1 TITLE: CLINICAL STUDY REPORT dTap-IPV

AN OPEN STUDY OF IMMUNE RESPONSE AND ADVERSE EVENTS AFTER A BOOSTER DOSE (FIFTH DOSE) OF COMBINED DIPHTHERIA-TETANUS-PERTUSSIS-POLIO VACCINE FOR SCHOOLCHILDREN AT AGE 15-16 YEARS.

(SM 07-01), EudraCT nr 2007-000199-17.

Investigational product:	Boostrix Polio ”GSK”
Sponsor:	Norwegian Institute of Public Health
Protocol number:	SM 07-01, EudraCTno 2007-000199-17
Development phase:	IV
Study initiation date:	12th April 2007
Study completion date:	31st May 2007
Coordinating investigator:	Synne Sandbu, Senior physician. Norwegian Institute of Public Health Lovisenberggata 6 PO Box 222 Skøyen, N-0213 Oslo, Norway
Investigator:	Per Wium, Chief Medical Officer, Lørenskog
Project leader:	Hilde Synøve Waleur Bakke Norwegian Institute of Public Health

The study was conducted in accordance with the guidelines "*Good Clinical (trial) Practice*" as described by *Forskrift om klinisk utprøving av legemidler til mennesker (FOR 2003-09-24 nr 1202), Note for guidance on Good Clinical Practice (CPMP/ICH/135/95) and the ethical guidelines* described in the Declaration of Helsinki as amended in Hong Kong (1989).

Written informed consent was obtained from all subjects and one of the parents or guardians of each subject prior to enrollment.

Final Report Date: 25 June 2026

2 SYNOPSIS of Study Report dTap-IPV (SM 07-01), EudraCT no 2007-000199-17

Name of Sponsor: Norwegian Institute of Public Health (NIPH)

Name of investigational product: Boostrix Polio "GlaxoSmithKline"
Name of active substance: Combined diphtheria, tetanus, acellular pertussis (adsorbed) and inactivated poliomyelitis) vaccine - dTap-IPV
Study phase: IV

Title of the study: An open study of immune response and adverse events after a booster dose (fifth dose) of combined diphtheria-tetanus-pertussis-polio vaccine for school children at age 15-16 years - (En åpen studie av immunrespons og bivirkninger etter boosterdose (5. dose) med kombinert difteri-stivkrampe-kikhoste-poliovaksine til skoleelever i alderen 15-16 år)

.Clinical Study SM 07-01

Coordinating Investigator: Synne Sandbu

Clinical Responsible Investigator: D Per Wium

Project coordinator: Hilde Synøve Waleur Bakke

Project group

- **at NIPH:** Synne, Sandbu**,** Hilde Bakke, Inger Lise Haugen, Berit Feiring, Ingeborg Aaberge, Audun Aase, Anne Cathrine Kristoffersen, Inger Sofie Samdal Vik
- **at Lørenskog Municipality Health Services:** Per Wium, Aud Befring, Anne B. Moen, Kirsti Thorstensen, Grethe Trongaard

Study Centre:	**Investigational site**	**Location**
Lørenskog school health services	Kjenn, Løkenåsen and Fjellsrud schools in Lørenskog	Lørenskog municipality

Publication (reference): Aase, A., T. K. Herstad, S. Merino, M. Bolstad, S. Sandbu, H. Bakke, and I. S. Aaberge. Immunization of Teenagers with a Fifth Dose of Reduced DTaP-IPV Induces High Levels of Pertussis Antibodies with a Significant Increase in Opsonophagocytic Activity. Clinical and Vaccine Immunology 2011; 18: 1269-74.

Study period: **12 April 2007 (first vaccination of first participant)** **31 May 2007 (last blood sample from last participant)** **Main analyses completed within end of 2008.**	**Clinical phase IV**

Objectives

The primary objectives were:

1) Investigate how many of the study participants, who were vaccinated according to the Norwegian immunization program with 3 doses DTwP and 3 doses polio vaccine during early childhood and in addition had received one dose DTaP-IPV during grade 2 in 1998 in the study VAVA 98-01, who achieved protective diphtheria antibody level of $\geq$ 0,1 IU/ml, protective tetanus antidody level of $\geq$ 0,1 IU/ml, protective antibody titer of $\geq$ 10 against polio virus types 1, 2 and 3 and antibody level $\geq$ 30 FDA-U/ml against pertussis toxin, after a booster dose (5th dose) dTap-IPV given at level 10 (age 15-16 years).

2) Register the occurrence of solicited local reactions and general unsolicited symptoms and other adverse events after the booster vaccination with dTap-IPV.

The secondary objectives were:

3) Investigate antibody levels approximately 8 years after a booster dose (4th dose in the study VAVA 98-01)

4) Investigate antibody levels against other antigens in the pertussis vaccine given as booster dose (5th dose).
5) In addition, at a later stage it may be appropriate to investigate antibodies against other vaccine antigens that are relevant in relation to the childhood vaccination programme.

Methodology:

Open, non-blinded, prospective clinical study phase IV with one study group.

Number of subjects:

Enrolled: 81

Vaccinated: 81

Reactogenicity: 80

Immunogenicity pertussis, tetanus, diphtheria: 75

Immunogenicity polio: 48

Criteria for inclusion:

Healthy teenagers who have

1) received one dose DTaP-IPV in the study VAVA 98-01in 1998
2) written informed consent from at least one parent/guardian and from himself/herself
3) family able to understand information and cooperate and communicate in written Norwegian language

Test product, dose, mode of administration, lot no.:

The vaccine was Boostrix Polio ”GlaxoSmithKline”, a combined diphtheria-tetanus-acellular pertussis-inactivated polio (dTap-IPV) vaccine, with Marketing Authorization No: 04-2685.

Vaccination on day 0, with one dose of 0,5 ml injected intramuscularly into the deltoid muscle of the non-dominant arm.

Duration of treatment:

One vaccination.

Reference therapy, dose, mode of administration, lot no.:

No control drug

SUMMARY

Reactogenicity: 80 study participants were included in the PP (Per Protocol) reactogenicity analysis. All of them reported by filling in a diary form during the seven-day follow-up period.

Only 13 persons (16%) reported none local or systemic symptoms during the seven days following vaccination. Two participants (2,5%) had systemic symptoms without simultaneous injection site reaction, 34 persons (43%) had injection site reactions only and 31 (39%) reported both systemic symptoms and injection site reactions. Most adverse events were mild and short lasting.

Table 1: The incidence of all solicited local and systemic symptoms reported during the seven-day follow-up period

Symptom	**Participants with symptom**	**dTap-IPV (N=80)**	
		n	**%**
Injection.site redness	Any	30	37,5%
	≥50 mm	1	1,3 %
Injection.site swelling	Any	22	27,5%
	≥50 mm	2	2,5%
Injection site tenderness/pain	Any	62	77,5%
	Severe	12	15,0 %
Any injection site reaction	All	65	81,3%
	Severe	14	17,5%
Fever ºC	≥37,5 ºC	3	3,8 %
	≥39,0 ºC	2	2,5%
Malaise	All	19	23,8 %
	Severe*	3	3,8 %
Headache	Any	25	31,3 %
	Severe*	2	2,5%
Nausea	Any	17	21,3 %
	Severe*	1	1,3 %
Any systemic symptom	Any	32	40%
	Severe	4	5%
Analgetic use, number of days	Any	9	11,3 %
School absence, number of days	Any	6	7,5%

n (%) = total number and percentage of documented doses followed by the specified symptoms
All = all specified symptoms reported during the 7-day follow-up period
*= symptom preventing normal everyday activity
Solicited symptoms, if present, were indicated as either:
Grade 1 = mild, easily tolerated
Grade 2 = moderate, sufficiently discomforting to interfere with daily activities
Grade 3 = severe, prevents normal everyday activities.
Injection site rubor and swelling, if present, was reported by the largest diameter recorded.
ºC =fever as measured by the rectal, axillary or oral route

Grade 1 = > 37,5 - 38 ºC
Grade 2 = 38,1 - 38,9 ºC
Grade 3 = ≥ 39,0 ºC

Tenderness at the injection site was the most frequently reported symptom.

Unsolicited symptoms were reported by three pupils. All of them recovered within 3 days. There were no SAEs reported and there were no discontinuations due to adverse events.

Immunogenicity: Only persons of whom we had paired samples were included in these analyses, i.e. 75 persons were included in the PP immunogenicity analyses.

Table 2: Pre and post booster vaccination GMTs for subjects included in the PP immunogenicity analysis

2A) Antibody	**Pre-booster GMTs** **dTap-IPV (N=75)**	**Post-booster GMTs** **dTap-IPV (N=75)**
Anti-diphtheria IU/ml	0.62	>8.91
Anti-tetanus IU/ml	0.6	10.8
Anti-PT FDA-U/ml	4.7	43.7

2B) Antibody	**Pre-booster GMTs** **dTap-IPV (N=48)**	**Post-booster GMTs** **dTap-IPV (N=75)**
Anti-polio type 1 titre	75.5	204.5
Anti-polio type 2 titre	65.4	198.7
Anti-polio type 3 titre	70.3	226.3

Pertussis antibodies showed lowest persistence, as 40 participants (56%) had undetectable levels of IgG-PT antibodies before the booster dose. Post booster, all reached detectable levels (>5 FDA-U/ml) and 49 (65 %) reached >30 FDA-U/ml (assumed protective level).

All participants had protective tetanus antibody levels ≥0.1 IU/ml pre booster and all reached IgG levels >2 IU/ml post booster.

All participants had protective diphtheria antibody levels >0.01 IU/ml per booster and all but one participant obtained antibody levels >1.0 IU/ml post booster.

Protective polio antibody titres (≥10) against all three polio virus types were found pre booster in all but three participants, who lacked antibodies against polio type 3. Post booster, all had antibody titres ≥80, except two participants who had titre 40 against polio type 2.

CONCLUSIONS

The results shows that the dTap-IPV vaccine Boostrix Polio met the objectives of the study. It is safe and immunogenic when given as a fifth dose to teenagers at age 15-16 years, and seems suitable to use in the immunization program.

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4 LIST OF ABBREVIATIONSS

AE	Adverse event
CI	Confidence interval
CRF	Case report form
DT	Combined diphtheria-tetanus vaccine
dT	Combined diphtheria-tetanus vaccine with reduced diphtheria antigen content
DTwP	Combined diphtheria- tetanus whole cell pertussis vaccine
DTaP	Combined diphtheria- tetanus acellular pertussis vaccine
DTaP-IPV	Combined diphtheria- tetanus acellular pertussis vaccine-inactivated polio vaccine
dTap	Combined diphtheria- tetanus acellular pertussis vaccine with reduced antigen content
ELISA	Enzyme Linked Immunosorbent Assay
FDA-U	Food and Drug Administration-Units (based on one particular reference serum: US reference pertussis serum, lot 3)
GMT	Geometric mean antibody titre
IPV	Inactivated polio vaccine
IU	International units
NIPH	Norwegian Institute of Public Health (FHI .Folkehelseinstituttet)
PP	Per protocol analysis set
PRN	Pertactin
PT	Pertussis toxin
SAE	Serious adverse event

5 ETHICS

The study was conducted in accordance with the guidelines for "Good Clinical (trial) Practice" as described by “Forskrift om klinisk utprøving av legemidler til mennesker (FOR 2003-09-24 nr 1202)”, “Note for guidance on Good Clinical Practice (CPMP/ICH/135/95)” and the ethical guidelines described in the Declaration of Helsinki as amended in Hong Kong (1989).

The study protocol, dated 2007-03-23 was reviewed by the Norwegian Regional Committee for Medical Research Ethics of Health Region South-Norway (REK Sør) on 22-02-2007 and the Norwegian Medicines Agency on 27-03-2007. Both had no objection to the study being conducted.

Written informed consent was obtained from each participant and from at least one of the parents/guardians of all study participants prior to enrolment. (16.1.2. Information and consent form not submitted.)

The investigational product was Boostrix Polio ”GSK”, that had marketing authorization and was marketed in Norway and was approved for adults and children over 4 years of age.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The study was organized by Department of Vaccines, Norwegian Institute of Public Health and performed in Lørenskog Municipality by the Puhlic Health Nurses in schools.

Lørenskog School Health Services carried out information, vaccination and follow up and took part in the inclusion in the study within their own budget. NIPH took part in the inclusion procedures and follow up, performed blood sampling and laboratory analyses, and otherwise funded the study within its normal budget.

