date):

15: **PAEDIATRIC HEALTH CENTRE VISIT AFTER 3rd VACCINE DOSE** form issued (date):

16: **PARTICIPATION DISCONTINUED** No ☐ Yes ☐ Date:

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Farmacéutica
Co - Directora Técnica
M.P. 15.148

Appendix 16.1.3 –Patient written information and consent form of Study 88A

POLIO VACCINATION IN THE VAVA 96-01 STUDY:

INFORMATION FOR PARENTS ABOUT A CLINICAL STUDY OF POLIO VACCINE IPV-VERO

The polio vaccine offered to Norwegian infants as part of the infant vaccination programme is produced in the Netherlands. The vaccine is safe and only rarely causes any side effects worth mentioning. It provides good protection against all three types of polio virus. In order to produce vaccine, polio virus is cultured on cells taken from the kidneys of apes. The manufacturer now wishes to change over to growing the virus on cells that grow in a culture (Vero cells). This will result in more standardised cells that are always identical, and the use of apes can be avoided. In every other respect the new vaccine is produced in precisely the same way as the vaccine that is currently in use.

The new vaccine has been tried out as a booster dose for previously vaccinated adults. It resulted in antibody formation that was just as good as with the vaccine that is currently in use, and there were just as few side effects. However, the vaccine cannot be used in the vaccination programme until it has been shown to also provide adequate protection in infants. The vaccine should in that case be given by itself, as is the case in the Norwegian infant vaccination programme.

The aims of the study are as follows:

1. *The children are vaccinated according to the usual programme. A certain proportion* of children are given the Verocelle vaccine and a certain proportion* are given the usual polio vaccine.*

2. *The parents fill in the form with reports of any unusual events in the children in the first 3 days following vaccination, regardless of whether they believe these have anything to do with the vaccination. This is done in order to compare the incidence of side effects for the two types of vaccine.*

3. *Four blood samples are taken from the arm: one sample before the first vaccine dose, one sample at least four weeks after the second dose, one sample before the third dose and one at least four weeks after the third dose.*

Polio vaccine causes few side effects. Children might be bad-tempered, distressed and screaming, or more sleepy than usual during the first few days. There may be short-lasting fever in rare cases. Soreness and swelling at the injection site are also rare. We do not anticipate any side effects after taking blood samples.

If any unexpected/serious side effects occur in conjunction with vaccination or taking samples, you must contact a doctor immediately. Please also contact the paediatric health centre so that they can report the event to the study director at the Norwegian Institute of Public Health's Department of Vaccines.

Parents may take their children out of the study at any time without having to give a reason. If they do, their child will continue to be vaccinated entirely as normal.

Department of Vaccines, the Norwegian Institute of Public Health,
1996

Appendix 16.1.3 –Patient written information and consent form of Study 88A

POLIO VACCINATION IN THE VAVA 96-01 STUDY:

CONSENT FORM

I/we have been provided with information about the aims of the study and consent to my/our child

Name:

date of birth:

taking part in the IPV-Vero polio vaccine study. I/we understand that I/we are free to take my/our child out of the study at any time.

Date

Signature

CAIF S.A.
María Bernarda Belay
Farmacéutica
Co - Directora Técnica
M.P. 15.148

Appendix 16.1.4 –Curriculum Vitae of principle investigator of Study 88A

CURRICULUM VITAE

Family name:	Sandbu
Given name:	Synne
Date of birth:	17. March 1946
Place of birth:	Vågå, Norway
Address:	Askerjordet 37, N-1383 Asker, Norway

EDUCATION:

- Medical Degree, Faculty of Medicine, University of Oslo, June 1973.
- Diploma of Tropical Medicine and Hygiene, Liverpool 1977 (Lent term)
- Summer Institute of Linguistics, High Wycombe, U.K., basic course 1977.
- Recognized specialist in pediatrics 1991 (Norwegian Medical Association).
- Nordic Summer School in Methods of Infectious Disease Epidemiology 1998.

