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RIVM report 000012 003

Monovalent RIVM meningococcal B OMP vesicle F91 vaccines in toddlers

AB Lafeber, CJP van Limpt, J Labadie, GAM Berbers, ED de Kleijn, R de Groot, HC Rümke, AJW van Alphen

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This investigation has been performed by order and for the account of the Chief Inspectorate of Health Care (IGZ), within the framework of project V/000012/03/AE, clinical studies with meningococcal B vaccine.

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

Abstract Nederlands

Dit rapport geeft een beschrijving van de resultaten van een gerandomiseerde fase II studie naar de veiligheid en immunogeniciteit van een monovalent P1.7^{h},4 OMV vaccin (MonoMen) in peuters. Veiligheid en immunogeniciteit zijn vergeleken voor twee vaccintypen die verschillen in adjuvant (aluminiumfosfaat of aluminiumhydroxide). MonoMen is toegediend in een 3- of 4-doses schema met vaccinaties op 0, 2 en 8 dan wel op 0, 1, 2 en 8 maanden.
In het totaal zijn 134 kinderen geïncludeerd in de studie. Tijdens de observatie periode traden geen ernstige bijwerkingen op, maar werden slechts milde lokale en systemische bijwerkingen gerapporteerd. Geen van de kinderen vertoonde bactericide activiteit tegen de PorA negatieve mutante stam H1.5, wat wijst op PorA specificiteit van de antistofrespons. Over het algemeen is de SBA respons het hoogste in de $AlPO_4$ groepen, zodat adsorptie aan $AlPO_4$ wordt geprefereerd boven $AL(OH)_3$. Na de primaire series zijn de titers iets hoger in kinderen die twee in plaats van drie vaccinaties ontvingen, wat mogelijk het gevolg is van langere intervallen tussen de primaire vaccinaties in het 2+1-schema. Na de boostervaccinatie werden significant hogere GMT's gemeten in kinderen die volgens het 3+1-schema zijn gevaccineerd. Hoewel het 3+1-schema beter lijkt wat betreft de hoogte van de GMT's, worden tussen de twee schema's slechts weinig verschillen gevonden in percentages imuunresponders. Zowel deze studie als de studie naar het booster effect van MonoMen in kinderen geprimed met hexavalent MenB vaccin[24] tonen aan dat MonoMen een veilig en immunogeen vaccin is.

Abstract English

This report gives the results of a randomised phase-II clinical study into the safety and immunogenicity of a monovalent MenB OMV vaccine expressing P1.7^{h},4 PorA (MonoMen) in toddlers. Safety and immunogenicity are compared for two types of vaccine that are differently adjuvated (either aluminium phosphate or aluminium hydroxide). MonoMen is administred a 3- or 4-dose schedule with vaccinations at 0, 2 and 8 or 0, 1, 2 and 8 months. A total of 134 children were included in the study.
No serious adverse events occurred during the study. Only mild local and systemic reactions were reported during the observation period. None of the children showed bactericidal activity against the PorA negative mutant strain H1.5, illustrating PorA specificity of the antibody response. In general, the SBA response was highest in the $AlPO_4$ groups, which means that adsorption of the RIVM meningococcal vaccines to $AlPO_4$ seems preferable to $Al(OH)_3$.
After the primary series slightly higher titres were found in children who received two vaccinations instead of three, which is probably due to the longer intervals between the vaccinations in the 2+1-schedule. After the booster vaccination significantly higher GMT's were found in children vaccinated according to the 3+1-schedule. Even though the 3+1-schedule seems better with respect to GMT's, the percentages of immune responders showed only minor differences between the two schedules. Both this study and the study concerning the booster effect of MonoMen in children primed with a hexavalent MenB vaccine[24] showed that MonoMen is a safe and immunogenic vaccine.

Preface

Participating organisations and investigators

1. ROTTERDAM
- Sophia Kinderziekenhuis / Academisch Ziekenhuis Rotterdam

2. BILTHOVEN
- LVO, Laboratory for Clinical Vaccine Research

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Abbreviations

$AlPO_4$	aluminium phosphate
°C	degrees centigrade
95%CI	95% Confidence Interval
CRF	Case Report Form
ELISA	Enzyme Linked Immunosorbent Assay
GMT	Geometric Mean Titre
HB-VAX® DNA	Hepatitis B vaccine
Hib	Haemophilus influenzae type b
HepB	Hepatitis B
ITT	Intention-To-Treat (analyses)
LPS	lipopolysaccharide
LVO	Laboratory for Clinical Vaccine Research *(Laboratorium voor Veldonderzoek vaccins)*
LVO-BI	LVO Bio- and Immunochemistry section *(LVO afdeling bio- en immunochemie)*
LVO-KO	LVO Clinical Research section *(LVO afdeling klinisch onderzoek)*
MenB	Meningococcal B
MonoMen	monovalent meningococcal vaccine expressing $P1.7^h$,4 PorA
OMP	Outer Membrane Protein (of *N. meningitidis*)
OMV	Outer Membrane Vesicle (of *N. meningitidis*)
PEA	Immunisation Administration *(Provinciale Entadministratie)*
PorA	class 1 OMP porin protein
PP	Per Protocol (analyses)
RC	Resort Centre of the School Health Service *(Resort Centrum Schoolartsendienst)*
RIVM	National Institute of Public Health and the Environment *(Rijksinstituut voor Volksgezondheid en Milieu*)
RVP	National Childhood Immunisation Programme *(Rijksvaccinatieprogramma)*
SBA	serum bactericidal activity assay
SIS	Serum Information System
SKZ	Sophia Kinderziekenhuis /Academisch Ziekenhuis Rotterdam
VR	variable region of class 1 OMP
UTN	Unique Trial Number

Contents

Samenvatting

Achtergrond
Bacteriële meningitis wordt in Nederland voornamelijk veroorzaakt door *Neisseria meningitidis* (meningococ). In West Europa is de meningococcen B serogroep verantwoordelijk voor 70-75% van alle gevallen. In het RIVM is een vesicle vaccin ontwikkeld dat zes verschillende meningococcen buitenmembraan eiwitten bevat. Klinische studies met dit vaccin hebben aangetoond dat de aard en ernst van de bijwerkingen na vaccinatie acceptabel zijn en dat het vaccin immunogeen is in zuigelingen, kleuters en schoolkinderen. De antistofrespons tegen P1.4 was lager dan de respons tegen de andere in het vaccin aanwezige PorA's. De P1.4 stam is echter het meest prevalente subtype in de patiënten isolaten in Nederland, andere West Europese landen en Nieuw Zeeland. Daarom is in het RIVM een monovalent P1.7^{h},4 OMV vaccin (MonoMen) ontwikkeld.

Methode
In Rotterdam is een gerandomiseerde fase II studie uitgevoerd met als doel het onderzoeken van de veiligheid en immunogeniciteit van MonoMen in 2-3 jarige peuters. Daarnaast werden twee verschillende adjuvantia (aluminium-fosfaat en aluminium-hydroxide) en twee vaccinatieschema's (2+1 vs 3+1, resp. 0-2-8 vs 0-1-2-8 months) vergeleken. Lokale en algemene bijwerkingen werden gedurende één week na elke vaccinatie geregistreerd. Bloedmonsters werden vlak voor elke vaccinatie afgenomen. Bovendien werd 4-6 weken na zowel de primaire serie als booster vaccinatie een bloedmonster afgenomen. Voor elk monster werd de serum bactericide antistof (SBA) respons tegen het serosubtype klasse 1 protein P1.7^{h},4 gemeten.