- Coordinating investigator: Synne Sandbu, Senio Physician, Department of Vaccines, Norwegian Institute of Public Health
- Prosject coordinator: Hilde Bakke, Department of Vaccines, Norwegian Institute of Public Health
- Sponsor: Norwegian Institute of Public Health
- Monitor: Inger Lise Haugen, Department of Vaccines, Norwegian Institute of Public Health.
- Medically responsible investigator: Per Wium, Chief Medical Officer Lørenskog Municipality.
- Vaccination: Public Health Nurse and leader of vaccination office Aud Befring and other Public Health Nurses in Lørenskog working in schools
- Blood sampling: Bioengineers from Norwegian Institute of Public Health in the premises of Lørenskog School Health Services.
- Laboratory analyses: Department of Bacteriology and Immunology and Department of Virology, Norwegian Institute of Public Health
- Project group at Lørenskog Municipality Health Services: Per Wium, Aud Befring, Anne B. Moen, Kirsti Thorstensen, Grethe Trongaard.

- Project group at Norwegian Institute of Public Health: Synne, Sandbu, Hilde Bakke, Inger Lise Haugen, Berit Feiring, Ingeborg Aaberge, Audun Aase, Anne Cathrine Kristoffersen, Inger Sofie Samdal Vik, Grethe Hermansen Krogh, Tove Karin Herstad, Samuel Merino, Merete Bolstad

The coordinating investigator submitted an application to the Regional Committee for Medical Research Ethics, Region South, and informed about all subsequent changes or additions to the protocol and any deviations from planned progress

The sponsor submitted an application to the Norwegian Medicines Agency for approval of the study and informed about all subsequent changes or additions to the protocol and any deviations from planned progress.

7 INTRODUCTION

In the Norwegian childhood immunization programme, a combined vaccine against diphtheria, tetanus, pertussis, Hib-infection and polio (DTaP-Hib-IPV) is given at age three, five and twelve months followed by a full dose DTP-IPV at age 7 years and, from the school year 2013/2014, a reduced dose (dTap-IPV) at age 15 years. Whole cell pertussis vaccine (wP) in a combined diphtheria-tetanus-pertussis vaccine (DTP) was introduced in the Norwegian childhood immunization program from 1952. From 1986 the program consisted of a three-dose program in infancy, with a school age diphtheria-tetanus booster dose with reduced antigen (dT) at the age of 11 years. Number and timing of booster doses was changed for the 1998 birth cohort, which was the first cohort to receive acellular pertussis vaccine (aP) from first dose in the program. Before introduction of the last booster dose, this study, that took place in 2007, was done to evaluate immunogenicity and safety of dTap-IPV as fifth dose at age 15 years, before leaving compulsory school.

A study (VAVA 98-01) done in 1998 in order to investigate the pre-existing immunity and to evaluate immunogenicity and reactogenicity of a combined full dose vaccine against diphtheria, tetanus, pertussis and polio (DTaP-IPV) in 7-year-old children revealed that a sizable part of the study population had low or non-protective antibody levels against diphtheria and pertussis already at age 7 years [Sandbu et al. 2001; Jacquet et al. 2006]. A booster dose of DTaP-IPV at the age of 7 years was introduced in the immunisation program in the school year 2005-2006, for children born in 1998 and later.

8 STUDY OBJECTIVES

The primary objectives of the study dTap-IPV (SM 07-01) were:

- Investigate how many of the 15-16 years old study participants, who were vaccinated according to the Norwegian immunization program in 1991-92 with 3 doses DTwP and 3 doses polio vaccine during early childhood and in addition had received one dose DTaP-IPV during grade 2 in 1998 in the study VAVA 98-01, would achieve protective diphtheria antibody level of $\geq$ 0,1 IU/ml, protective tetanus antibody level of $\geq$ 0,1 IU/ml, protective antibody titer of $\geq$ 10 against polio virus types 1, 2 and 3 and antibody level $\geq$ 30 FDA-U/ml against pertussis toxin, after a booster dose (5th dose) dTap-IPV given at level 10 (age 15-16 years).

- Register the occurrence of solicited local reactions and general symptoms and other adverse events after the booster vaccination with dTap-IPV.

The secondary objectives were:

- Investigate vaccine induced antibody levels approximately 8 years after a booster dose (4th dose) of DTaP-IPV.
- Investigate antibody responses against other pertussis antigens in the dTap-IPV vaccine given as booster dose (5th dose).
- In addition, at a later stage it might be appropriate to investigate antibodies against other vaccine antigens that are relevant in relation to the childhood vaccination program.

9 INVESTIGATIONAL PLAN

9.1 Overall study design and plan

Open, prospective study without a control group. The participants of the previous study VAVA 98-01 [Sandbu et al. 2001] were invited to take part in a new study shortly before completing primary school (level 10) at age 15-16 years. The study participants had been vaccinated with a dose of DTaP-IPV (Infanrix Polio; GlaxoSmithKline) (containing 0.025 mcg PT, 0.025 mcg FHA, and 0.008 mcg pertactin [PRN] and 40, 8 and 32 antigen units of poliovirus type 1, 2 and 3, respectively, per dose) as a booster dose (fourth dose) at the age of 6-7 years.

According to the Norwegian childhood immunization program at that time, pupils at level 10 (age 15-16 years) were offered a booster dose of IPV. Study participants of the previous DTP-IPV-study VAVA 98-01 should in addition be offered a dose of dT, postponed from level six in the current program for persons born before 1998. Instead they received the study vaccine containing aP as well.

Pupils who had participated in the study VAVA 98-01 were identified by the public health services of Lørenskog in cooperation with the coordinating investigator at NIPH. Pupils and their parents/guardians received written information about the study and invitation to participate by letter sent directly home. They were invited to call the coordinating investigator or the public health nurse if they had any questions. Information was also given by the health services at inclusion. On the day of vaccination, the pupil had to give written consent and bring written informed consent from at least one parent/guardian.

A venous blood sample of 10 ml was taken at the same visit as the vaccination and a second venous blood sample of 10 ml was taken 4-8 weeks after the vaccination. The participants were asked to record injection site reactions and all adverse events on the day of vaccination and the following six days and report in a diary (see 16.1.2.2 sample form).

General health condition and any simultaneous medication, were documented in the CRF at study start. A venous blood sample of 10 ml was drawn at the same time as the vaccination and a second 10 ml blood sample was drawn 4-8 weeks after the vaccination. The study participants were asked to record injection site reactions and all adverse health events occurring on the day of vaccination and the following six days and report in the diary form, which also contained the subject number (sample form at 16.1,2.2). The diary forms were included in the CRFs (sample CRF see 16.1.2.1).. Inclusion, vaccination and blood sampling began 12th April 2007 and the last blood sample was drawn on 31st May 2007. Analyses of the samples were completed by the winter of 2007-2008.

9.1.1 Visit 1 (day 0): 1st blood sample and vaccination

- Written informed consent was required before the person could be included and any study related procedures could be done.
- Inclusion-and exclusion criteria were controlled

After inclusion:

- Venous blood sample (10 ml)
- Vaccination: One dose of the study vaccine Boostrix Polio injected in deltoid muscle of the non-dominant arm. No other simultaneous vaccination.
- After vaccination, every study participant was under observation for 20 minutes.
- Each participant got a diary form with their unique vaccinee number (subject number) and was instructed how to observe and fill in solicited adverse events and other possible adverse events for 7 days.
- The study participants were told to call the public health nurse, their GP or the emergency room as soon as possible in case of any serious or severe adverse event.

9.1.2 Visit 2 (day 28-84): 2nd blood sample

- The diaries for adverse events were reviewed and the participants were asked whether any other health events had occured after day 6.
- Venous blood sample taken (10 ml).

9.2 Discussion of study design

The study was built on the previous study VAVA 98-01, performed in Lørenskog in 1998. Participants in that study were therefore the only possibly eligible participants, and the time for them to take part, was limited to the last semester of level 10, before leaving compulsory schooling. They had followed the regular three-dose immunization regimen within their first year of life (DTwP + IPV), and they had received a fourth dose DTaP-IPV (Infanrix-Polio; GlaxoSmithKline) when they were 6-7 years old, participating in a vaccine study as described earlier [Sandbu et al. 2001].

The study consisted of one vaccination, namely fifth dose given as DTaP-IPV (Boostrix® Polio; GlaxoSmithKline) (containing 8 µg PT, 8 µg FHA, and 2.5 µg pertactin [PRN] per dose) instead of the dose of dT that belonged as last dose in the vaccination program. For evaluation of safety, the study participants reported adverse events in a diary form and for evaluation of immunogenicity, sera were collected before and 4-8 weeks after vaccination.

9.3 Selection of study population and inclusion/exclusion criteria

Eligible for the study, and invited to participate, were the 124 pupils who were vaccinated with one dose of DTaP-IPV in the study in the study VAVA 98-01 (DTaP-IPV 037) in 1998. Consent from both the participant and at least one parent/guardian was required.

Study participants could withdraw from the study at any time without having to give a reason. If a participant withdrew before end of the study, diary information and results from the 1st blood test would still be included in the data analyses.

9.3.1 Inclusion criteria

1. Healthy 10th grade pupils who had received one dose of DTaP-IPV in the study VAVA 98-01 in 1998
2. Written informed consent obtained from at least one of the parents/guardians and from the pupil herself/himself
3. The family could understand the information given, be cooperative and able to communicate in verbal and writing in the Norwegian language

9.3.2 Exclusion criteria

1. Serious chronic disease
2. Tetanus vaccination during the last 12 months
3. Diphtheria vaccine component given after grade 2 (i.e. after the DTaP-IPV in 1998 in the study VAVA98-01). Other vaccines after the dose of DTaP-IPV in grade 2 were to be registered but did not cause exclusion from the study.
4. Suspected or confirmed immune suppression (included HIV infection)
5. Immunologic treatment (cyclosporine, alkylating agents, antimetabolites, antilymphocyte globulin, monoclonal antibodies, oral corticosteroids).
6. Pregnancy
7. Serious adverse reaction against previous dose of any of the vaccine components or known hypersensitivity against any substance in the vaccine
8. Acute febrile illness with temperature of more than 38 °C at the time of planned vaccination (warrants deferral of the vaccination pending recovery of the subject).
9. Not able to attend study centre during school hours.

Health at start of the study was documented in the CRFs. Any concomitant medication was noted in the CRF.

9.3.3 Cohort definition, subject completion and drop-out

The total cohort for analysis of immunogenicity and reactogenicity included all subjects meeting all inclusion and none exclusion criteria and complying with the procedures defined in the protocol, for whom data were available.

Eighty-three male and female teenagers were enrolled in the study according to the inclusion- and exclusion criteria specified in the protocol (see 9.3.1 and 9.3.2). With one exception, none of the pupils who attended schools outside Lørenskog were participants, because they were unable to be present at time of inclusion and vaccination.

A drop-out was defined as any participant who neither came back for the concluding visit (visit 2) nor filled in and returned the diary form.
All except one of the included participants gave blood sample at the time of immunisation. Two participants were excluded after visit 1, because they had not met the inclusion criteria (had not been vaccinated in the previous study). Of the remaining 81 participants (females

54%), 80 returned their diary forms. Seventy-five participants (56% females) completed the study with a blood sample 4-8 weeks after the booster vaccination.

9.4 Vaccine

9.4.1 Vaccine administered

The vaccine given in the study was Boostrix® Polio "GSK", the only combination vaccine against diphtheria, tetanus, pertussis and polio with a reduced content of diphtheria, tetanus and pertussis antigens (dTap-IPV) that was available in Norway at the time of the study. Boostrix Polio was marketed in Norway and is approved for children over 4 years of age and adults. The vaccine was at that time used as a travel vaccine and in other contexts outside the vaccination program.

9.4.2 Identity of investigational product

One dose (0.5 ml) of Boostrix® Polio "GSK" contained:

Pertussis toxoid (PT)	: 8 mcg
Filamentous haemagglutinin (FHA)	: 8 mcg
Pertactin (PRN)	: 2,5 mcg
Diphtheria toxoid	: ≥2 IU
Tetanus toxoid	: ≥20 IU
Polio virus type 1 (Mahoney strain)	: 40 D antigen units
Polio virus type 2 (MEF-1 strain)	: 8 D antigen units
Polio virus type 3 (Saukett strain)	: 32 D antigen units
Aluminium ($Al(OH)_3$) and ($AlPO_4$)	: 0.5 mg
Phenoxyethanol	: 2.5 mg

The vaccine was delivered in pre-filled syringes. Lot no. 20711A9/M was used.

The vaccine was injected IM in the deltoid muscle, usually in the left arm, according to usual practices by the vaccinating school nurses.

9.4.3 Selection of doses in the study

The vaccine had marketing authorization with dose 0,5 ml for all age groups four years and older, therefore 0,5 ml dose was used in the study

9.4.4 Selection of timing of dose for each participant

The single dose was given as school vaccination during the last term of level 10.

9.4.5 Blinding

No control group.