JOB EXPERIENCE:

- Kristiansund Hospital, internship 12 months 1973-74.
- Sel Municipality Health Services, internship 6 months 1973-75.
- Oslo City Hospital, Out-patient emergency department, house officer 9 months 1975.
- Narvik Hospital, Department of surgery, house officer 15 months 1975-77.
- Rural health project in Bangladesh with the Norwegian Santal Mission, 1977-81 (4 years 10 months) and 1986-88 (2 years 10 months). The health project gave integrated health care with emphasis on MCH in a district with approx. 20 000 pop. For the first period I was the only physician and responsible for educating staff and building up the medical services, organizing epidemiologic surveillances and making reporting and evaluation systems. For part of the second period I was Chief Medical Officer with a a medical staff of more than thirty persons, and with 35000-42000 out-patient consultations each year beside a limited number of in-patients.
- Telemark Sentralsjukehus, Department of Pediatrics, house officer 6 months 1983.
- Rogaland Sentralsjukehus, Department of Pediatrics, house officer 30 months 1983-86.
- National Hospital of Norway, Department of Pediatrics, house officer 26 months 1989-91. As this is the University Hospital of Oslo, I also had my small part of teaching medical students.
- Norwegian Institute of Public Health (NIPH), Department of Vaccination and Immunity (previously National Institute of Public Health, Department of Vaccine), senior house officer from Feb. 1991, senior medical officer from May 1997. My job does focus on correct use of vaccines and mainly consists of three parts: 1) give advice to vaccinators who call us, 2) look at adverse events reports, evaluate them and advise on further vaccination and 3) do clinical studies on vaccines. In addition responsible supervisor of a travel vaccination clinic at the institute. Occasional duties are teaching for public health nurses and other health professionals. From 2002 responsible for Pharmacovigilance. From 2003 project leader for SYSVAK (National immunisation registry).

Clinical studies: till now I have been principal investigator of six studies (five completed with reports to Norwegian Medicines Control Authority). Two studies on IPV (VAVA92-01, VAVA 94-02) lead to adjustments of Norwegian vaccination recommendations. One study on IPV-Vero (VAVA96-01) was done in cooperation with RIVM. Two simultanous studies on pertussis booster vaccination of school children (VAVA98-01/SB 213503/037 and VAVA98-02/SB 208355/122) were done in cooperation with SmithKlineBeecham AS. One study on meningococcal B-vaccine (VA01-01 A) not yet completed with laboratory analyses.

Appendix 16.1.4 –Curriculum Vitae of principle investigator of Study 88A

PUBLICATIONS

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Synne Sandbu, Hanne Nøkleby, Oddveig Sellæg Helland, Berit Feiring, Margreta Bondevik, Folke Sundelin, Jann Storsæter. Bør skolebarn få kikhostevaksine? [Should school children receive pertussis vaccine?] Tidsskr Nor Laegeforen. 2001 May 10;121(12):1464-8.

S. Sandbu, H. Nøkleby, O. Helland, L.B. Flugsrud, H.C. Rümke. IPV-VERO VACCINE GIVES HIGH ANTIBODY RESPONSE AND IS WELL TOLERATED IN INFANTS. Poster at 19th annual meeting of the European Society for Paediatric Infectious Diseases (ESPID), Istanbul, Turkey, March 26 – 28, 2001.

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Vaksinasjoner i barne- og ungdomsalder (Foreldrebrosjyre), utgitt av Statens helsetilsyn i samarbeid med Statens institutt for folkehelse 1994, IK-2031B.

Vaksinasjon i barne- og ungdomsalder (Foreldrebrosjyre), utgitt av Folkehelseinstituttet 2004, IN-0000-2072-1

Veiledning om vaksinasjon 1996 (red: Hanne Nøkleby), Statens institutt for folkehelse 1996. Kapitlene 1.6, 2.1, 2.3, 2.6, 2. 8, 2.9, 3.1, 3.5, 3.6, 3.7, 3.8, 3.11, 3.12, 3.13 og delaktighet i det redaksjonelle arbeid.

Veiledning om vaksinasjon 1998 (red: Hanne Nøkleby), Statens institutt for folkehelse 1998. ISBN 82-7364-128-7. Kapitlene 1.6, 2.1, 2.3, 2.6, 2. 8, 2.9, 3.1, 3.5, 3.6, 3.7, 3.8, 3.11, 3.12, 3.13 og delaktighet i det redaksjonelle arbeid.

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RIJKSINSTITUUT VOOR VOLKSGEZONDHEID EN MILIEU
NATIONAL INSTITUTE OF PUBLIC HEALTH AND THE ENVIRONMENT

RIVM report 105000 001

A randomised controlled study with whole-cell or acellular pertussis vaccines in combination with regular DT-IPV vaccine and a new poliomyelitis (IPV-Vero) component in children 4 years of age in the Netherlands

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J. Labadie, P.E. Vermeer-de Bondt,
D.J.A. Bolscher, A.D. Plantinga January 1999

This investigation has been performed by order and for the account of Chief Inspectorate of Health Care, within the framework of project 105030, clinical trials new RIVM vaccines.