Resultaten
In het totaal hebben 134 kinderen deelgenomen aan de studie. Tijdens de studie traden geen ernstige bijwerkingen op, maar werden alleen milde lokale en systemische bijwerkingen in een laage percentage van de kinderen gerapporteerd. Geen van de kinderen vertoonden bactericide activiteit tegen de PorA negatieve mutante stam H1.5, wat wijst op PorA specificiteit van de antistofrespons. Bij kinderen ingeënt met $AlPO_4$ geadjuveerd vaccin werd de hoogste SBA respons gemeten. In kinderen die twee in plaats van drie vaccinaties ontvingen waren titers na de primaire serie iets hoger. De GMT's na de boostervaccinatie waren significant hoger bij kinderen gevaccineerd volgens het 3+1-schema, terwijl er tussen de twee schema's weinig verschil was in de percentages kinderen die respondeerden.

Discussie
Aard, ernst en hoeveelheid van de bijwerkingen na vaccinatie zijn acceptabel, er zijn geen ernstige bijwerkingen opgetreden. Op grond van deze studie resultaten wordt adsorptie aan $AlPO_4$ geprefereerd boven $AL(OH)_3$. Het verschil tussen de twee vaccinatie schema's wat betreft de persistentie van de SBA respons moet op langere termijn bekeken worden. De resultaten van deze studie tonen aan dat MonoMen een veilig en immunogeen vaccin is.

Summary

Background
Bacterial meningitis is in the Netherlands predominantly caused by *Neisseria meningitidis* (meningococcus). Meningococcus B serogroup causes 70-75% of meningococcal disease in Western Europe. The RIVM has developed a vesicle vaccine that contains class 1 outer membrane proteins of six different meningococci. Clinical studies with this vaccine have shown that vaccine is well tolerated and immunogenic in infants, toddlers and school children. The anti-P1.4 SBA response was weaker than the response to other PorA's present in the vaccine. However, the P1.4 strains are the most prevalent subtypes in case isolates in the Netherlands, other Western European countries and New Zealand. Therefore, the RIVM has developed a monovalent P1.7^{h},4 OMV vaccin (MonoMen).

Methods
A controlled, randomised phase-II study investigating safety and immunogenicity of MonoMen was performed in 2-3 years old toddlers in Rotterdam. Moreover two types of the vaccine that are differently adjuvated (with either aluminium-phosphate or aluminium-hydroxide) and also two different vaccination schedules were compared. Local and systemic adverse reactions were assessed during the week after vaccination. Blood for antibody assays was taken just before each vaccination and 4-6 weeks after the primary series as well as after the booster vaccination. For each sample the serum bactericidal antibody (SBA) response was assessed against P1.7^{h},4.

Results
A total of 134 children were included in the study. No serious adverse events were reported during the study, only mild local and general adverse reactions were reported. None of the children showed bactericidal activity against the PorA negative mutant strain H1.5, indicating PorA specificy of the antibody response. The SBA response was highest in the $AlPO_4$ groups. After the primary series slightly higher titres were found in children who received two vaccinations instead of three. After the booster vaccination significantly higher titres were found in children vaccinated according to the 3+1-schedule. However, the percentages immune responders showed only minor differences between the two schedules.

Discussion
The frequency and nature of adverse reactions after vaccination are acceptable. No serious adverse events occurred. Based on these study results adsorption of the RIVM meningococcal vaccines to $AlPO_4$ seems preferable to $Al(OH)_3$. The differences between the two schedules with respect to the persistence of the SBA response should be assessed at a longer term. This study showed that MonoMen is a safe and immunogenic vaccine.

1. Introduction

Neisseria meningitidis (meningococcus) is the major causative microorganism of bacterial meningitis in the Netherlands[1] and in many other countries. Meningococci are heterogeneous with respect to the expression of surface antigens. They can be divided into twelve serogroups on the basis of variation in polysaccharides on the bacterial capsula. Second classification (serotyping) is based on differences in the class 2/3 outer membrane proteins (OMP, porin B), while serosubtyping is based on variations of class 1 OMPs (porin A or PorA). Since class 1 OMPs have two separate variables regions (VR1 and VR2), two separate serosubtyping epitopes can be recognised on one PorA protein, resulting in designations as P1.5,2 and P1.7,16[2,3,4].

Effective polysaccharide vaccines against the serogroups A and C are available, but serogroup B polysaccharide vaccines are poorly immunogenic in humans. Moreover, the use of this vaccine has been discouraged because of the presence of closely related and probably cross-reacting antigens in the human brain tissue[5,6,7]. This creates an obstacle for the development of a safe polysaccharide vaccine against group B meningococci, as such a vaccine has the potential to induce autoimmune phenomena. Unfortunately, group B meningococci are the most prevalent in NorthWestern European countries: in the Netherlands 75-80% of meningitis cases are caused by group B meningococci[1].
Hence, for successful vaccination against group B meningococci other antigens than polysaccharides are needed to induce immunity. PorA is considered to be one of the most relevant protein antigens for the induction of a serum bactericidal antibody (SBA) response[8,9]. Vaccines based on PorA (but including also other OMPs) have been proven to be protective in older children or adolescents. However, efficacy in younger children was still poor[5,10,11,12].

For a broad coverage against a variety of meningococcal serosubtypes a multivalent vaccine is required. Therefore, a genetically engineered vaccine containing class 1 outer membrane proteins of six meningococcal B subtypes has been developed in the RIVM [8,9,13]. These six subtypes (P1.7,16, P1.19,15, P1.5,2, P1.5^{c},10, P1.12,13 & P1.7^{h},4) currently represent 75-80% of case isolates of serogroup B in the Netherlands. Other OMPs such as class 2/3 and 4 protein, as well as the B-capsular polysaccharide are not expressed in the vaccine due to gene deletions. The expression of class 5 protein is low. Side effects observed after vaccination were infrequent and mild[14,15]. In infants, the hexavalent vaccine was shown to be immunogenic, although four doses of vaccine were required to induce a significant SBA response. There were differences in the magnitudes of SBA responses on the different PorA's[14]. Similar results were found for toddlers and school children[15].

The anti-P1.4 SBA response induced by the RIVM hexavalent vaccine was weaker as compared to the response to other PorA's present in the vaccine. In the Netherlands as well as in other Western European countries and New Zealand, P1.4 strains are the most prevalent ones among the meningococcal subtypes in patient isolates. For this reason a monovalent vaccine was developed, using a production strain expressing P1.7^{h},4 PorA (designated F91). Production methods were further improved compared to the production of the hexavalent vaccine[13]. In addition, another adsorbent aluminum-hydroxide ($Al(OH)_3$) was used, to investigate whether the vaccine could be made more immunogenic. This adsorbent is used in many childhood vaccines currently available.