9.4.6 Prior and concomitant therapy

Prior and concomitant medication documented in the CRFs.

9.4.7 Treatment compliance

The total medication was one vaccine injection given on the day of inclusion in the study.

9.5 Immunogenicity and safety variables

9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

The immune responses were evaluated by measuring antibody levels against each vaccine antigen before and after vaccination.

Venous blood samples (10 ml) were drawn on Vacutainer on the vaccination day (day 0) and 4-8 weeks later. The blood samples were fractioned the same day and serum stored at – 20 ºC until analysed. All laboratory analyses were done at NIPH.

All blood sample and serum tubes were labelled with the following information:

SM 07-01 Besøk nr. (Visit number) Deltagernummer (Participant number) Deltagerens initialer (Participant's initials)

Pre-vaccination seropositivity rate against the different vaccine antigens measured at visit 1 to determine the baseline immunity approximately eight years after the previous vaccine dose.

Post-vaccination seropositivity rate measured 4-8 weeks later, at visit 2, to evaluate the immune response generated by the vaccine.

The occurrence of specified local reactions and systemic symptoms and other adverse events after booster vaccination (5th dose) with dTap -IPV were recorded by each participant in their diary forms.

9.5.1.1 Efficacy Measurements Assessed

Anti pertussis antibody analyses

IgG antibodies against pertussis toxin were analysed by ELISA using a Bordetella pertussis Toxin IgG kit from Virion\Serion (Institute Virion\Serion, GmbH, Würzburg, Germany), as previously described [Aase et al. 2011]. The limit of quantization was approximately 5 FDA-U/ml and levels below this were assigned a value of 2.5 FDA-U/ml for statistical determination.

Although there is no established serological correlate of protection against pertussis; several studies demonstrate a positive association between antibody levels against pertussis toxin and protection [Cherry et al. 1998; Storsaeter et al. 1998; Taranger et al. 2000]. IgG antibodies against pertussis toxin ≥30 FDA-U/ml analysed by ELISA is defined as positive result in the test method used (Institute Virion/Serion GmbH, Würzburg, Germany), while 20-30 FDA-U/ml was grey zone and < 20 negative.

The immune response against pertussis would also be analysed against filamentous hemagglutinin and possibly against pertactin and other *B. pertussis* antigens by ELISA and other methods.

Anti-tetanus antibody analyses

IgG antibodies against tetanus were analysed using an in-house ELISA against tetanus toxoid as previously published [Nordøy et al. 2001; Simonsen et al. 1986]. The results are reported as IU/ml; the level of sensitivity was 0.1 IU/ml, and levels above this were considered protective against tetanus [Borrow et al. 2006, Simonsen et al. 1986].

Anti-diphtheria antibody analyses

The immunity against diphtheria was measured as toxin-neutralizing activity using Vero cells [Nordøy et al. 2001; Skogen et al. 1999]. Values < 0.01 IU/ml are considered non-protective, values from 0.01 to 0.1 short-term protective and values ≥ 0.1 IU/ml are regarded long-term protective [Ipsen 1946; Galazka 1993]. The highest activities that were quantified in different experiments varied with +/- one titre, to give values of 20.48 IU/ml or 40.96 IU/ml, these values were thus used for statistical calculation.

Anti polio antibody analyses

The immunity against poliomyelitis was measured as poliovirus-neutralization activity in a microculture assay using Vero cells as indicator [Nordøy et al. 2001]. Neutralizing activity was determined separately against poliovirus types 1, 2 and 3. Sera were investigated in a 2-fold dilution series with 7 steps starting with a 1:5 dilution. Serum neutralizing activity is expressed as the inverse value of highest dilution of serum showing neutralization. Titre 10 or higher is regarded as protective [Robertson et al. 1993], though it is accepted that any level of type specific neutralization of infection in cell culture is protective [Plotkin 2001]. Neutralization titres higher than 320 were not determined and these sera were given a titre of 320 for statistical calculation.

For each of the 3 poliovirus types, neutralizing antibody titers of >8 are considered protective by WHO. In the method used in this study, the limit for protective titers is 10.

Other laboratory analyses

Consent was obtained to later use the material for analysis of immunity against other agents relevant to the childhood immunization program.

9.5.1.2 Safety Measurements Assessed

After vaccination, the participants were observed for at least 20 minutes. They were requested to record adverse events in a diary form and specifically asked for grading of redness, swelling and pain at the injection site, fever, malaise, head ache, nausea, school absenteeism and use of analgetic drugs during the first seven days after vaccination. They were also asked to report non-Solicited events and any other medical event occurring up to next visit if causal relation to the vaccine was suspected.

Definition of Adverse Events (AE)

- *Adverse event* (AE): Any adverse medical event in a subject who has received a medicinal product in a clinical trial, whether or not the event was causally related to the medicinal product.
- *Side effect:* An adverse medical event in a subject who has received a medicinal product in a clinical trial, where a causal relationship between the event and the medicinal product cannot be ruled out (probable or possible causal relationship).

Definition of Serious Adverse Events (SAE)

Serious Adverse Event: Harmful and non-intended response or effect, which at any dose results in death, is life-threatening, requires hospitalization or prolonged hospital stay, results in permanent or significant handicap or disability, or is a congenital malformation.

- *Death.*
- *Life threatening event*: an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- *Disability*: An event resulting in a significant and/or lasting disability or incapacity to carry out normal life functions
- *Hospitalization:* Incidents necessitating hospitalization shall be considered serious. In general, hospitalization means that the patient must stay at least one night in a hospital or emergency room for observation and/or treatment that could not have taken place in a doctor's office or outpatient clinic. If there is doubt as to whether the hospitalization took place or was necessary, the incident shall be considered serious.

A hospitalization for a planned surgical intervention or routine clinical procedure, which is not related to the vaccination, shall not be considered an intercurrent event, but shall be included in the section on previous medical history in the CRF. (Routine clinical procedure is procedure that can be carried out during the trial period, but which does not interfere with injection of the study vaccine or other protocol-specific procedure.) If something unexpected occurs during the procedure or procedure, this event must be included as an adverse event.

Local and Systemic Adverse Events

Local (injection site) Symptoms	*Systemic Symptoms*
Redness (largest diameter mm)** Swelling (largest diameter mm)** Tenderness*	Fever (Preferably rectal temperature)*** Nausea* Headache* Malaise*

* Tenderness and other symptoms, if present, were indicated as either:
grade 1 = mild, easily tolerated
grade 2 = moderate, sufficiently discomforting to interfere with daily activities
grade 3 = severe, prevents normal everyday activities.
** If present, the largest diameter was recorded; grade 2 was define as diameter 25-49 mm and grade 3(severe) defined as diameter 50 mm or more
*** Grade 1 = > 37,5-37,9 ºC, Grade 2 = 38 – 38,9 ºC, Grade 3 = ≥ 39,0 ºC.
Fever is measured, by the rectal, axillary or oral route, if the participant or a guardian is suspecting fever.

The participants were asked to contact the school health services if redness or swelling of more than 50 mm occured.

Detection and documentation of adverse events

Each participant delivered the diary to the school health nurse as soon as it has been completed. At study visit 2, the diary was reviewed with the participant by a study employee, who also asked whether the participant had seen a doctor or used any medicine after the vaccine was administered, or had any adverse events or serious adverse events after day 6. Information from the diary was included in the CRF.

The participants were asked to grade non-measurable local and systemic symptoms in their diary form, according to the following scale:

0 = none
1 = *mild*: limitations in normal daily activities that can be well tolerated
2 = *moderate*: discomfort that limits daily activities
3 = *severe*: discomfort that prevents daily activities

Assessment of causality

The investigator shall, to the extent possible, assess the causal relationship between the incident and the study vaccine. Causation is indicated as one of the following categories:

Not related -	The Adverse Event is definitely not related to the study vaccine.
Unlikely -	There are other, more likely causes and the study vaccine is not suspected as a cause.
Suspected -	A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug.
Probable -	There probably is a direct cause and effect relationship between the adverse event and the study vaccine.

Solicited local symptoms were always considered as related to the study vaccine.

Non-solicited adverse events

Other medical adverse events reported should also be evaluated according to grading and causality as described above.

Follow-up of study participant after an adverse event

The investigator/medically responsible physician is responsible to make sure that examination and any treatment is implemented. The treating physician will take care of the participant according to his or her own assessment and medical judgment and in accordance with current guidelines for good medical practice. The investigator will follow up and document the course of events until the adverse event has resolved or the condition has stabilized.

9.5.1.3 Flow chart

	Visit 1	**Visit 2**
	Day 0	Day 28-56
Written informed consent	X	
Inclusion and exclusion criteria	X	
Blood sample	X	X
Vaccination	X	
Diary review		X

9.5.2 Appropriateness of Measurements

Unless stated otherwise, standard approaches were utilized for immunogenicity and safety measurements

9.5.3 Primary Efficacy Variables

To investigate how many of the study participants achieve protective diphtheria antibody levels of >0.1 IU/ml, protective tetanus antibody levels of >0.1 IU/ml, protective antibody titers of >10 against poliovirus types 1, 2 and 3 and antibody levels of >30 FDA-U/ml against pertussis toxin, after a booster dose (5th dose) of dTap-IPV given at age 15-16 years.

9.6 DATA QUALITY ASSURANCE

The CRF and source data (informed consent form, inclusion form, diary and raw data from laboratory analyses) on paper will be kept at the Norwegian Institute of Public Health for at least 15 years after the final report is available. All personal data will be treated strictly confidentially. The students' medical records at the school health service are not source data in this study.

Microsoft Excel, GraphPad Prism and GraphPad Instat were used for data processing and analysis. Data entry and other data processing were quality assured by proofreading or other suitable method. See 16.1.10.

9.6.1 Clinical Procedures

The investigator provided the sponsor with complete test results, all study data, and access to all study records.

9.6.1 Monitoring

Monitoring was performed by NIPH. NIPH Quality Assurance reviewed documents and performed internal audits

9.7 Statistical methods planned in the protocol and determination of sample size

9.7.1 Statistical and analytical plans

Proportion of participants with presumed protective antibody levels, and 95% confidence intervals, against the various vaccine antigens, are calculated before and after vaccination. Geometric mean for antibody levels is calculated before and after vaccination. Paired t-test analysis is performed on log-transformed values in sera taken before and after vaccination. $P \leq 0.05$ is considered significant.

For Solicited adverse events, number, stratification and percentage were calculated. For school absenteeism and use of analgetic drugs, number of days and percentage were given. Non-solicited adverse events were analysed descriptively.

9.7.2 Determination of sample size

The maximal number of participants would be 124, based on the number of participants in the study VAVA 98-01 in 1998.

With 75 participants, the study is designed to answer if at least 90% of study participants achieve protective antibody levels against diphtheria, tetanus and poliomyelitis after a booster dose of dTap-IPV. If the true value is 95%, the lower limit of a 95% confidence interval will be 90% for the specified study population (75 persons).

Statistical analyses are performed with GraphPad Prism or GraphPad Instat.

The proportion of study participants with presumed protective antibody levels, and 95 % confidence intervals, against the various vaccine antigens, is calculated before and after vaccination. Geometric mean antibody levels are calculated before and after vaccination. Paired t-test analysis is performed on log-transformed values in sera taken before and after vaccination. $P \leq 0.05$ is considered significant.

For solicited adverse events number, stratification and percentage are calculated. For school absenteeism and use of analgetic drugs, number of days and percentage are given. Non-solicited events are analysed descriptively.

10 STUDY PARTICIPANTS

10.1 Disposition of participants

124 eligible persons vaccinated in the previous study VAVA 98-01 in 1998, were identified and invited. After consent of both the participant and at least one parent/guardian, 83 of them were included in the study dTap-IPV (SM 07-01). All the study participants were 15-16 years old, born in 1991, and previously had been vaccinated according to the Norwegian childhood vaccination program with three doses of DTwP and three doses of IPV during infancy, and at age 7 years had received one booster dose of DTaP-IPV in the clinical study VAVA 98-01. All of them were at that time pupils of secondary schools, and all but one at schools in Lørenskog municipality.

10.2 Protocol deviations

Two persons were excluded after first study visit, when it was confirmed that they had not been vaccinated in the previous study, though their parents had given written consent (i.e. wanted them to have the vaccine).

10.3 Study completion and drop-out

Of the 81 participants enrolled PP, 80 (44 (55%) female and 36 (45%) male) returned their diary forms. Seventy-five participants (42 (56%) female and 33 (44%) male) completed the study with a blood sample 4-8 weeks after the booster vaccination. Participant no 1027 was lost to follow-up for the final visit and blood sample. No participants dropped out because of an adverse event.

11 IMMUNOGENICITY EVALUATIONS

11.1 Data sets analysed

Individual immunogenicity data can be found in chapter 14.1.