RIVM, P.O. Box 1, 3720 BA Bilthoven, telephone: 31 - 30 - 274 91 11; telefax: 31 - 30 - 274 29 71

Abstract

In this trial we have studied the immunogenicity and reactogenicity of 3 different acellular pertussis vaccines and the whole cell vaccine from the RIVM combined with DT-IPV administered as a booster in children 4 years of age. In these children, the immune response of IPVvero (produced on Vero cells) was also evaluated together with the regular IPV-MK (produced on monkey kidney cells). The children in this study were immunized 3 years earlier with 4 doses of the RIVM DTP-IPV at the age of 3, 4, 5 and 11 months. The acellular vaccines were composed of PT and FHA (2 component vaccine from Pasteur Merieux), PT, FHA and PRN (3 component vaccine from Smithkline Biologicals) and PT, FHA, PRN and FIM (4 component vaccine from Wyeth Lederle/Takeda). The study was an open, randomised, controlled study with a blinded serological evaluation. All the responses to the different vaccine components clearly demonstrate that the children are well primed with the DTP-IPV.

In conclusion, this study demonstrates that an addition of a pertussis vaccination in 4 year old children might be useful in an epidemical situation, in which a combination vaccine (with acellular or whole cell pertussis component) is to be preferred because of the single administration. Furthermore, the IPVvero shows to be a very immunogenic vaccine and the response is at least the same as observed for the regular IPV-MK.

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LVO: Laboratory for Clinical Vaccine Research
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LIS: Diagnostic Laboratory for Infectious Diseases and Perinatal Screening
Hans Boshuis, Bert Elvers (IgA whole cell assay)

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Abbreviations

ACV	Acellular Vaccine
°C	Degrees Centigrade
CB	Child Health Clinic *(consultatiebureau)*
$CCID_{50}$	Cell Culture Infectious Dose
CI	Confidence Interval
CRF	Case Report Form
D-ag	poliovirus D-antigen units
DT-IPV	Diphtheria, Tetanus and Inactivated Poliovirus Vaccine *(Difterie, Tetanus, Polio (DTP) vaccin)*
DTP-IPV	Diphtheria, Tetanus, Pertussis (-whole cell) and Inactivated Poliovirus Vaccine *(Difterie, Kinkhoest, Tetanus, Polio (DKTP) vaccin)*
ELISA	Enzyme Linked Immuno Sorbent Assay
EU	ELISA units
FHA	Filamentous Hemagglutinin
FIM	Fimbriae
GCP	Good Clinical Practice
GMT	geometric mean titer
IgA	Immunoglobulin A
IgA-WC	IgA Whole Cell ELISA
IgG	Immunoglobulin G
IU	International Units
IOU	International Opacity Units
IPV-MK	Inactivated Polio Vaccine grown on monkey kidney cells
IPVv	Inactivated Polio Vaccine grown on Vero cells
IPVvero	Inactivated Polio Vaccine grown on Vero cells
kD	kiloDalton
KRZ	Bureau for Quality and Regulatory Affairs *(Bureau Kwaliteits en Registratiezaken RIVM)*
LCB	Laboratory for Control of Biological products *(Laboratorium voor Controle Biologische Produkten)*
LIO	Laboratory for Research of Infectious Diseases *(Laboratorium voor Infectieziektenonderzoek)*
LIS	Diagnostic Laboratory for Infectious Diseases and Perinatal Screening *(Laboratorium voor Infectieziektendiagnostiek en Screening)*
Lf	Flocculation units *(Limes flocculationes)*
Ln	Natural Logarithm
LPO	Laboratory for Product and Process Development *(Laboratorium voor Produkt- en Procesontwikkeling)*
LVO	Laboratory for Clinical Vaccine Research *(Laboratorium voor Veldonderzoek vaccins)*
LVO-BI	LVO Bio- and Immunochemistry section *(LVO afdeling bio- en immunochemie)*
MLD	Minimum Level of Detection
OR	Odds ratio

PEA	Immunisation Administration *(Provinciale Entadministratie)*
PM	Pasteur Merieux MSD
PRN	Pertactin
PT	Pertussis Toxin
RIVM	National Institute of Public Health and the Environment *(Rijksinstituut voor Volksgezondheid en Milieu)*
RVP	National Childhood Immunisation Programme *(Rijksvaccinatieprogamma)*
SB	Smithkline Biologicals
SDS	Sodium Dodecyl Sulphate
SOP	Standard Operating Procedure
SVM	Foundation for the Advancement of Public Health *(Stichting Bevordering Volksgezondheid en Milieu)*
ToBI	Toxin Binding Inhibition assay
UTN	Unique Trial Number
WCV	Whole cell vaccine
WHO	World Health Organization
WL	Wyeth Lederle /Takeda