The present study addresses the reactogenicity and immunogenicity of this $Al(OH)_3$-adsorbed monovalent vaccine in young children as compared to that of the same vaccine adsorbed to aluminum-phosphate ($AlPO_4$)[16]. Another objective of this study was to compare two different vaccination schedules.

2. Materials and methods

The study protocol "Monovalent RIVM meningococcal OMP vesicle F91 vaccines in toddlers (version 2.1)"[16] was approved by the Institutional Ethics Review Board of the Sophia Children's Hospital and the University hospital in Rotterdam.

2.1 Vaccine

The products used in this study are white opaque suspensions, filled in 3 ml glass vials, closed with rubber stopper and sealed with an aluminium capsule. The filling volume is 0.7 ml. The study vaccines contain per dose of 0.5 ml:

- 17 µg meningococcal OM vesicle protein, corresponding with 15 µg of specific $P1.7^{h}$,4 class 1 protein (PorA) from seed strain F91
- 11 µmol Al-salt (1.34 mg $AlPO_4$ or 0.86 mg $Al(OH)_3$)
- 50 µg (0,01% w/v) thiomersal
- 50 mg (10 % w/v) sucrose

in 10 mM Tris/HCl buffer, pH 7.4

Both vaccines have identical appearance, and could be distinguished only by differently coloured caps and different lot numbers. Their identity were not disclosed to the clinical investigators and parents, allowing the study to be performed double blinded with respect to the adjuvantia. For emergencies, the Principal Investigator had a procedure for unblinding. The manufacturer distributed the vials of the trial vaccines to the Immunisation Administration (PEA) without breaking the cold chain and all vaccines were stored at 2-8 °C throughout the study. The study personnel transported the vaccines from the PEA to the study site on the day of administration, using insulated containers. At the end of the study each vaccine that has not been used was returned to the Clinical Trial Monitor.

2.2 Participants

Parents of 2-3 years old children (born in 1995-96) in Rotterdam were invited to participate in the study through a circular explaining the purpose of the study and the expected contribution of the participant. At their positive initial response an appointment was made for the first study visit. At this visit (30 to 7 days before the first vaccination) the parents or legal representatives were informed about the study proposal, schedules and (dis)advantages. After a written informed consent for participation was signed and a medical intake investigation (history and physical examination) was done, the exclusion criteria were checked. Participants were excluded because of criteria specified in the study protocol[16]. These exclusion criteria were reassessed before each (re)vaccination. In case of doubt, volunteers were excluded from participation.

2.3 Study design and procedures

After the intake as described above, the participants were given an Unique Trial Number (UTN). Participants were randomised according to a list of random numbers, assigning them by UTN to one of the four study groups. These groups were based on the two different adsorbents as well as two different vaccination schedules. Children vaccinated by the 2+1-schedule received two vaccinations with 6-10 weeks interval, followed by a booster vaccination 6 months (20-40 weeks) after the second vaccination. Children vaccinated according to the 3+1-schedule received three vaccinations with 3-6 weeks interval, followed

by a booster vaccination 6 months (20-40 weeks) after the third. Blood samples were taken before each vaccination, with a maximum interval of 14 days. Post vaccination samples were taken 4-6 weeks after the primary series and after the booster vaccination. The evaluation of adverse reactions is described in §2.3.4.

2.3.1 Study design by immunisation group

Table 1 Study design by immunisation group

Time (months)		<0	0	1	2	3	8	9
Schedule:								
2+1	***Activity***		MM1		MM2		MM3	
		intake	B_{pre}		B_{pre}	B_{post}	B_{pre}	B_{post}
			O_1		O_1		O_3	
					E_1	E_2		E_3
3+1	***Activity***		MM1	MM2	MM3		MM4	
		intake	B_{pre}	B_{pre}	B_{pre}	B_{post}	B_{pre}	B_{post}
			O_1	O_2	O_3		O_4	
				E_1	E_2	E_3		E_4

Legend:

2+1: children vaccinated according to a 2+1-schedule

3+1: children vaccinated according to a 3+1-schedule

MM: MonoMen, monovalent MenB vesicle vaccine adjuvated with $AlPO_4$ or with $Al(OH)_3$

B_{pre}: blood sample 0-14 days before vaccination

B_{post}: blood sample 4-6 weeks after vaccination

O_{1-4}: observation of adverse reactions by trained observer 18-30 hours after vaccination 1, 2, 3 and 4

E_{1-4}: evaluation of adverse reactions observed by parents in the week after vaccination 1, 2, 3 and 4

2.3.2 Injection

The MenB vesicle vaccine was administered by intramuscular injection in the upper arm (deltoid or triceps muscle) depending on physician or research nurse preference. The date, site, time of injection and vaccine lot number were recorded in the CRF.

2.3.3 Blood sampling and storage

Blood was sampled by venipuncture after application of the local anaesthetic lidocain/prilocain [EMLA™] by physicians or trained research nurses at the participant's home. Blood samples were sent to the RIVM in Bilthoven by regular mail. Upon arrival serum was separated and stored at -20°C at LVO-BI. Aliquots for blinded specific antibody measurements were distributed with a Multiprobe (Canberra Packard, SOP 12N-APP-34). To secure blinded measurements, tubes with serum specimens were marked with a code, which did not reveal the timing of the blood sample or the study group.

2.3.4 Evaluation of adverse reactions

Parents were asked to record specific symptoms and other possible adverse reactions in a 7-days diary. A trained observer phoned the parents 18-30 hours after administration of the vaccine to ask in a structural interview for the occurrence of specific systemic (fever

[temperature ≥ 38.5 ^{o}C], headache, drowsiness, unusual crying, less appetite, nausea, joint complaints, cutaneous symptoms, use of medication, visit doctor or hospital, and illness in family) and local symptoms (redness, swelling, pain, itching and reduced use of the arm). Serious adverse events were to be communicated immediately to the RIVM by the investigator. The diary was used to complete the CRF at the next study visit.

2.4 Antibody assays

2.4.1 Serum Bactericidal Antibody (SBA) Assay

Bactericidal activity of antibodies against an isogenic variant of strain H44/76 was determined as described by Peeters and Rouppe van der Voort[17,18].
In short, 2-fold dilutions of heat inactivated sera (30 min at 56^{o}C), 2.5-5.0 x 10^2 c.f.u. bacteria and complement (final concentration 10% (v/v)) were incubated in a microtitre plate for 60 minutes at 37 ^{o}C in 5% CO_2. Subsequently 7µl of this suspension was spotted onto GC agar plates. An isogenic strain expressing the serosubtype class 1 protein P1.7^{h},4 was used to determine the bactericidal activity of these serum antibodies. As control for ProA specificity the PorA negative mutant strain H1.5 was used. After 18-20h incubation at 37^{o}C in 5% CO_2, the colonies from time zero were counted. The average number of c.f.u. at time zero was set at 100%. The serum bactericidal titre was reported as the reciprocal of the lowest serum dilution yielding ≥90% killing.
Antibodies detected in the SBA Assay show class 1 OMP (bactericidal) specificity that is assumed to correlate with protective immunity. In earlier studies, SBA titres of 1:4 or more were presumed to be associated with protection against clinical disease[19,20,21].