Sera from 79 pupils were collected at the time when the fifth dose was administered, and 75 participants (94%) completed the study and gave a blood sample on the final study visit 4 - 8 weeks later.
Participants no 1043, 1065, 1109 and 1158 failed to give 2nd blood sample and for participant no 1008, venipuncture failed both pre- and post-booster vaccination. No participants dropped out because of an adverse event.

For polio antibody analyses, the data set consisted of paired sera from 48 persons, as 29 study participants had, before study start, been vaccinated against polio according to the Norwegian immunization program for level 10-pupils; 27 of them were among the 75 persons who had given two blood samples (Tab 11-1).

The results for pertussis IgG, tetanus IgG and diphtheria toxin neutralisation are reported as geometric mean concentrations with 95% confidence intervals (CI) and the polio virus neutralisation as geometric mean titre.

Tab 11-1: Study participant inclusion and eligibility for analysis

Number of subjects enrolled	83
Not included per protocol	2
Not returned diary	1
Number of subjects included in the PP analysis of reactogenicity	**80**
Blood sample pre and post booster not taken	1
Blood sample post booster not taken	5
Number of subjects included in the PP analysis of immunogenicity	**75**
Previously received polio vaccine	27
Number of subjects included in PP analysis of polio-immunogenicity	**48**

11.2 Demographic and other baseline characteristics

All study participants were born during 1991.

Tab 11-2: Study participants included in the PP analysis of reactogenicity

	N	%
All participants	80	100
Female	44	55
Male	36	45

N = total number of subjects;

11.3 Measurements of treatment compliance

The total treatment was one vaccine injection.

11.4 Efficacy results and tabulations of individual participant data

11.4.1 Analysis of efficacy

Blood samples drawn on the day of vaccination and on the final study visit 4-8 weeks later were fractioned the same day and serum stored at – 20 ºC until analysed. All laboratory analyses were done at NIPH.

Pertussis antibody responses

In the pre-booster sera the GMC of IgG against pertussis toxin was 4.7 FDA-U/ml (95% CI: 3.6, 6.3) and 4-8 weeks after the booster dose it had increased to 43.8 FDA-U/ml (95% CI: 36.3, 52.8) (Fig. 11-1 A). Forty participants (56%) had undetectable levels of IgG-PT antibodies (<5 FDA-U/ml) before the booster dose, whereas all reached levels >5 FDA-U/ml and 65 % attained >30 FDA-U/ml post booster (Fig. 11-2 A). In the pre booster sera, three of the participants had high levels of IgG-PT antibodies (>80 FDA-U/ml).

The vaccine response rates for each pertussis antigen for subjects included in the PP analysis of immunogenicity is presented in Table 14-2. Details of other pertussis antibody responses are previously published [Aase et al. 2011].

Tetanus antibody responses

Before the booster dose, all participants had IgG anti-tetanus toxoid levels ≥0.1 IU/ml (Fig. 11-1 B and 11-2 B and Tab 14-1), but nine subjects (12%) had low antibody levels ≤0.2 IU/ml. All participants reached IgG levels >2 IU/ml post booster. The GMC was 0.6 IU/ml (95% CI: 0.5, 0.7) before the booster dose and 10.8 IU/ml (95% CI: 9.1, 12.8) post booster (Fig. 11-1 B).

Diphtheria antibody responses

In the pre-booster sera, all participants had protective antibody levels (>0.01 IU/ml) against diphtheria, and the GMC was 0.62 IU/ml (95% CI: 0.47, 0.83) (Figs. 11-1 C and 11-2 C and Tab 14-1). Five subjects (7%) had anti diphtheria antibody levels below 0.1 IU/ml, indicating short-term protection. After the booster dose all but one participant obtained antibody levels >1.0 IU/ml, and the calculated GMC was >8.91 IU/ml (95% CI: 7.08, 11.22). However, the end-titre was not reached for the 15 samples with highest activity.

Polio antibody responses

Of the 48 persons included in the PP analysis for polio immunogenicity, three persons (5.8%) had titre <10 against poliovirus type 3 before booster vaccination, whereas all subjects had titres ≥10 against type 1 and 2 virus (Fig. 11-2, D-F and Tab 14-3). After the booster dose all pupils acquired antibody titres ≥80 against polio virus type 1 and 3 (One person lacking result for polio virus type 1). Against polio virus type 2, all participants had antibody titres ≥40 and all but two acquired antibody titres ≥80. Also, the four persons with pre-booster blood sample only, showed protective antibody titre of 40 or higher against all three poliovirus types. The anti-polio antibody titres before and after vaccination is shown as geometric mean titres in Fig. 11-1, D-F, and as reverse cumulative distribution plots in Fig. 11-2, D-F. The immune responses to all analysed polio antigens were highly significant ($P < 0.0001$).

Tab 11-3: Distribution of antibody titres against poliovirus types 1, 2 and 3 before and 4-8 weeks after the booster vaccination, 48 persons.

	Pre Booster			Post booster		
Titer	Type 1	Type 2	Type 3	Type 1	Type 2	Type 3
≤5			3			
10		2	2			
20	7	9	4			
40	12	10	9		2	
80	11	13	9	6	6	6
160	14	8	14	17	15	12
≥320	4	6	7	24	25	30

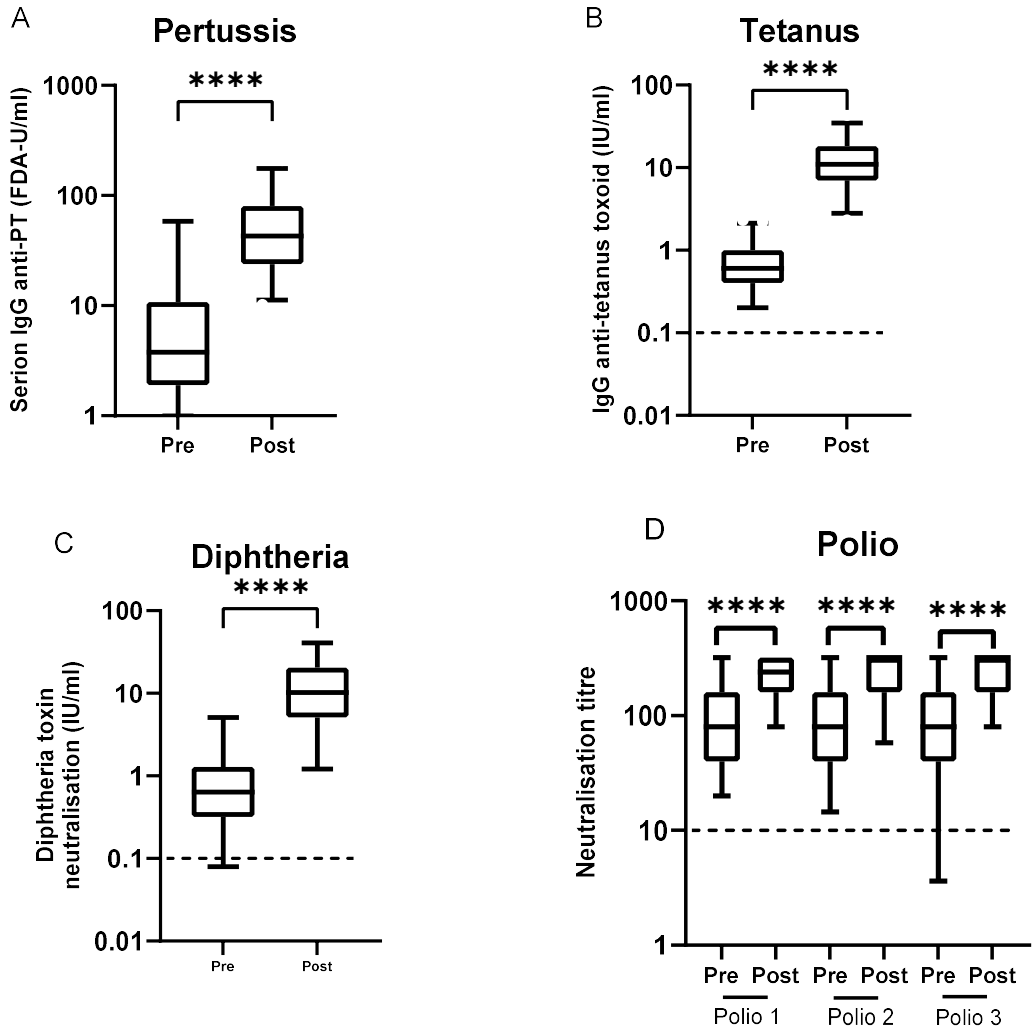

Fig 11-1: Box plot showing the pre- and post-vaccination activities against pertussis toxin, diphtheria toxin, tetanus toxoid and polio virus 1,2 and 3. The boxes span the 25th to 75th percentiles, the whiskers indicate the 5th and 95th percentiles.

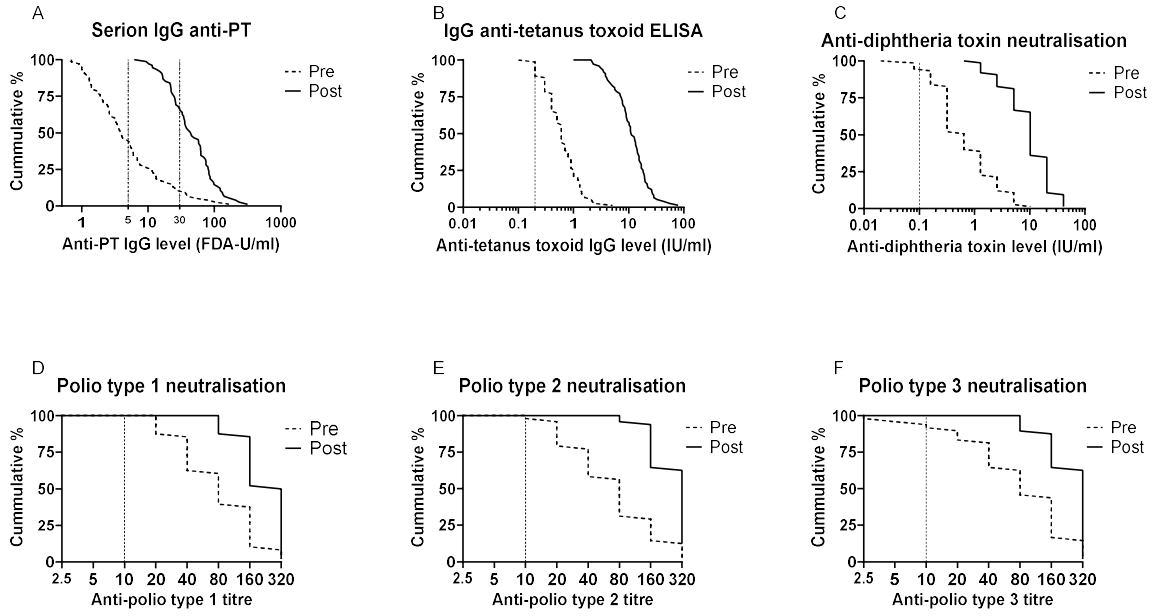

Fig 11-2: Cumulative distribution of pre- and post-vaccination of antibody activity against pertussis (A), tetanus (B), diphtheria (C), polio virus 1 (D), polio virus 2 (E) and polio virus 3 (F) [Reed 1995].

11.4.2 Statistical/analytical issues

Geometric mean concentrations (GMCs) and the corresponding 95% confidence interval (CI) in pre and post vaccination sera were calculated. The percentage of subjects with antibody levels above selected values were calculated to generate reverse cumulative distribution plots [Reed et al. 1995]. Wilcoxon signed rank test was used to test for differences between pre- and post-booster antibody activities. Statistical analyses were done using Sigma Plot 3.1 program (Systat Software, Chicago, USA) and GraphPad Prism, Ver 2.02 (GraphPad Software, Inc.). P value < 0.05 was considered significant.

Individual immunogenicity data for all subjects can be found in in Tables 14-1, 14-2 and 14-3.

The results of the total cohort for immunogenicity analysis are not presented here, since only 5 pupils (6%) (with a pre booster sample only) were excluded from the PP analyses. See 10.3 and Tab 11-1.

For solicited adverse events number, stratification and percentage were calculated. For school absenteeism and use of analgetic drugs number of days and percentage were given. Non-solicited adverse events were analysed descriptively.

11.4.2.1 Adjustment for covariates

No adjustments for covariates were performed.

11.4.2.2 Handling of dropouts and missing data

Participant no 1027 was lost to follow-up after first study visit and therefore neither delivered diary nor 2nd blood sample.

11.4.2.3 Interim analysis and data monitoring

No interim analyses were performed. Before analysis, data were checked for consistency, and criteria for the analysis were finalised.