Contents

Samenvatting

Doel/Opzet
In deze studie hebben we de immunogeniciteit en de reactogeniciteit van 3 verschillende ACV's en WCV van het RIVM onderzocht, gecombineerd met DTP toegediend als booster bij 4-jarige kinderen. Bij deze kinderen is tevens de immuunrespons op IPVvero (geproduceerd op Vero cellen) vergeleken met het reguliere IPV-MK (geproduceerd op MK cellen). De kinderen in deze studie zijn eerder gevaccineerd met 4 doses DKTP van het RIVM op de leeftijd van 3, 4, 5 en 11 maanden. De ACV's bevatten PT en FHA (ACV-PM), met PRN als derde component (ACV-SB) en FIM als vierde component (AVC-WL). Het was een open, gerandomiseerde, gecontroleerde studie met geblindeerde serologische bepalingen.

Resultaten en conclusies

De immuunrespons tegen de verschillende vaccincomponenten geeft duidelijk aan dat de kinderen in hun eerste levensjaar goed geprimed zijn met het WCV als component van DKTP van het RIVM. De GMT's tegen de pertussis antigenen, zoals in deze studie bepaald, komen goed overeen met de titers in internationale veldonderzoeken met deze ACV's.

ACV
Alle drie de ACV's induceren een uitstekende respons tegen de pertussis componenten, in zoverre deze antigenen deel uitmaken van de vaccins. Alhoewel de hoeveelheid PT in het ACV-WL 8 maal lager is dan in de andere twee ACV's, is de respons toch gelijk tot 2 maal hoger, hetgeen kan wijzen op verschillende detoxificatie procedures van PT. De immuunrespons tegen Aggl. en FIM in de ACV-PM groep duidt erop dat er waarschijnlijk toch een kleine hoeveelheid FIM in dit vaccin zit.

WCV
De WCV groepen vertonen een zeer brede immuunrespons, waarbij vooral de respons tegen Aggl. en FIM opviel en zelfs beter was dan voor het ACV-WL. De respons tegen FHA en PRN was voldoende, maar tegen PT wat aan de lage kant. De absolute titers tegen PT, FHA en PRN zijn beduidend lager dan die gemeten bij de ACV's, hetgeen toe te schrijven is aan de lagere hoeveelheid van deze antigenen in het WCV van het RIVM. In het merendeel van de kinderen van de WCV groepen werd een onverwachte IgA-respons gemeten, waarvan de biologische relevantie nog vastgesteld dient te worden.

Bijwerkingen
Er vonden geen ernstige bijwerkingen plaats in deze studie. Zoals verwacht veroorzaakte de toediening van het WCV meer algemene en lokale bijwerkingen dan de ACV's, maar er was slechts sprake van mild tot matig ongemak vooral beperkt tot de eerste dag na vaccinatie. De frequentie van de milde bijwerkingen was gunstig vergeleken met die gevonden bij baby's en lijkt hogere reactogeniteit van het WCV bij oudere kinderen niet te bevestigen.

IPV
Beide IPV-vaccins werkten uitstekend in deze studie. Het viervoudige verschil in de hoeveelheid antigeen van polio type 3 in de twee vaccins kan de oorzaak zijn van het significante verschil in respons, dat overigens waarschijnlijk niet klinisch relevant is gezien de extreem hoge titers. Er was geen verschil in bijwerkingen tussen het IPVvero en IPV-MK.

D en T
De immuunrespons tegen het Difterie toxoïd en het Tetanus toxoïd was ook zeer goed. In de DKTP groepen bleek de respons tegen Difterie toxoïd significant hoger te zijn dan in de andere vaccin groepen, hetgeen verklaard kan worden door de grotere hoeveelheid toxoïd in dit vaccin en het adjuverende effect van de WCV-component.

Samenvattend geeft deze studie aan dat een toevoeging van een pertussis vaccinatie op 4-jarige leeftijd zinvol kan zijn bij een epidemische verheffing, waarbij de voorkeur uitgaat naar een combinatievaccin met een ACV- of een WCV-component vanwege de enkelvoudige toediening. Het IPVvero blijkt een zeer immunogeen vaccin te zijn en op zijn minst gelijkwaardig aan het huidige IPV-MK.

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Summary

Aim/Design
In this trial we have studied the immunogenicity and reactogenicity of 3 different ACV's and the RIVM-WCV combined with DT-IPV administered as a booster in children 4 years of age. In these children, the immune response of IPVvero (produced on Vero cells) was also evaluated together with the regular IPV-MK (produced on MK cells). The children in this study were previously immunized with 4 doses of the RIVM DTP-IPV at the age of 3, 4, 5 and 11 months. The ACV's were composed of PT and FHA (ACV-PM), with PRN as 3rd component (ACV-SB) and FIM as 4th component (ACV-WL). The study was an open, randomised, controlled study with a blinded serological evaluation.