2.4.2 OMV-ELISA

Since a monovalent vaccine vesicle (lot: 98MEN111 code 6.1) was used as the ELISA-coat, antibodies detected in the ELISA show specificity against OMP from the F91 monovalent meningococcal P1.7^{h},4 strain, which constitutes the monovalent vaccine[17].
In short, after overnight coating of the microtitre plates at room temperature, threefold serial dilutions of serum samples were incubated for 2 hours at 37^{o}C. After incubation with peroxidase conjugated goat anti-human IgG-F_c for 2 hours at 37^{o}C, the TMB-substrate colouring reaction was subsequently read at 450nm. IgG antibody titres are expressed as the dilution that gives an extinction of 50% from the sum of OD_{max} and OD_{min}, where OD_{max} is the maximum OD_{450} of a known high positive serum and ODmin is a correction for the background signal and OD_{min} is the correction for the background.

2.5 Data handling and validation

CRF data have been entered into a computer by a company, specialised in data entry (Wegener Direct Marketing Group Data Services, the Netherlands). Antibody titres were obtained later, but are an integral part of the final CRF. These antibody data are entered into the Serological Information System (SIS, SOP 12C-ALG-40 & 12C-ALG-41) by LVO-BI, and handed over to LVO-KO as an Excel worksheet. Clinical and serological data have been imported in a LVO database [MS Access 2.0[22]] for storage and analysis. For further statistical analysis the data have been exported to SPSS [version 9.0 for Windows[23]]. After each step, checks were made to ensure that the correct data were used for final reporting.
During all clinical stages of the study, monitoring visits were made to each study facility (PEA, SKZ). The monitor checked all of the informed consents and CRF's.

2.6 Data editing and protocol adherence

After entering all data in a computer database, a final assessment of protocol adherence was made. Based on the protocol adherence, data analyses were divided in Per Protocol (PP-) analyses and Intention-to-treat (ITT-) analyses. Because the outcome of both analyses were almost identical, results of the PP-analyses are not shown in this report.
All serological data were excluded from the PP- as well as the ITT-analyses for children with 'unaccountable bactericidal activity'.
Children were excluded from the serological PP-analyses from the moment the protocol violation occurred in situations listed below:

- interval between pre vaccination blood sample and vaccination differed from the interval specified in the protocol (0-14 days before vaccination),
- interval between post vaccination blood sample and vaccination differed from the specified interval (4-6 weeks after vaccination),
- interval between vaccinations differed from the intervals specified:
    - 6-10 weeks between vaccinations in primary series for the 2+1-schedule,
    - 3-6 weeks between vaccinations in primary series for the 3+1-schedule,
    - 20-40 weeks between primary series and the booster vaccination.

Children were excluded from the adverse reactions PP-analyses with respect to the vaccination for which the protocol evaluation had occurred if the interval between vaccination and observation of adverse reactions differed from the interval specified in the protocol (18-30 hours after vaccination).

2.7 Statistical analyses

For the analyses the participants were divided into groups based on vaccine adjuvant as well as vaccination schedule. Numbers and percentages of systemic and local adverse events were assessed for each observation and each vaccination per adjuvant. Chi square or Fisher's exact tests were used to compare the groups with respect to adverse reactions after vaccination.
All serological results are described by individual line listings. Because SBA titres $\geq$ 1:4 are presumed to be associated with protection against clinical disease, percentages of participants with these titres were calculated. ELISA and SBA results were transformed to logarithmic values to calculate GMT's and 95% CI's. Mann-Whitney-U test was used to compare the two adjuvantia as well as the two vaccination schedules with respect to GMT. For the SBA assay an immune response was defined as $\geq$ 4-fold rise in antibody titre. Percentages of immune responders were assessed after the primary series as well as after the booster vaccination, and compared between the study groups (Chi square test of Fisher's exact test).

3. Results

3.1 Participants

A total of 134 participants, born in 1995 or 1996, were enrolled in the study. After informed consent was obtained from all parents, the children were randomised into one of the four study groups (Table 2 - Appendix 2). The population included 76 female and 58 male participants (ratio: 0.76). Table 3 shows the number of participants who dropped-out during the study, and the moment of drop-out. There was no obvious difference in the numbers of drop-outs between the different study groups. Two children were lost to follow-up because of holidays, for the other children the reasons were unknown. The numbers of participants who were partially excluded for the PP-analyses with respect to the adverse reactions analyses are shown in Table 4, and with respect to the serology in Table 5. The second blood sample (just before the second vaccination) of the participant with UTN 170 is excluded for the ITT -as well as for the PP-analyses, because this blood sample showed 'unaccountable bactericidal activity', probably because of the use of antibiotics.

3.2 Adverse reactions

None of the children experienced any adverse reaction within 15 minutes after vaccinations. Furthermore, no serious adverse events were reported in the week after the vaccinations. The frequencies of adverse reactions in children vaccinated according to the 2+1-schedule were compared with those in participants vaccinated according to the 3+1-schedule (data not shown). Because no relevant differences were found, data of these two groups were pooled. Table 6 (Appendix 3) shows the frequencies of systemic adverse reactions for both adjuvant groups monitored for 7 days after the first vaccination according to the ITT-analyses. The results for vaccinations 2, 3 and 4 are shown in the Tables 7 to 9. In general, only few systemic adverse reactions were reported. Drowsiness is the most frequently reported systemic reaction after each vaccination followed by less appetite, especially in the $AlPO_4$-group (16% or less). After vaccination 1 and 2, most systemic reactions were present during day 2-3. Remarkably, only few adverse reactions were reported after the last two vaccinations. The occurrence of systemic adverse reactions was compared between the two adjuvant groups using Chi Square or Fisher's exact test. No statistically significant differences were found. After the first vaccination three children used analgesics because of symptoms (drowsiness and local reactions) probably related to vaccination. After the second vaccination this was reported for two children, and after the third and fourth vaccination for none of the participants. During the study, 12 children used medication (including analgesics and antibiotics) because of upper airway infections, pneumonia, intestinal complaints and inflammation of the ear and throat.

The frequencies of local reactions are shown in Table 10 to 13 (Appendix 3). In most participants with local reactions, complaints lasted for three days. Little local reactions were seen after vaccination 3 and 4, with the exception of the most common reaction mild pain. Pain was most frequently reported in the $AlPO_4$-group (upto 50%). One girl (UTN=277) had serious pain during day 2 and 3 after the first vaccination. She also reported reduced use of the injected arm, but showed no other local symptoms. Chi Square or Fisher's exact test was used to compare the dichotomized local reactions between the two adjuvantia. Mild pain was statistically significant more common in the $AlPO_4$-group at day 1 after vaccination 1, and day 2-3 after vaccination 2 and 3 ($p<0.05$). Swelling was statistically significant more common in the $Al(OH)_3$-group at day 2-3 after vaccination 1 ($p<0.05$).

These data are visualized in a diagram for which reactions from both adjuvantia as well as both schedules were pooled. Besides, data with respect to the local reactions were dichotomized. Because local reactions were most frequently seen after the first two vaccinations only these data are shown in Figure 1-4.