11.4.3 Tabulation of individual response data

Individual immunogenicity response data are displayed in tabs 14-1, 14-2 and 14-3.

11.4.4 Drug dose, drug concentration and relationships to response

N/A

11.4.5 Immunogenicity conclusions

*Primary end points, t*o investigate how many of the study participants achieve protective antibodies after the booster dose at level 10.

After the booster dose all pupils reached PT-IgG levels >5 FDA-U/ml and 65 % attained >30 FDA-U/ml. All participants reached IgG anti-tetanus toxoid levels >2 IU/ml and all but one participant obtained antibody levels >1.0 IU/ml against diphtheria post booster. All pupils acquired antibody titres ≥80 against polio virus type 1 and 3 (One person lacking result for polio virus type 1). Against polio virus type 2, all participants had antibody titres ≥40 and all but two acquired antibody titres ≥80.

Secondary end point, to examine vaccine induces antibodies approximately 8 years after the booster dose (4th dose) DTaP-IPV at level 2.

With regard to the persistence of antibodies in pupils in grade 10 who were vaccinated with three doses DTwP in infancy and one dose DTaP-IPV in grade 2, anti-PT antibodies showed the least persistence. Forty participants (56%) had undetectable levels of IgG-PT antibodies (<5 FDA-U/ml) before the booster dose, whereas all reached levels >5 FDA-U/ml and 65 % attained >30 FDA-U/ml post booster. Of the 48 persons included in the PP analysis for polio immunogenicity, three persons (5.8%) had titre <10 against poliovirus type 3 before booster vaccination, whereas all subjects had titres ≥10 against virus types 1 and 2. Before the booster dose, all participants had IgG anti-tetanus toxoid levels ≥0.1 IU/ml and protective antibody levels (>0.01 IU/ml) against diphtheria.

The vaccine response rates for each pertussis antigen for subjects included in the PP analysis of immunogenicity is presented in Table 14-2. A more comprehensive description of the antibody activity against *B. pertussis* antigens has been reported previously [Aase et al. 2011].

12 SAFETY EVALUATION

12.1 Extent of exposure

All the study participants received the same vaccine, one 0.5 ml dose only.

12.2 Adverse events

12.2.1 Brief summary of adverse events

Eighty study participants returned their diary forms for days 0-6 after vaccination, which makes 560 person-days. Reactogenicity was analysed descriptively for the PP cohort of reactogenicity, 80 persons. Individual subject data are presented in Tab 14.4.

Solicited signs and symptoms

Sixty-five study participants (81,25%) reported injection site reactions and 33 (41,25%) reported systemic symptoms. Thirty-one of them (39 %) reported both systemic symptoms and injection site reactions. Two participants (2,5 %) had systemic symptoms only, 34 persons (43 %) had injection site reactions only and 13 persons (16 %) reported neither local nor systemic symptoms during the seven days following vaccination. Most adverse events were mild and short lasting, and none withdrew from the study because of adverse events.

The number and percentage of participants with at least one local adverse event, at least one general adverse event and with both a local and a systemic adverse event during the 7-day follow-up period is presented in Table12-1.

Table 12-1: Number and percentage of persons reporting injection site reactions and systemic symptoms.

	Injection site reaction	Systemic symptoms	Both local and systemic symptoms
Severe symptoms*)	14 (17,5%)	4 (5%)	12 (15%) (3 had double gr 3)
Any symptoms	65 (81,25%)	32 (40%)	30 (37,5%)
No symptoms	15 (18,75%)	48 (60%)	13 (16,25%)

*) Severe symptoms are local redness or swelling of ≥ 50 mm, fever ≥ 39,0 °C and other symptoms strong enough to prevent normal daily activity.

Three persons (Id 1010, 1055 and 1065) had both local and systemic symptoms of grade 3.

12.2.2 Display of adverse evens

Solicited local signs and symptoms

Injection site pain/tenderness was the most frequent adverse event (AE), reported by 62 participants (77,5%), all but three from day 0. Six of them (4 females) had pain grade 3 and five (5 males) had pain grade 2 as the only injection site symptom. Injection site reactions mostly lasted for 1-4 days.

- Of the 33 (41,3%) with tenderness of grade 1, 24 (39%) reported 1- 2 days duration, eight reported pain grade 1 for three days and one for four days.
- Of the 16 persons (20%) reporting pain/tenderness grade 2, the duration was 2-3 days in nine persons (11%), 4-5 days in six and 6-7 days in two persons (2,5%).

- Injection site pain grade 3 affected 13 persons (16%), of whom two reported pain for one day only, (one of them without visible local reaction), nine had duration of 2-4 days and one for seven days.
- Three (3,75%) reported swelling and 1 (1,25%) reported redness of 50 mm or more at injection site. Some fever after vaccination was reported by three (3,75%) of the participants; 2,5% had temperature up to 39°C for 2 days.

Injection site rubor and swelling. Thirty (37,5%) of the 80 participants reported rubor at the injection site and 22 (27,5%) reported injection site swelling. Five persons reported injection site reactions lasting for seven days and then subsiding (one pain and swelling, one redness and swelling and one each of pain, redness and swelling). Only one person had a very large local reaction lasting for more than 7 days; duration of 13 days (days 1-13), with redness and swelling reaching 80 mm, but tenderness lasted only for 6 days and did not exceed grade 2.

*Tab 12-2: N*umber and *percentage of persons with each solicited local reaction and grading of severity (i.e. maximal severity per person) reported during days no 0-6.*

	Pain/tenderness	Rubor	Swelling	Any local reaction
	No (%)	No (%)	No (%)	No (%)
Grade 1	33 (41,25%)	27 (33,75)	14 (17,5)	34 (42,5)
Grade 2	16 (20,0 %)	2 (2,5)	6 (7,5)	17 (21,25)
Grade 3	13 (16,25%)	1 (1,25)	2 (2,5)	14 (17,5)

Solicited systemic signs and symptoms

Of the 32 persons reporting one or more systemic symptoms, 25 (31,25%) reported headache, 19 (23,75%) reported malaise and 17 (21,25%) reported nausea. Two of the persons with headache declared that the cause was migraine, but for this report they are counted as AEs.

Tab 12-3: Number and percentage of persons with each solicited systemic adverse event reported during days no 0-6 with grading of severity (only the highest grade for each person).

	Fever	Malaise	Headache	Nausea	Any systemic symptom	Analgretic days
Grade 1	1 (1,25%)	12 (15%)	17 (20,0%)	9 (11,25%)	20 (25,0%)	4 (5%)
Grade 2	0 (0%)	4 (5,0%)	7 (8,75%)	7 (8,75%)	8 (10%)	3 (3,8%)
Grade 3	2 (2,5%)	3 (3,75%)	2 (2,5%)	1 (1,25%)	4 (5%)	2 (2,5%)
Total	3 (3,75%)	19 (23,75%)	25 (31,25)	17 (21,25%)		32 (40%)

Three (3,75%) of the 80 participants reported fever for 1-2 days each. The highest temperature was 39 ºC, reported by two persons for one and two days, respectively. Six pupils reported school absenteeism for 1-2 days each. None had systemic symptoms lasting more than 5 days. Nine persons (11,25%) had taken analgetic drugs for 1-3 days each, totally 16 person days.

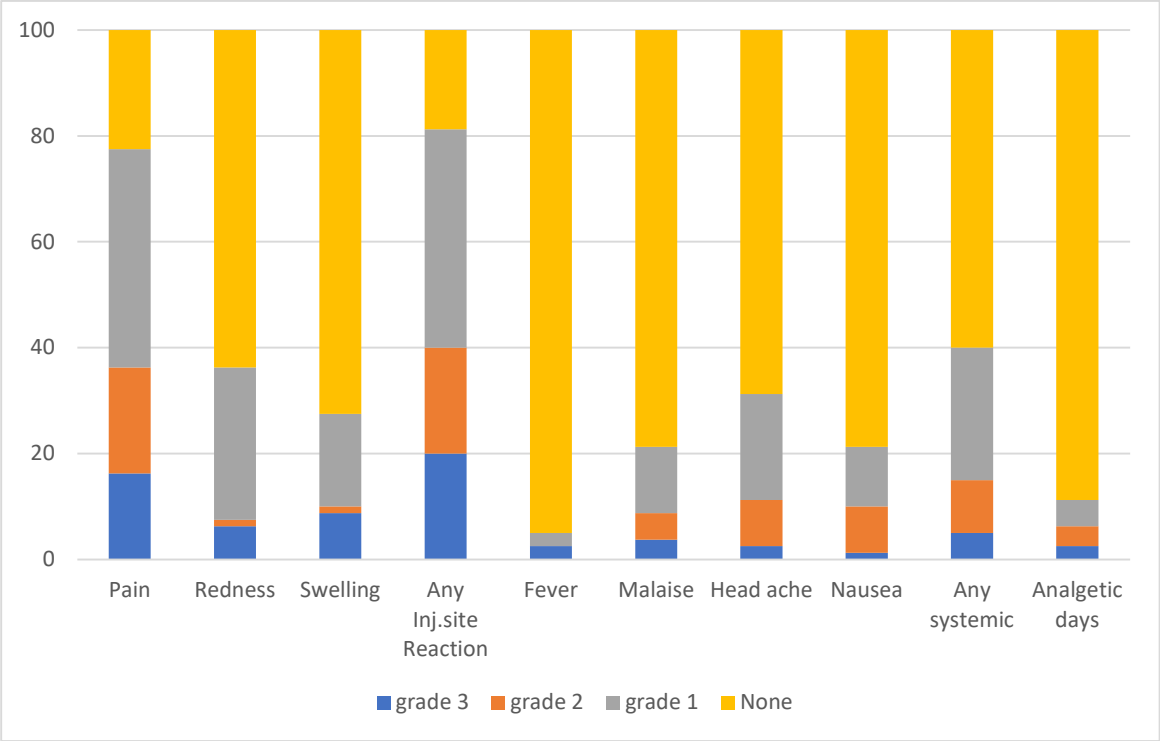

Fig no 12-1: Percentage of local and systemic signs and symptoms reported by the 80 participants during the seven-day follow-up period. The diagram shows the most severe grade reported per person

Unsolicited signs and symptoms

Three persons reported non-solicited symptoms during the 7 days observation period:
One male reported dizziness and nausea immediately after the vaccine injection, one male reported loose stools on days 1-2 and one female reported coryza, with slight nausea in the mornings, on days 4-6.
No significant AEs were reported between day 6 and the 2nd study visit at day 28-56.

12.2.3 Analysis of adverse events

Reactogenicity was analysed descriptively for the PP cohort of reactogenicity, 80 persons.

The percentage of documented doses followed by a report of any symptom (solicited or unsolicited) and the percentage of documented doses followed by at least one local or general symptom during the 7-day follow-up period after vaccination were reported.

No serious or unexpected adverse events were reported.

12.2.4 Listing of adverse events per day for days 0-6 after vaccination

Tab no. 12-4: Solicited Adverse Events per day for 7 days after vaccination

	Day 0		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Persons with Each AE		Person-days per AE	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	% of 80	n	% of 560
Inj site redness	17	21,3	22	27	18	22,5	17	21,3	8	10,0	5	6,3	3	3,8	30	37,5	90	16,1
Inj site swelling	15	18,8	17	21,3	12	15,0	8	10,0	5	6,3	4	5,0	5	6,3	23	28,8	65	11,6
Inj site pain	59	73,8	54	67,5	31	38,8	15	18,8	7	8,8	4	5,0	3	3,8	61	76,3	169	30,2
Fever	1	1,3	2	2,5	4	5,0	0	0,0	0	0,0	0	0,0	0	0,0	4	5,0	7	1,3
Malaise	10	12,5	9	11,3	6	7,5	4	5,0	4	5,0	3	3,8	2	2,5	19	23,8	38	6,8
Headache	15	18,8	14	17,5	11	13,8	6	7,5	4	5,0	3	3,8	3	3,8	26	32,5	56	10
Nausea	11	13,8	9	11,3	4	5,0	4	5,0	3	3,8	1	1,3	1	1,3	17	21,3	33	5,9
Analgetics	4	5,0	4	5,0	1	1,3	1	1,3	3	3,8	1	1,3	2	2,5	9	11,3	16	2,9
School absence	0	0,0	4	5,0	3	3,8	0	0,0	1	1,3	0	0,0	0	0,0	6	7,5	8	1,4

12.3 DEATHS AND OTHER SERIOUS OR SIGNIFICANT ADVERSE EVENTS

12.3.1 Listing of serious adverse events

No serious or unexpected adverse events or deaths were reported during the study period.