Results and conclusions

All the responses to the different vaccine components clearly demonstrate that the children are well primed with WCV as component of DTP-IPV. The GMT's of the pertussis antigens determined in this study are in agreement with the titers observed in other trials with these ACV's.

ACV
All three ACV's induce an excellent response to the pertussis components that are included in the vaccines. The near equal GMT-PT in the different ACV groups, despite the 8-fold lower PT content in ACV-WL may reflect different detoxification procedures of PT. The immune responses to Aggl. and FIM in the ACV-PM group indicate that a small amount of fimbriae is likely to be present in this vaccine.

WCV
The WCV groups showed a very broad immune response. Especially the response against Aggl. and FIM was very good and better than for ACV-WL, the response against FHA and PRN satisfactorily, but against PT somewhat low. The absolute titers to PT, FHA and PRN were considerably lower than observed for the ACV's reflecting the smaller amounts of these antigens present in the RIVM-WCV. Vaccination with DTP-IPV also evoked an unexpected IgA-response in the majority of the children. The biological relevance of this finding is still under investigation.

Adverse events
No serious adverse events occurred during the study. As expected the WCV recipients had more frequent systemic and local symptoms, but generally there was only mild to moderate discomfort, mainly limited to the first day after vaccination. Compared to studies in infants, the rate of adverse events in this group of four year olds is favourable and does not suggest higher reactogenicity of WCV in older children.

IPV
Both IPV-vaccines performed very well in this study. The significant difference in response to polio type 3 may reflect the fourfold difference in the antigen content of this type in the two vaccines, which is most probably of insignificant clinical relevance because of the extreme high antibody titers. No difference in adverse events was observed between the administration of IPV-MK and IPVvero.

D and T
The immune response to Diphtheria toxoid and Tetanus toxoid was also very good. In the DTP-IPV groups the immune response to Diphtheria toxoid was significantly larger than in the other vaccine groups due to the greater antigen content of toxoid in this vaccine and the adjuvant effect of the pertussis WCV-component.

In conclusion, this study demonstrates that an addition of a pertussis vaccination in 4 year old children might be advantageous in an epidemical situation, in which a combination vaccine with an ACV- or a WCV-component is to be preferred requiring a single administration. IPVvero shows to be a very immunogenic vaccine and at least similar to the regular IPV-MK.

2. Materials and methods

2.1 Vaccines

The composition of the different vaccines used in the study is given in Table 1. The following vaccine combinations (lotnumbers between brackets) were studied:

1. DT-IPV as control group (108A)
2. DTP-IPV (184A)
3. DT-IPVv (70373A)
4. DTP-IPVv (70374A)
5. DT-IPV + ACV-SB (108A + 19002B2)
6. DT-IPVv + ACV-SB (70373A + 19002B2)
7. DT-IPV + ACV-WL (108A + 97F04D)
8. DT-IPV + ACV-PM (108A + S3515)

Vaccines were stored in Apeldoorn at a central CB under standard conditions (dedicated vaccines/medicines refrigerator; temperature at 2-8° C; continuous temperature monitoring with auto-dial telephone alert; secured power supply). Adequate packaging under supervision of SVM assured exclusive use of vaccines with lotnumbers assigned for this study. The vaccinations were registered on cards ("blauwe randkaarten") for the PEA to be entered in the central vaccination record of the child.

Table 1. The composition of the acellular and whole cell pertussis vaccines and the regular DT-IPV and DTP-IPV per dose. The pertussis components are expressed in µg, the whole cell vaccine in IOU, diphtheria toxoid (DT) and tetanus toxoid (TT) in Lf and the polio strains (type 1, 2 and 3) in D-antigen units.

ACV/WCV	PT	FHA	PRN	FIM
Wyeth Lederle/Takeda (ACV-WL)	3.2	34.4	1.6	0.8
Smithkline Biologicals (ACV-SB)	25	25	8	-
Pasteur Merieux (ACV-PM)	25	25	-	-
RIVM-WCV	0.25	5.3	?	?

RIVM vaccines	Pertussis	DT	TT	P1	P2	P3
DTP-IPVv	16	15.0	5.0	42	8	32
DTP-IPV	16	15.0	5.0	38	4	8
DT-IPVv	-	2.5	5.0	42	7	43
DT-IPV	-	2.5	5.0	37	4	7