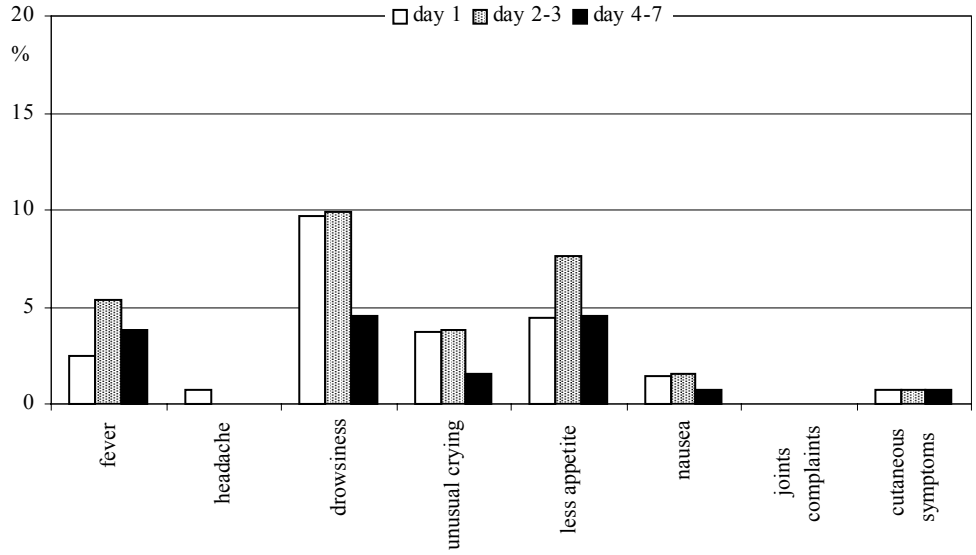


Figure 1. Systemic adverse reactions after the first vaccination

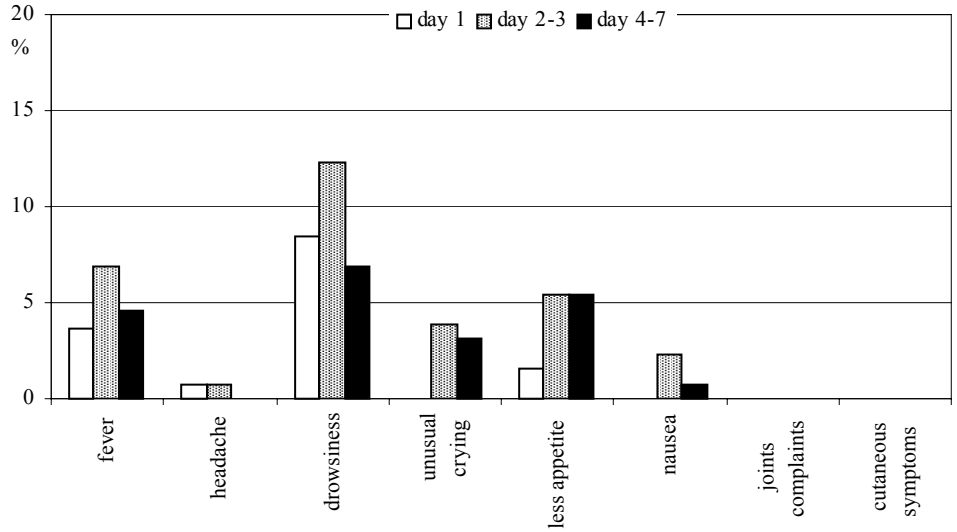


Figure 2. Systemic adverse reactions after the second vaccination

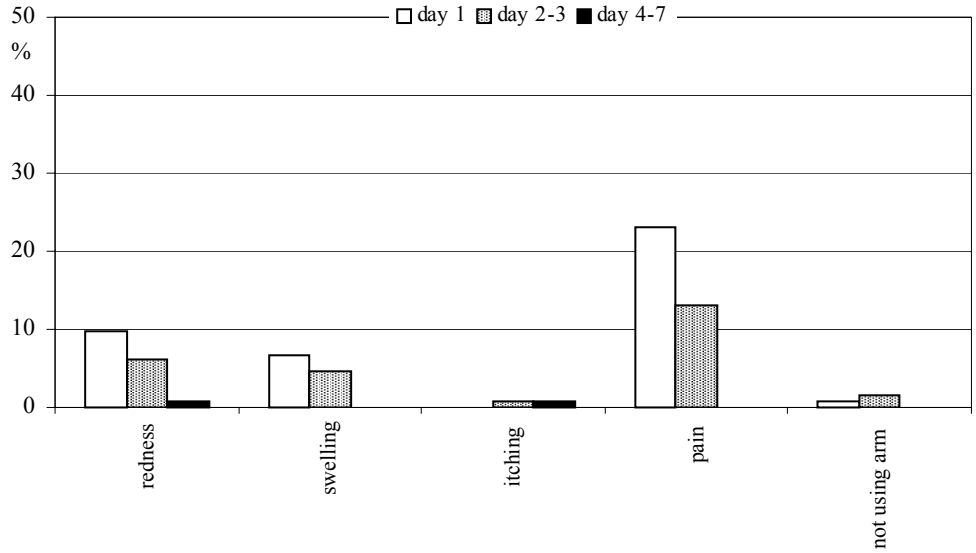


Figure 3. Local adverse reactions after the first vaccination

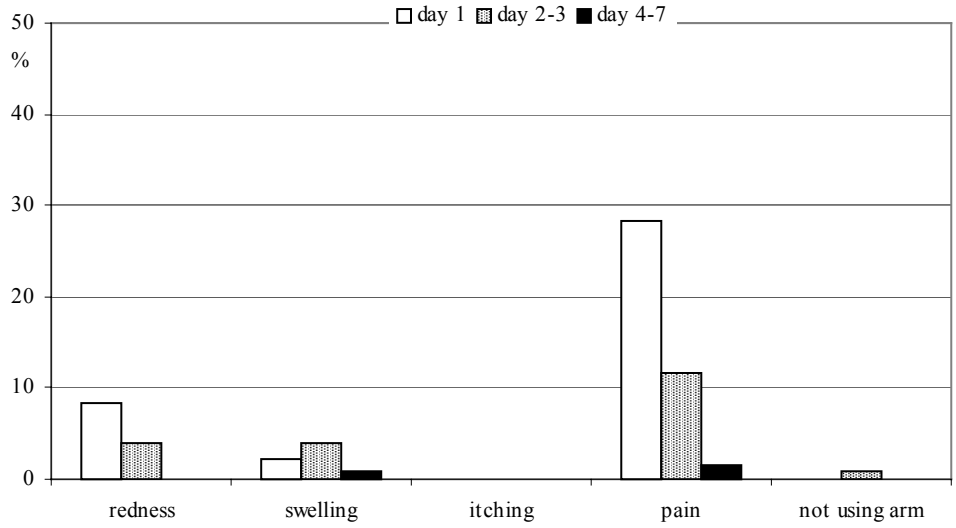


Figure 4. Local adverse reactions after the second vaccination

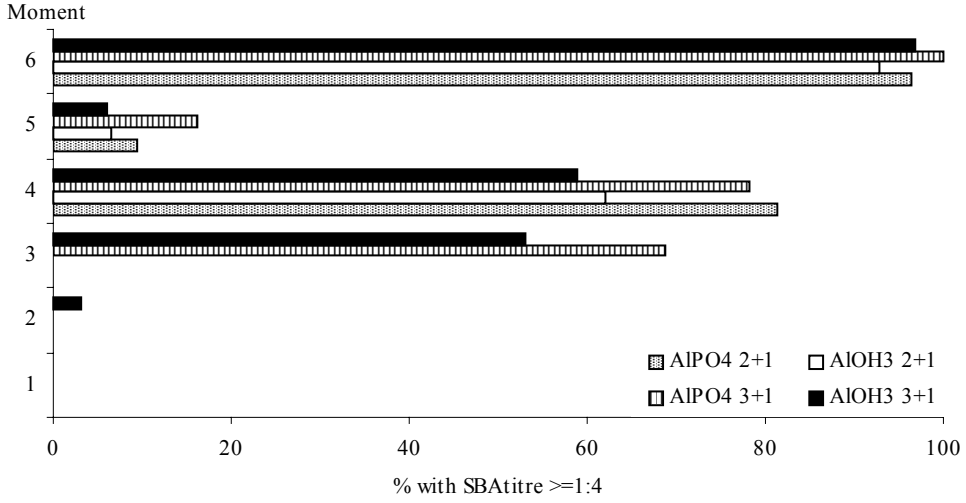
3.3 Antibody response

The serological results for ELISA as well as SBA are described by individual line listings (Appendix 5). None of the children showed bactericidal activity against the PorA negative mutant strain H1.5. The few discrepancies in the totals of serological tests are due to the missing of some blood samples, because of an unsuccessful venipuncture or because children were lost to follow-up. For some participants, the volume of blood samples obtained was too small to permit completion of the serological tests.

3.3.1 SBA Assay

Percentages of participants with reciprocal SBA titres ≥ 1:4 against P1.7^{h},4 are shown in Table 14. These data are visualized in Figure 5. Before the first vaccination none of the participants had a titre ≥ 1:4. In general, the percentages of children with a titre ≥ 1:4 are

highest in the $AlPO_4$-groups. This difference between the adjuvantia is most pronounced after the primary series. Vaccination according to the 2+1-schedule resulted in somewhat higher percentages with SBA titres ≥ 1:4 after the primary series as compared to vaccination according to the 3+1-schedule. However after the booster vaccination, these percentages were slightly higher in children vaccinated according to the 3+1-schedule.



LEGEND:

moment	2+1 schedule	3+1 schedule
1	pré primary series	pré primary series
2	during primary series	during primary series
3	not assessed	extra during primary series
4	post primary series	post primary series
5	pré booster vaccination	pré booster vaccination
6	post booster vaccination	post booster vaccination