12.3.2 Pre-existing diseases and concomitant medication

A significant proportion of the healthy study participants had chronic diseases and conditions that did not constitute exclusion criteria, but were documented in the CRFs, though without details as e.g. names and dosing of drugs used. At study entry, 29 (36,25%) of the 80 participants reported long lasting medical conditions. Four (three females) reported to have frequent migraine and more or less regular use og anti migraine drugs. Three of them reported head ache during the seven-day follow-up period and two of them stated that it was migraine. One reported frequent head ache and vertigo caused by a head trauma a few years back, but reported no head ache during the seven days observation period.

Seven study participants (three females) reported asthmatic conditions and regular or occasional use of anti-asthmatics. One of them (male) had exercise-induced asthma. Eleven others reported allergic conditions: Eight (three females) had rhino-conjunctivitis, mostly during spring. Three (one female) reported specific allergies (one each cat, peanuts, wasp sting).

Two (one female) used acne medication (tetracycline and isotretinoin respectively). Four girls reported respectively iron deficiency anaemia, hypothyroidism, psoriasis and long-lasting pain of left arm of unknown cause.

12.4 Clinical laboratory evaluation

Except for antibody analyses, no laboratory evaluations were done.

12.5 Safety Conclusions

The primary end point for safety was to register the occurrence of solicited injection site reactions and solicited systemic symptoms and other adverse events after a booster dose (fifth dose) of dTap-IPV in the age group 15-16 years

Most adverse events were mild and short lasting, and none withdrew from the study because of adverse events. The incidence of fever, malaise, head-ache, nausea and injection site pain, redness and swelling after booster vaccination with dTap-IPV was of the same order of magnitude as stated in the product information. No SAEs were reported.

13 DISCUSSION AND OVERALL CONCLUSIONS

Vaccines against diphtheria, tetanus and pertussis with reduced antigen content (dTap) have been shown to be safe and immunogenic in adolescents and adults [Li et al. 2009; Minh et al. 1999; Pichichero et al. 2006; Vergara et al. 2005; Zepp et al. 2007]. Few countries use the "Nordic" childhood immunisation program with only three doses during infancy and the next dose in school age. The study participants had their 4th dose of pertussis vaccine as a dose of DTaP-IPV at the age of 7

years, in a clinical trial in 1998 [Sandbu et al. 2001]. This 4th dose was later included in the vaccination program in 2006. The next dose was decided to be a booster dose of diphtheria- and tetanus vaccine (dT) for pupils of grade 10, which is the last opportunity for school vaccination in Norway, along with the 5th dose of IPV which has been given at that age for decades. Instead, the study participants received a dose of dTap-IPV as fifth dose.

To our knowledge similar studies had not been done in persons having received the "Nordic" three-dose-program in infancy. However, it turned out that part of a study in Sweden, had similar objectives and similar results and was done at approximately the same time as ours [Carlsson et al. 2015].

The previous study had revealed that before the booster dose at age seven, none of the study participants had antibody levels indicating long term protection against diphtheria [Sandbu et al. 2001]. At age 15, all had protective antibody levels (>0.01 IU/ml) against diphtheria and ≥0.1 IU/ml against tetanus toxoid in their pre-booster sera, though seven persons (8%) had anti diphtheria antibody levels below 0.1 IU/ml, and ten persons (13 %) had low anti-tetanus antibody levels (≤0.2 IU/ml), indicating short-term protection. After the booster dose all but one participant obtained diphtheria antibody levels >1.0 IU/ml, and IgG anti-tetanus toxoid levels >2 IU/ml, indicating long term immunity.

Forty two participants (53%) had undetectable levels of IgG-PT antibodies (<5 FDA-U/ml) before the booster dose, whereas all reached levels >5 FDA-U/ml and 84 % attained >20FDA-U/ml post booster.

Before booster vaccination, three subjects (5.8%) had titre <10 against poliovirus type 3, whereas all subjects had titres ≥10 against type 1 and 2 virus (Fig. xx). After the booster dose all pupils acquired antibody titres ≥80 against polio virus type 1 and 3. Against polio virus type 3, all participants had antibody titres ≥40 and all but two acquired antibody titres ≥80.

Though a high number of AEs were reported, the vaccine was generally well tolerated.

When receiving a 5th dose of dTap-IPV vaccine, the participants of this study, though having been vaccinated with wP in infancy, acted as a "vanguard" for a change in the immunisation program, as such a booster dose was introduced for grade 10 from the school year 2013-2014.

Teenagers vaccinated according to the Norwegian childhood immunisation program had good immune response to all the four vaccine components. The same response would be expected in other age groups.

Hence, these data suggest that the study vaccine is immunogenic and safe when administered as a booster dose at the age of 15-16-years, and is well suited to use as the 5th dose of DTP-polio vaccine in the Norwegian childhood immunisation program.

14 Tables, figures and graphs referred to in the text

14.1 Individual efficacy response data

Table 14-1 Tetanus (TET) and diphtheria /DIFT) antibodies before (1.VISIT) and after (2.VISIT) the booster vaccination. Units: IU/ml

Id	TET 1.VISIT	TET 2.VISIT	DIFT 1.VISIT	DIFT 2.VISIT	Id	TET 1.VISIT	TET 2.VISIT	DIFT 1.VISIT	DIFT 2.VISIT
1001	1,2	3,1	0,32	1,28	**1065**	0,3		0,32	
1002	0,6	6,1	0,64	2,56	**1066**	0,9	5,6	0,64	20,48
1003	0,6	43,3	0,32	>20,48	**1068**	1,4	3,8	5,12	10,24
1005	0,8	2,3	0,32	2,56	**1069**	1,6	2,9	2,56	5,12
1006	0,6	14,4	0,08	10,24	**1071**	1,3	79,8	1,28	20,48
1007	1,2	3,8	5,12	20,48	**1072**	0,5	10,3	5,12	10,24
1008					**1074**	1,0	7,5	2,56	20,48
1009	0,1	5,0	0,32	5,12	**1077**	0,5	10,3	0,64	5,12
1010	5,1	14,1	5,12	20,48	**1078**	0,3	26,4	0,32	2,56
1011	1,3	8,6	2,56	10,24	**1079**	0,3	19,5	0,02	1,28
1012	0,7	18,8	1,28	40,96	**1080**	0,9	7,7	0,16	2,56
1013	0,6	2,1	0,16	5,12	**1081**	0,2	10,9	0,08	5,12
1016	0,6	9,5	1,28	>40,96	**1083**	0,3	16,1	0,32	5,12
1019	0,8	32,6	2,56	>40,96	**1084**	0,4	7,7	0,32	0,64
1020	0,2	15,5	0,32	10,24	**1086**	0,4	9,0	0,32	2,56
1022	0,2	20,0	0,32	20,48	**1089**	0,5	28,5	0,16	10,24
1024	0,8	28,6	5,12	>40,96	**1090**	0,3	26,2	0,16	10,24
1027	1,5		1,28		**1092**	0,2	13,7	0,64	>20,48
1028	0,6	55,0	0,32	>40,96	**1094**	2,2	8,9	2,56	>20,48
1029	0,7	21,8	2,56	10,24	**1098**	0,2	14,8	0,16	2,56
1030	1,3	7,9	0,64	20,48	**1101**	0,6	4,7	0,16	10,24
1032	0,8	12,8	0,32	10,24	**1104**	0,9	6,9	1,28	>20,48
1033	0,6	27,2	1,28	>40,96	**1106**	0,5	7,3	0,64	10,24
1036	0,4	10,8	0,32	10,24	**1107**	0,2	2,2	0,16	1,28
1037	1,0	19,4	2,56	10,24	**1108**	0,3	9,1	0,08	5,12
1039	0,2	18,3	0,32	>20,48	**1109**	0,2		0,04	
1041	0,6	4,1	0,32	5,12	**1110**	0,9	7,0	0,64	1,28
1042	0,4	12,4	0,16	10,24	**1111**	0,4	17,1	1,28	20,48
1043	5,0		0,64		**1112**	1,3	4,4	0,32	5,12
1045	0,2	15,4	0,32	>20,48	**1114**	0,3	8,7	0,32	5,12
1047	0,6	18,2	0,64	10,24	**1115**	0,3	21,5	0,08	1,28
1048	2,3	9,3	10,24	10,24	**1117**	0,5	10,7	1,28	10,24
1049	0,7	15,5	5,12	20,48	**1124**	0,4	17,1	1,28	>20,48
1051	0,3	5,6	0,32	2,56	**1125**	1,0	3,4	0,32	10,24
1053	0,4	11,2	0,32	5,12	**1152**	1,3	22,4	2,56	>20,48
1054	0,4	13,0	1,28	10,24	**1153**	0,4	14,3	0,64	>20,48
1055	2,1	13,4	1,28	5,12	**1155**	0,4	19,7	1,28	10,24
1056	1,5	13,3	1,28	10,24	**1156**	0,7	17,0	0,32	20,48
1058	0,5	8,5	0,32	1,28	**1157**	1,0	10,7	0,32	>40,96
1061	1,4	3,5	5,12	10,24	**1158**	0,7		0,08	
1064	0,9	4,0	1,28	10,24					

Table 14-2 Pertussis antibodies before (VISIT 1) and after (VISIT 2) the booster vaccination (FDA-U/ml). 75 participants PP.

ID	IgG - PT VISIT 1	IgG - PT VISIT 2	FHAIgG VISIT 1	FHAIgG VISIT 2	FHAIgA VISIT 1	FHAIgA VISIT 2	PTIgG VISIT 1	PTIgG VISIT 2	PTIgA VISIT 1	PTIgA VISIT 2	RB VISIT 1	RB VISIT 2	IgG binding VISIT 1	IgG binding VISIT 2
1001	3	62	103	300	85	108	84	337	80	75	64	512	151	1265
1002	2	38	135	240	93	132	52	216	51	55	64	256	36	392
1003	81	131	165	462	90	187	370	364	56	80	64	2048	231	3237
1005	166	168	162	282	91	125	463	463	78	80	64	256	133	465
1006	1	135	72	370	79	103	59	394	54	55	16	512	48	581
1007	5	23	96	229	93	109	90	163	44	51	64	256	106	457
1009	13	57	281	454	121	177	147	292	64	67	128	1024	281	1967
1010	7	74	194	322	146	182	125	315	81	76	64	256	159	486
1011	2	36	96	226	89	108	75	353	96	94	8	128	34	119
1012	1	11	95	291	106	118	63	129	116	149	16	256	56	358
1013	6	15	100	303	36	57	84	168	39	40	16	128	72	201
1016	1	62	126	429	31	56	53	333	36	37	32	512	80	506
1019	3	13	122	414	42	57	85	170	43	39	256	256	298	778
1020	1	36	83	401	54	122	42	244	45	49	32	512	31	592
1022	38	57	426	436	134	219	239	340	52	61	256	512	217	947
1024	9	98	203	388	69	99	132	471	98	96	128	512	234	1491
1028	6	83	30	458	37	139	86	411	47	49	64	1024	55	623
1029	3	62	103	429	53	115	90	378	80	89	64	256	140	530
1030	4	45	125	391	40	52	90	272	67	50	128	256	344	944
1032	3	233	166	479	48	297	66	567	53	62	64	1024	126	620
1033	2	25	105	475	62	602	93	308	130	204	64	2048	158	1278
1036	1	61	71	390	43	67	76	372	79	81	16	512	19	280
1037	4	34	142	431	57	127	103	347	99	109	64	256	123	428
1039	2	33	160	434	67	207	76	255	118	114	32	512	38	1322
1041	3	35	132	384	55	80	87	248	110	87	32	256	57	1112

ID	IgG - PT VISIT 1	IgG - PT VISIT 2	FHAIgG VISIT 1	FHAIgG VISIT 2	FHAIgA VISIT 1	FHAIgA VISIT 2	PTIgG VISIT 1	PTIgG VISIT 2	PTIgA VISIT 1	PTIgA VISIT 2	RB VISIT 1	RB VISIT 2	IgG binding VISIT 1	IgG binding VISIT 2
1045	6	26	141	318	75	89	109	238	93	87	64	512	123	1260
1047	4	49	155	332	56	62	90	337	90	75	16	128	68	384
1048	11	97	180	370	63	90	156	484	125	87	128	1024	259	1056
1049	53	92	285	396	102	178	284	398	89	91	128	256	511	1428
1051	3	17	61	311	34	46	66	155	44	50	16	256	38	644
1053	7	22	273	338	65	76	96	179	69	65	256	512	296	1368
1054	4	24	229	353	116	215	105	216	67	75	256	1024	430	2185
1055	5	140	220	411	53	148	67	463	56	59	64	256	268	1091
1056	5	82	295	391	51	109	95	331	59	65	128	256	321	997
1058	1	28	71	272	98	367	46	186	64	73	64	256	40	403
1061	1	6	128	221	46	43	60	96	77	70	32	64	104	144
1064	24	74	501	484	174	185	167	231	60	72	1024	1024	1689	2455
1066	6	35	233	383	51	118	70	196	50	57	128	512	417	1316
1068	3	22	118	281	42	61	65	164	57	46	32	256	123	414
1069	27	43	350	423	161	192	204	309	54	53	512	1024	2281	3045
1071	7	316	151	587	79	431	96	693	117	357	128	2048	191	1662
1072	39	72	252	391	105	162	243	356	86	87	256	512	1486	3652
1074	12	122	107	346	44	62	111	413	69	61	128	512	302	1238
1077	3	45	101	319	40	127	58	238	59	52	32	128	91	647
1078	1	25	60	318	51	68	58	144	55	58	8	64	15	53
1079	5	26	166	333	77	92	76	172	58	53	128	256	517	1140
1080	7	37	87	332	100	63	71	220	62	70	32	128	101	496
1081	24	75	371	470	178	521	193	372	59	134	128	512	748	2929
1083	103	113	552	581	502	557	477	511	86	76	512	512	3166	3141
1084	1	9	127	236	45	61	62	115	55	55	64	256	399	835
1086	1	40	61	330	36	51	56	255	50	48	32	256	73	503
1089	4	86	134	347	53	146	67	240	42	44	64	256	273	800

	IgG - PT	IgG - PT	FHAIgG	FHAIgG	FHAIgA	FHAIgA	PTIgG	PTIgG	PTIgA	PTIgA	RB	RB	IgG binding	IgG binding
1090	25	209	252	379	56	241	216	542	66	77	128	512	357	1143
1092	3	16	143	299	45	82	94	137	55	51	64	256	141	1001
1094	2	61	144	415	38	150	54	306	45	45	128	512	533	1736
1098	16	80	243	363	48	74	123	322	53	58	64	256	160	1007
1101	1	26	124	329	51	77	61	167	75	79	16	128	76	303
1104	5	33	109	374	36	110	69	184	45	51	64	512	119	1090
1106	2	22	132	367	50	116	64	171	47	63	64	256	346	1923
1107	4	17	145	241	52	57	98	180	59	50	64	128	82	366
1108	2	81	90	340	42	60	66	364	60	65	32	128	84	520
1110	18	29	296	403	141	206	165	254	57	54	512	1024	1055	3268
1111	3	31	143	389	66	171	88	251	88	87	64	512	404	2264
1112	1	22	92	347	36	43	58	216	54	52	16	128	33	962
1114	13	62	265	433	83	140	113	305	84	91	128	512	378	2027
1115	1	18	71	358	35	88	53	149	54	54	16	512	54	714
1117	2	12	135	284	60	105	64	126	94	86	32	128	25	516
1124	12	82	193	379	51	153	109	333	39	44	64	1024	443	1731
1125	1	21	169	375	51	76	64	171	68	44	32	512	75	932
1152	36	69	338	415	93	109	223	341	42	38	128	512	1162	2390
1153	13	57	310	394	137	176	150	292	55	56	64	256	182	822
1155	8	123	131	407	62	270	89	393	79	80	64	512	185	631
1156	1	10	256	309	45	63	74	118	49	42	64	256	516	1796
1157	3	86	240	387	46	61	62	375	65	57	32	256	98	973

Table 14-3: Antibody titres for Poliovirus type 1, 2 and 3 before (nr1) and after (nr2) the booster vaccination for 48 study participants PP.

ID	Pol1 nr1	Pol1 nr2	Pol2 nr1	Pol2 nr2	Pol3 nr1	Pol3 nr2
1002	160	160	80	≥320	160	≥320
1003	40	≥320	160	≥320	80	≥320
1005	160	≥320	20	≥320	40	≥320
1006	160	≥320	80	160	160	160
1007	40	≥320	20	160	20	≥320
1009	80	≥320	80	80	40	80
1010	40	≥320	40	≥320	10	160
1011	40	80	40	80	20	80
1012	40	160	20	≥320	40	160
1013	80	160	40	80	80	80
1016	20	80	80	160	5	160
1019	160	160	160	≥320	160	≥320
1020	40	160	40	160	20	≥320
1022	20	80	40	80	<5	≥320
1024	80	≥320	40	≥320	40	≥320
1028	20	≥320	20	≥320	40	160
1029	20	≥320	10	≥320	40	≥320
1030	160	≥320	80	≥320	80	≥320
1032	80	≥320	80	≥320	80	≥320
1033	20	≥320	10	≥320	40	≥320
1036	80	≥320	40	160	160	≥320
1037	40	160	20	160	20	≥320
1039	80	≥320	40	≥320	10	160
1041	20	160	20	160	40	160
1042	40	80	80	40	40	160
1045	40	160	40	80	80	160
1047	160	160	≥320	≥320	≥320	≥320
1049	20	80	40	40	<5	80
1054	160	160	≥320	≥320	160	≥320
1055	≥320	≥320	≥320	≥320	≥320	≥320
1058	80	80	80	160	≥320	≥320
1068	160	≥320	≥320	≥320	160	160
1069	80	160	160	≥320	160	≥320
1074	≥320	≥320	160	≥320	≥320	160
1077	160	160	80	160	160	≥320
1078	160	≥320	160	160	≥320	≥320
1079	≥320	≥320	160	≥320	≥320	≥320
1080	80	160	≥320	≥320	160	≥320
1083	160	160	160	160	80	80
1094	≥320	160	≥320	160	160	≥320
1101	160	≥320	160	160	160	≥320
1111	160	80	80	160	≥320	≥320
1112	80	160	80	160	160	160
1152	40	≥320	80	≥320	160	≥320
1153	40	160	20	80	80	80
1155	80	≥320	20	≥320	80	≥320
1156	160	≥320	80	≥320	160	≥320
1157	40	≥320	20	≥320	80	≥320

Tab 14-4: Solicited adverse events on days 0-6 after vaccination by participant, highest reported grading.

ID	Sex	Rubor	Swelling	Pain	Any inj-site	Fever	Malaise	Headache	Nausea	Any systemoc	Analgetic days	Absence days
1001	F			3	3		1		1	1		
1002	F	1		1	1		1	1	1	1		
1003	M			1	1		2			2	3	3
1005	M		1	2	2			2		2	2	2
1006	F	1	1	1	1		1	1		1		
1007	F	1		1	1			1		1		
1008	F			1	1							
1009	F			1	1							
1010	F		1	3	3		2	3	2	3	2	2
1011	M			1	1							
1013	F	3	3	3	3							
1019	F			1	1	1	3	1	2	3		
1020	F	1		2	2		1	2	2	2	2	2
1024	M	1		2	2			1		1	1	1
1028	M	1	1	1	1				1	1		
1029	M			2	2							
1030	F	3	3	2	3							
1032	M			1	1		2	2	2	2		
1033	M			1	1							
1036	M			2	2		1			1		
1037	M	3		1	1							
1039	M			2	2		2	1	2	2		
1041	M			1	1							
1042	F	1		1	1			1		1	1	1
1043	F			1	1							
1045	F	1	1	2	2							
1047	F							1		1		
1048	F	3	3	3	3			2		2		
1049	M	1	3	2	3		1			1		
1051	F			1	1			1		1		
1053	F	1	1	2	2		1	1		1		
1054	M			3	3							

1055	M			3	3	3	3	2	3	3			
1058	F	1		1	1								
1061	F	1	1	2	2								
1065	M	1	1	2	2	3	3	3	1	3	3	3	
1066	F	3	3	3	3			1	1	1			
1068	F	1		2	2			1		1	1	1	
1069	F	1		2	2			1		1			
1071	M	1	3	1	3		1		1	1			
1072	M			1	1								
1074	F	1	1	1	1								
1077	F		2	1	2								
1080	M	1	1		1								
1083	F	1		3	3								
1084	F			3	3		1	1	1	1			
1086	M	1	1	1	1								
1089	F			1	1								
1090	F			1	1								
1094	M		1	1	1								
1098	F			1	1		1	1		1			
1101	F			1	1								
1107	F	1		1	1								
1108	F			1	1								
1109	M	1	1		1								
1110	F			1	1								
1111	F			1	1								
1114	F								1	1			
1115	F			3	3		1	2	2	2			
1124	F			3	3								
1125	F	2	3	3	3		1	1	1	1	1	1	
1152	M			2	2			1		1			
1153	F	1		1	1			2	2	2			
1155	M			1	1								
1156	M		1		1								
1157	M			2	2								
1158	M			2	2								

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16 APENDICES

The following appendices are available in Norwegian but not submitted with the report.

- Protocol and protocol amendments
- Information and consent form
- Sample case report form
- Sample diary form
- Reports on internal inspections at NIPH

The following appendices are submitted as included in the report:

- No objection letters from from the Norwegian Regional Committee for Medical Research Ethics of Health Region South-Norway (REK Sør) (in Norwegian)
- No objection letter from the Norwegian Medicines Agency (in Norwegian)
- List of the project groups members and their tasks in the study
- CV of the Coordinating Investigator and Clinical Responsible Investigator and Project Coordinator

16.1 Study information

16.1.1 Protocol and protocol amendments

Available in Norwegian, not submitted

16.1.2 Sample Case Report Form

Information and consent form, Case report form and Diary form are available in Norwegian, but not submitted.

16.1.3 No objection letters

16.1.3.1 No objection from the Norwegian Regional Committee for Medical Research Ethics (EK Sør)

TE. 7/3-07 HB.

UNIVERSITETET I OSLO
DET MEDISINSKE FAKULTET

07 342 - 10

Overlege Synne Sandbu
Nasjonalt Folkehelseinstitutt
Pb. 4404 Nydalen
0403 Oslo

Regional komité for medisinsk forskningsetikk
Sør- Norge (REK Sør)
Postboks 1130 Blindern
NO-0318 Oslo

Telefon: 228 50 670
Telefaks: 228 44 661
E-post: juliannk@medisin.uio.no
Nettadresse: www.etikkom.no

Dato: 02.03.07
Deres ref.:
Vår ref.: S-07063b

S-07063b En åpen studie av immunrespons og bivirkninger etter boosterdose (5. dose) med kombinert difteri-stivkrampe-kikhoste-poliovaksine til skoleelever i alderen 15-16 år [2.2007.217]

Vi viser til søknad mottatt 01.02.07 med følgende vedlegg: Protokoll; Informasjon og samtykke til deltaker og foreldre/foresatte; CV koordinerende utprøver; CV utprøver/medisinsk ansvarlig lege; Dagbok; Søknad om opprettelse av forskningsbiobank nr. 1513 datert 31.01.07; Kopi av melding til SLV; Produktbeskrivelse Boostrix-Polio; EudraCT skjema

Komiteen behandlet søknaden i sitt møte torsdag 22.2.07.

Nestleder Ulrich Abildgaard erklærte seg inhabil og gikk ut av møtet under behandling av søknaden.

Komiteen fattet følgende vedtak:
Komiteen har ingen merknader til prosjektet og tilrår at det gjennomføres.

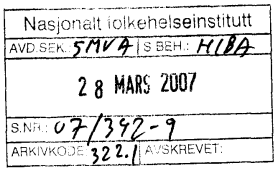
Med vennlig hilsen

Tor Norseth
Leder

Julianne Krohn-Hansen
Sekretær

16.1.3.2 No objection from the Norwegian Medicines Agency

Statens legemiddelverk
Norwegian Medicines Agency



Nasjonalt folkhehelseinstitutt

Postboks 4404 Nydalen
0403 OSLO
Norge

Offl. § 5a jf lml. § 30

Deres ref.	Dato	Vår ref.	Arkivkode	Seksjon/Saksbehandler
07/342-6 /SMVA/HIBA	27-03-2007	07/01603-9	**343.1**	Seksjon for klinisk utprøving/ Ingvild Aaløkken

BOOSTRIX POLIO - KLINISK UTPRØVING - EUDRACTNR 2007-000199-17

Vi viser til Deres søknad om klinisk utprøving av Boostrix Polio, og til Deres brev av 13. mars .2007.

For vurdering av Deres dag-30 respons henviser vi til vedlagte vurdering.

Når det gjelder vår anbefaling om å endre ordlyden i eksklusjonskriterium nr 4.3 så bør dette gjøres i form av et protokolltillegg. Det forutsettes at protokolltillegget utarbeides, signeres og dateres av Folkehelseinstituttet og av utprøver før studien settes i gang. Protokolltillegget kan sendes Legemiddelverket til orientering.

Vi har for øvrig ingen bemerkninger til studien.

Vi ønsker lykke til med studien og ser frem til å motta studierapporten.