Figure 5. Percentages participants with SBA titre >=1:4

SBA GMT's and 95% CI's against the meningococcal strain P1.7^{h},4 were calculated per adjuvant and per vaccination schedule (Table 15+16). Figure 6 shows the development of SBA titres during the study. In general, the GMT's in the $AlPO_4$-groups are higher as compared to the $Al(OH)_3$-groups. For the 2+1-schedule, these differences between the two adjuvantia are not statistically significant (Mann-Whitney U test). For the 3+1-schedule on the other hand, the GMT is only significantly higher in the $AlPO_4$-group after two vaccinations ($p<0.01$; Mann-Whitney U test). In the blood sample taken one month after the primary series, slightly higher GMT's were found in participants vaccinated according to the 2+1 schedules as compared to the 3+1-schedules, but these differences are not statistically significant. However, after the booster vaccination higher GMT's were found for the 3+1-schedule. This difference was statistically significant for the the $AlPO_4$-group ($p<0.01$; Mann-Whitney U test), but not for the $Al(OH)_3$-group.

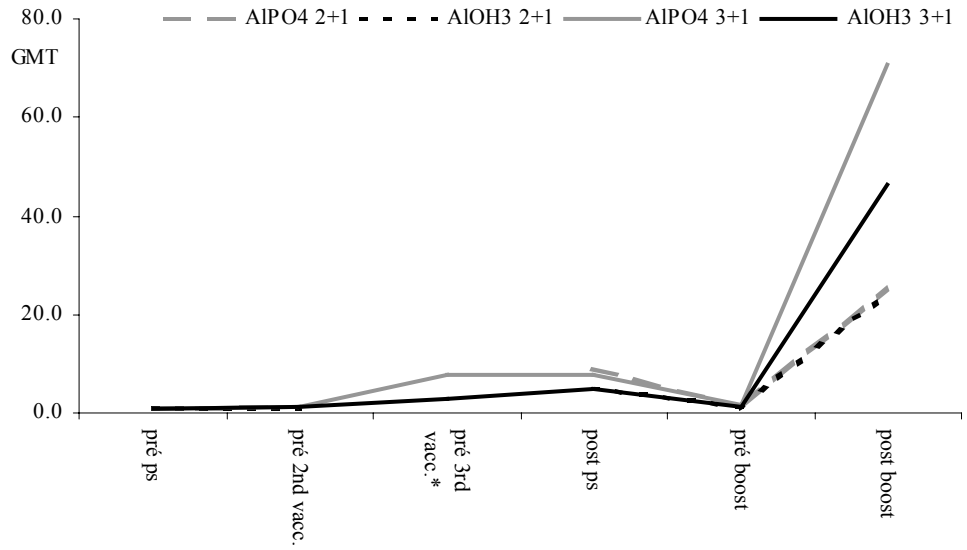
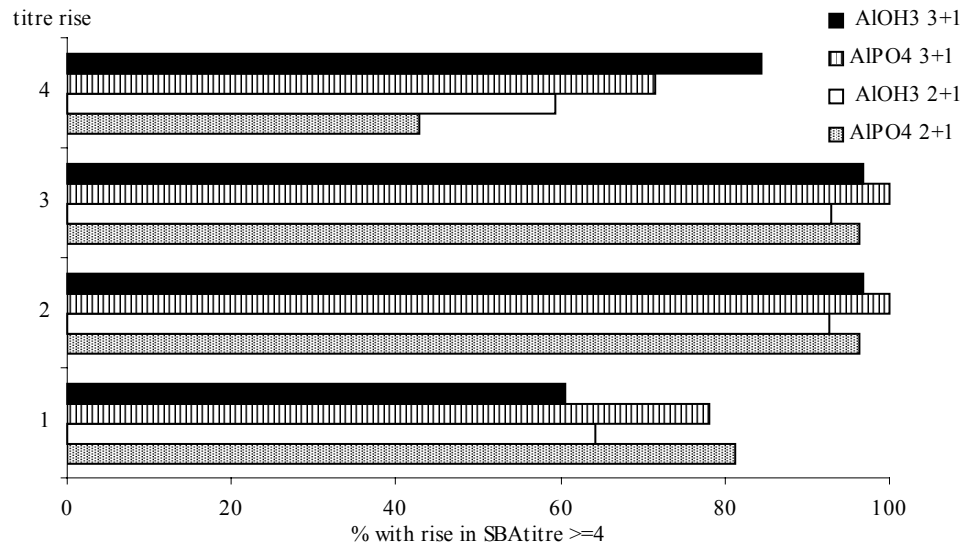


Figure 6. Development of SBA titres

Percentages immune responders, i.e. children showing a fourfold rise in SBA titre, are shown in Table 17 and Figure 7. After the primary series, the highest percentages were found for the 2+1-schedules, especially in the $AlPO_4$-group (81%). After the booster vaccination, an immune response was seen for more than 90% of the children, and even for all children in the $AlPO_4$-group vaccinated according to a 3+1-schedule. The effect of the booster vaccination with respect to the immune response was higher in the 3+1-schedule (71-84%) as compared to the 2+1-schedule (43-59%). Differences between the adjuvantia as well as between the vaccination schedules with respect to the percentages of immune responders were not statistically significant (X^2- or Fisher's exact test).