Med vennlig hilsen
STATENS LEGEMIDDELVERK

Ingvild Aaløkken
Seksjonssjef

Kopi REK Sør

Vedlegg: Kopi av vurdering av kvalitet og klinikk

Brev stilles til Statens legemiddelverk. Vennligst oppgi vår referanse

Statens legemiddelverk
Sven Oftedals vei 6, 0950 Oslo
Tlf.: 22 89 77 00
Fax: 22 89 77 99
www.legemiddelverket.no
post@legemiddelverket.no
Kto. 7694 05 00903
Org.nr. 974 761 122

16.1.4 List and description of investigators

16.1.4.1 Function list of the project group members and their tasks in the study, with foot notes

Function/Task	Responsible	Deputy(s)
Project leader	Hilde Bakke	Synne Sandbu
Coordinating investigator	Synne Sandbu**	
Investigator	Per Wium	
Monitor	Inger Lise Haugen	
Reception of study participants at the trial site	Hilde Bakke	Synne Sandbu
Inclusion	Synne Sandbu**	Ellen Furuseth
Vaccinator(s)	Aud Befring*, Municipal Health Services, Lørenskog	Anne B. Moen*, Kirsti Thorstensen*, Grethe Trongård*
Blood sampling	Tine Kristoffersen*	Synne Sandbu
Observation of study participants after vaccination	Synne Sandbu	Hilde Bakke
Blood sample handling at the trial site	Tine Kristoffersen*	
Diaries – reception and follow-up	Synne Sandbu	Hilde Bakke Tine Kristoffersen
Quality assurance	Gunn Stabbetorp	Ellen Anette Stickler
Analyses and data management:		
Pertussis antibody analyses	Audun Aase***	Samuel Merino*, Tove Karin Herstad*
Diphtheria antibody analyses	Ingeborg Aaberge***	Samuel Merino*
Tetanus antibody analyses	Ingeborg Aaberge***	Tine Kristoffersen*
Polio antibody analyses	Inger Sofie S. Vik***	Grethe Krogh*, Marianne Morken*
Analyses of adverse events	Synne Sandbu***	Ellen Furuseth

* This is routine work for the person concerned and there is no need for training.

** Training is not considered necessary as the person in question is a physician and has many years of experience with clinical studies and satisfies the requirements (cf. GCP) for the role of coordinating investigator.

*** This is in line with the person's competence in the position he/she holds at the Norwegian Institute of Public Health and training is therefore not necessary.

16.1.4.2 CVs of Coordinating Investigator, Clinical Responsible Investigator and Project Coordinator

CURRICULUM VITAE 2025, abbreviated

Family name: Sandbu
Given name: Synne
Date of birth: 17. March 1946
Place of birth: Vågå, Norway

EDUCATION:

- Medical Degree, University of Oslo, June 1973.
- Diploma of Tropical Medicine and Hygiene, Liverpool 1977 (Lent term)
- Recognized specialist in pediatrics 1991 (Norwegian Medical Association).
- One day course GCP in clinical trials, 4. March 1996
- Nordic Summer School in Methods of Infectious Disease Epidemiology 1998
- several other short courses after 2007.
- INDVAC – Advanced Vaccinology Course in India 2012.

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, 1977-82 and 1986-88. Medical Officer/Chief Medical Officer.
- 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 1989-1991.
- Norwegian Institute of Public Health (NIPH), Department of Vaccines, senior house officer from Feb. 1991, senior medical officer from May 1997 till retirement March 2016.
  2003 - 2005 project leader for SYSVAK (National immunisation registry), NIPH.
  2002- 2010 responsible for Pharmacovigilance for vaccines, national level, NIPH.

CLINICAL STUDIES:

Principal investigator of six vaccine studies:

- Two studies on IPV (VAVA92-01, VAVA 94-02)
- One study on IPV-Vero (VAVA96-01), 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), in cooperation with SmithKline-Beecham AS.
- Two studies on meningococcal B-vaccine (VA01-01 A, VA01-01 B).
- One study on dTp-IPV as booster dose for teenagers (EudraCTnr 2007-000199-17)

PUBLICATIONS

15 publications.

Curriculum Vitae november 2024

Per Wium

Born February 5, 1943 in Drammen

Married to Christine Wium, 3 children born in 1968, 71 and 74.

Education:

• Medical degree from University of Oslo after studies in Freiburg/Germany and Fribourg/Switzerland.

• Master's degree in Health Services Research (MPH) from Leeds University 1980/81

• Approved specialist in general medicine 1976 + 85, and in community medicine in 1984

-Supervisor for the specialty education in community medicine from 2001 to 2015

Experiences in Norway:

- Internship Namsos Hospital 1969-70
- Local Medical Officer and Chairman of Health Council in Midsund municipality 1970-1978.
- Local Medical Officer in Oslo Health Council 1978 – 1985. Romsås and Marka district, including 6 months at Gaustad Hospital, psychogeriatric department.
- Consultant and senior consultant at the Oslo Hospital Councilor's office 1985-1988.
- Medical Advisor in complaints cases for the Norwegian Patient Association 1988 – 1993.
- Chief physician in NHO (Confederation of Norwegian Enterprise) with responsibility for health and working environment 1988-1993
- Board member of the Directorate of Labour Inspection 1998 - 1993.
- Senior advisor in the Norwegian National Health Authority 1993 – 2001, Dept. for community medicine, with a special task of coordinating the international work in the agency. In addition, work with regulations for the Infectious Diseases Act and SYSVAK.
- Senior advisor in the newly established Directorate of Social Affairs and Health 2001 to May 03, with work area international affairs, The Municipal Health Services Act (including the new Family Doctor Scheme) and the nursing and care sector as well as cooperation between health services and social services in the municipalities.
- Deputy chairman of the national steering group for the 400th anniversary of the health service in Norway.
- Municipal Health director and Chief Physician and finally 80% position as a nursing home physician in Lørenskog municipality until 2013.
- Medical advisor in the municipal Welfare Administration of Oslo, Transport Services, 2015 - 2018.
- Member and leader (2006-2007) of the Cooperation Committee for municipalities in Romerike and Ahus 2003 to 2010.

International experiences:

• Work for Rotary International with Vietnamese boat people in the refugee camps Jubilee and Kai Tak in Hong Kong 1984.

• Member of the Norwegian delegation to the ILO conference in Geneva 1988-92

• Norwegian representative in the EU's Research Committee on Biomedicine 1993 - 1999.

• Member of the Norwegian delegations to the WHO Executive Board meetings in Geneva, the WHO Health Assemblies and the WHO Europe Regional Committee meetings from 1993 - 2002.

• Delegate to the Council of Europe's Health Committee (CDSP) from 1993 to 2001 and chair of the committee 1997-1999.

Publications:

• Initiator and editor of Journal of the Norwegian Public Health Service and Community Medicine0 (Utposten) 1972 -1977.

• The working conditions of the Norwegian District Physician 1977.

• Quality control of general practice. Self-control and the way forward, 1980.

• Health for the old: A Norwegian study of how old people are institutionalized. Master's thesis at the University of Leeds 1981.

• Editor of the Norwegian Journal of Geriatrics 1985 – 1990.

• Public health service in Oslo. Past, present, future. SIFF Group for Health Service Research 1986.

Curriculum Vitae – Hilde Bakke

Oslo, Norway | +47 93 25 47 49 | hswb73@hotmail.com

Profile

Experience in vaccines, clinical trials, and regulatory affairs. Strong background from both public health (Norwegian Institute of Public Health) and industry (GlaxoSmithKline). Expertise in vaccination programmes, registry management (SYSVAK), and immunology.

Work Experience

Norwegian Institute of Public Health (NIPH)
Researcher / Professional Coordinator, the Norwegian immunisation registry SYSVAK | 2019–present

GlaxoSmithKline (GSK), Norway
Head of Regulatory Affairs | 2016–2019
Regulatory Advisor, Vaccines | 2010–2016
Regulatory Affairs Manager | 2008–2010

Norwegian Institute of Public Health (NIPH)
Senior Advisor / Project Manager | 2005–2008

- Led the Norwegian immunisation registry SYSVAK
- Managed multiple vaccine clinical trials (MMRV, pneumococcal, meningococcal)

Additional experience includes clinical trials, vaccination programmes, international fieldwork (Tanzania), and supervision of pharmacy students.

Education

PhD (Philosophiae Doctor), University of Oslo – 2005
Cand. Pharm. (Master of Pharmacy equivalent) – 1998

Key Competencies

- Electronic immunisation registry SYSVAK
- Regulatory affairs (EU/industry)
- Public health & immunisation programmes
- Vaccines & immunology
- Clinical trials management

Publications

Bakke H, Lie K, Haugen IL, Korsvold GE, Høiby EA, Næss LM, Holst J, Aaberge I, Oftung F, Haneberg B.
Meningococcal outer membrane vesicle vaccine given intranasally can induce immunological memory and booster responses without evidence of tolerance. Infect Immun 2001;69:5010–5015.

Bakke H, Setek TN, Huynh PN, Haugen IL, Høiby EA, Holst J, Aaberge IS, Haneberg B.
Immunisation schedules for non-replicating nasal vaccines can be made simple by allowing time for development of immunological memory. Vaccine 2004;22:2278–2284.

Janakova L, Bakke H, Haugen IL, Berstad AKH, Høiby EA, Aaberge IS, Haneberg B.
Influence of intravenous anesthesia on mucosal and systemic antibody responses to nasal vaccines. Infect Immun 2002;70:5479–5484.

Haugan A, Dao PXT, Glende N, Bakke H, Haugen IL, Janakova L, Berstad AKH, Holst J, Haneberg B.
Bordetella pertussis can act as adjuvant as well as inhibitor of immune responses to non-replicating nasal vaccines. Vaccine 2003;22:7–14.

Samdal HH, Bakke H, Oftung F, Holst J, Haugen IL, Korsvold GE, Kristoffersen AC, Krogh G, Nord K, Rappuoli R, Berstad AKH, Haneberg B.
A non-living nasal influenza vaccine can induce major humoral and cellular immune responses in humans without the need for adjuvants. Human Vaccines 2005;1:85–90.

Bakke H, Samdal HH, Holst J, Oftung F, Haugen IL, Kristoffersen AK, Haugan A, Janakova L, Korsvold GE, Krogh G, Andersen EAS, Djupesland P, Holand T, Rappuoli R, Haneberg B.
Oral spray immunization may be an alternative to intranasal vaccine delivery to induce systemic antibodies but not nasal mucosal or cellular immunity. Scandinavian Journal of Immunology 2006;63:223–231.

Bakke H, Haneberg B.
Development of mucosal vaccines. Tidsskrift for Den norske legeforening 2006;126(21):2818–2821.

Vestrheim DF, Løvoll Ø, Aaberge IS, Caugant DA, Høiby EA, Bakke H, Bergsaker MR.
Effectiveness of a 2+1 dose schedule pneumococcal conjugate vaccination programme on invasive pneumococcal disease among children in Norway. Vaccine 2008;26:3277–3281

Clinical study dTap-IPV (SM 07-01), EudraCTnr 2007-000199-17

16.1.5 Signature page

STUDY TITLE: **An open study of immune response and adverse events after a booster dose (fifth dose) of combined diphtheria-tetanus-pertussis-polio vaccine for school children at age 15-16 years.**

I have compiled this clinical study report and confirm that to the best of my knowledge, the report and associated appendices accurately describe the conduct and results of the study

Coordinating investigator: Synne Sandbu

Signed: Synne Sandbu Date: 29. JUNE 2026

Title: Retired, previous Senior Physician, NIPH

16.1.5 Listing of patients receiving investigational product from spf. batches

Only one batch was used.

16.1.6 Randomisation

No control group

16.1.7 Audit certificates

Only internal inspections at NIPH were done.

16.1.8 Documentation of statistical methods

Described in chapter 9.7.

16.1.9 Documentation of inter-laboratory standardisation and quality assurance

The pertussis IgG was analysed using a Bordetella pertussis toxin kit from Virion\Serion. The laboratory methods for quantitation of antibodies against diphtheria, tetanus and polio are in-house methods, and are the same that we use for our patient analysis. The methods are calibrated against international reference material, and control samples are included in each assay and trended to ensure high reliability and accuracy.

16.1.10 Publications based on the study

One paper is published: **Aase, A., T. K. Herstad, S. Merino, M. Bolstad, S. Sandbu, H. Bakke, and I. S. Aaberge**. 2011. Immunization of Teenagers with a Fifth Dose of Reduced DTaP-IPV Induces High Levels of Pertussis Antibodies with a Significant Increase in Opsonophagocytic Activity. Clin.Vaccine Immunol. **18**:1269-1274. (https://pubmed.ncbi.nlm.nih.gov/21677109/ or https://journals.asm.org/doi/epub/10.1128/cvi.05067-11)