LEGEND:

titre rise	
1	post primary series against pré primary series
2	post booster against pré primary series
3	post booster against pré booster
4	post booster against post primary series

Figure 7. Percentages participants with rise in SBA titre ≥ 4

3.3.2 ELISA

Table 18 and 19 show ELISA GMT's and 95% CI's for both adjuvantia as well as for both vaccination schedules. Figure 8 shows the development of ELISA antibodies during the study. ELISA titers were compared between both adjuvant groups and both vaccination schedules using Mann-Whitney U test. In general, the anti-P1.7^{h},4 ELISA titres were higher in the $AlPO_4$ -group as compared to the $Al(OH)_3$-group for both schedules. During and after the primary series (i.e. before vaccination 2nd vaccination in the 2+1-schedule of before the 3rd vaccination in the 3+1-schedule, and also after resp. 2nd and 3rd vaccination) these differences were statistically significant. Though after the booster vaccination it was only significant for participants vaccinated according to the 2+1-schedule. Vaccination according to the 3+1-schedule resulted in higher titres as compared to the 2+1-schedule, this was only statistically significant during the primary series.

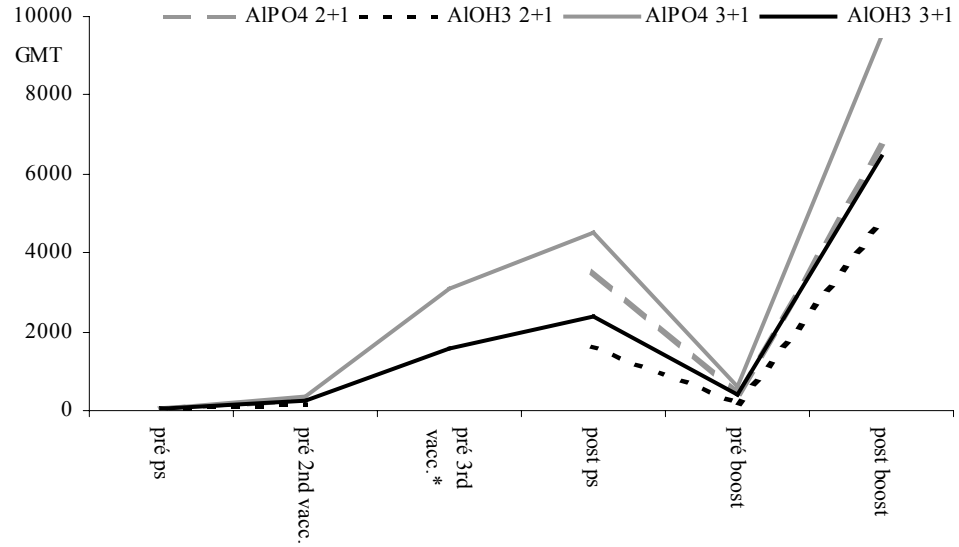


Figure 8. Development of ELISA antibodies

4. Discussion

4.1 Adverse reactions

This study showed that the monovalent OMP vesicle vaccine was well tolerated. No serious adverse events were reported during the observation period. As expected, no differences were found in the observed frequencies of adverse reactions in children vaccinated according to the 3+1-schedule as compared to the 2+1-schedule. Moreover, no statistically significant differences were found when comparing frequencies of systemic reactions between the two adjuvant groups. Fever, one of the most common systemic reactions after vaccination in children, was reported in 3-8% of the participants during day 2-3. Other frequently reported systemic reactions like drowsiness (upto 16%) and less appetite (upto 8%), are less vaccine-specific as compared to fever. Remarkably few reactions were reported after vaccination 3 and 4. There seems to be an inverse relationship between the frequency of systemic reactions and the number of received vaccinations. As mentioned before, 12 children used medication because of none vaccine related symptoms. Adverse reactions reported by these children might be caused by infections instead of the vaccine. Of the local reactions, which generally lasted for 3 days, pain was the most reported (upto 50%), especially in the $AlPO_4$ group. However, it must be stated that this only concerned mild pain. Of the children reporting pain in any of the observations, 16% also reported redness whereas 11% reported swelling.
A study in 5-6 and 10-11 years old children, primed with a hexavalent meningococcal OMP vesicle vaccine, showed that a booster vaccination with MonoMen was also well tolerated[24]. In that study, after MonoMen vaccination frequencies of some systemic reactions were even somewhat lower as compared to the current study. In the mentioned study most adverse reactions were reported during day 2-3, with the highest frequencies for drowsiness, headache and less appetite (resp. 8%, 7% and 6%)[24]. Whereas headache was a very uncommon reaction in the present study with MonoMen in toddlers. Previously, the hexavalent RIVM vesicle vaccine was shown to be safe in studies in Rotterdam (toddlers and school children) and Gloucestershire UK (infants)[14,15], the rate and severity of the observed adverse reactions were acceptable and no serious adverse reactions occurred. These results are comparable to those of the studies with MonoMen.

4.2 Antibody response

Antibodies detected in the SBA assay show class 1 OMP (bactericidal) specificity that is assumed to correlate with specific protective immunity. None of the children showed bactericidal activity against the PorA negative mutant strain H1.5, indicating PorA specificity of the antibody response.
In general, the SBA response was highest in the $AlPO_4$ groups, which means that adsorption of the RIVM meningococcal vaccines to aluminum phosphate seems preferable as compared to adsorbtion to aluminum hydoxide.
After the primary series slightly higher titres were found in children who received two vaccinations instead of three. This is probably caused by the longer interval of two months during the primary series in the 2+1-schedule as compared to one month interval in the 3+1-schedule. Tappero et al. demonstrated that a three dose meningococcal B vaccination schedule of with two months interval was associated with a higher proportion of SBA responders than two a dose schedule[26].
After the booster vaccination with MonoMen in the present study significantly higher titres were found in toddlers vaccinated according to the 3+1-schedule. However, the percentages

immune responders or children with SBA titres ≥ 1:4 showed only minor differences: 93-96% for the 2+1-schedules against 97-100% for the 3+1-schedules. Perkins et al.[21] showed a short term benefit of a booster vaccination with serogroup B meningococcal vaccines, though the effect after 8 months was less pronounced. To asses the long term effect of an extra dose MonoMen during the primary series as in the 3+1-schedules in the present study, vaccinees should be followed for a longer period.

We compared the results of the present study with those of an earlier study in toddlers in Rotterdam vaccinated with a hexavalent meningococcal B vesicle vaccine according to a 2+1-schedule[15]. Although the total amount of specific P1.7^{h},4 class 1 protein is equal in both vaccines, the immediate immunogenicity of the monovalent vaccine is superior to that of the hexavalent one. After a complete vaccination series with the hexavalent vaccine about 38% of the participants showed an immune response, as opposed to about 95% after vaccination with MonoMen. Furthermore the GMT against P1.7^{h},4 after vaccination with MonoMen was approximately 10 times higher. The hexavalent vaccine contained the class 1 OMP of six meningococcal subtypes (P1.7,16 , P1.19,15 , P1.5,2 , P1.5^{c},10 , P1.12,13 & P1.7^{h},4) expressed on two trivalent vesicles[13]. In the Rotterdam study with the hexavalent vaccine[15] as well as in a study with the same vaccine in Gloucestershire[14] high SBA titres were found against one of the three PorA proteins of each vesicle, that is P1.5,2 and P1.5^{c},10. The anti-P1.7^{h},4 and P1.19,15 SBA responses were the weakest, these strains are situated each on a different vesicle. The same phenomenon was observed in baby cynomolgus monkeys[25]. Possibly, the trivalent expression of the PorA's together on one vesicle in the hexavalent vaccine did cause interference in immune stimulation, which did not occur in the monovalent vaccine. Another possible reason for the higher immunogenicity of MonoMen is the improvement of production methods as compared to the production of the hexavalent vaccine[13].

Some of the children vaccinated with hexavalent meningococcal vaccine in the mentioned Rotterdam study[15] were boostered with MonoMen 2.5 years later [24]. After this booster vaccination about 50% of the children showed an immune response against P1.7^{h},4. Even though the GMT's after this booster were higher as compared to those after vaccination with the hexavalent vaccine, they were still considerable lower than those after vaccination with MonoMen in the present study in toddlers. This indicates that vaccination with MonoMen gives a better immune response as compared to priming with the hexavalent vaccine followed by a booster with MonoMen. Tappero et al.[26] demonstrated that recipients of meningococcal B vaccines showed higher SBA titres against homologous vaccine type strains than against heterologous strains. The SBA responses against the homologous vaccine strain P1.7^{h},4 after three vaccinations (2+1-schedule) in the present study in toddlers are comparable with that reported by Tappero et al.[26]. In the last mentioned study 78-98% of the children responded with an immune response against homologous vaccine strains.

5. Conclusions and recommendations

The nature and frequency of the adverse reactions after vaccination with MonoMen are acceptable.

Based on the adequate response against P1.7^{h},4 after vaccination, MonoMen seems a highly immunogenic vaccine.

$AlPO_4$ is preferable as adjuvant as compared to $Al(OH)_3$

GMT's measured in children vaccinated according to the 3+1-schedule are higher as compared to those in children vaccinated according to the 2+1-schedule. To assess the long term effect of the extra dose during the primary series, vaccinees may be need to followed for a longer period.

MonoMen is preferable to use in MenB epidemics caused by P1.4 rather than the hexavalent MenB vaccine.

6. References

1. Netherlands Reference Laboratory for Bacterial Meningitis (AMC/RIVM). Bacterial meningitis in the Netherlands; annual report 1994. Amsterdam: University of Amsterdam, 1995.
2. Rümke HC. Onderzoek naar immunogeniteit en bijwerkingen van hexavalent meningococcen B vesicle vaccin bij kleuters en schoolkinderen. Protocol versie 2.1, 1995.
3. Scholten RJPM. General introduction. In: The increased incidence of meningococcal disease in the Netherlands 1980-1990; an attempt at an epidemiological explanation. 1993: 4-16.
4. Poolman JT, Ley PA van der, Tommassen JPM. Surface structures and secreted products of meningococci. In: Meningococcal disease. Ed. K. Cartwright. Publ.: John Wiley & Sons, 1995: 21-34.
5. Bjune G, Høiby EE, Grønnesby JK, Arnesen O, Fredriksen JHO, Haltstensen A, Holten E. Lindbak AK, Nokleby H, Rosenqvist E, Solberg LK, Closs O, Froholm LO, Lystad A, Bakketeig LS, Hareide B. Effect of outer membrane vesicle vaccine against group B meningococcal disease in Norway. Lancet 1991; 338: 1093-1096.
6. Wyle FA, Artenstein MS, Brandt BL, Tramont EC, Kasper DL, Altieri PL, Berman SL, Lowenthal JP. Immunologic response of man to group B meningococcal polysaccharide vaccines. J.Inf Dis 1972;126:514-522.
7. Finne JM, Leinonen M, Mäkelä PH. Antigenic similarities between brain components and bacteria causing meningitis. Implications for vaccine devolopment. Lancet 1983;ii:355-357.
8. Van der Ley P, Poolman JT. Construction of a multivalent meningococcal vaccine strain based on the class 1 outer membrane protein. Infection and Immunity 1992;60:3156-3161.
9. Poolman JT. Development of a group B meningococcal vaccine, interim report. RIVM rapport no 343602003, August 1996.
10. De Moraes JC, Perkins BA, Camargo MCC, Hidalgo NTR, Barbosa HA, Sacchi CT, Land Gral IM, Gattas VL, Vasconcelos HDG, Plikaytis BD, Wenger JD, Broome CV. Protective efficacy of a serogroup B meningococcal vaccine in Sao Paulo, Brasil. Lancet 1992;340:1074-78.
11. Milagres LG, Ramos SR, Sacchi CT, Melles CEA, Vieira VSD, Sato H, Brito GS, Moraes JC, Frasch CE. Immune response of Brazilian children to a Neisseria meningitidis serogroup B outer membrane protein vaccine: comparison with efficacy. Infection and Immunity 1994;62:4419-4424.
12. Boslego J, Garcia J, Cruz C, Zollinger W, Brandt B, Ruiz S, Martinez M, Arthur J, Underwood P, Silva W, Moran E, Hankins W, Gilly J, Mays J and the Chilean National Committee for Meningococcal Disease. Efficacy, safety, and immunogenicity of a meningococcal group B (15:P1.3) outer membrane protein vaccine in Iquique, Chile. Vaccine 1995;13: 821-829.
13. Claassen I, Meylis J, Van der Ley P, Peeters C, Brons H, Robert J, Borsboom D, Van der Ark A, Van Straaten I, Roholl P, Kuipers B, Poolman J. Production, characterization and control of a Neisseria meningitidis hexavalent class 1 outer membrane protein containing vesicle vaccine. Vaccine 1996;14:1001-1008.
14. Cartwright K, Morris R, Rümke H, Fox A, Borrow R, Begg N, Richmond P, Poolman J. Immunogenicity and reactogenicity in UK infants of a novel meningococcal vesicle

vaccine containing multiple class 1 (PorA) outer membrane proteins. Vaccine 1999; 20-21: 2612-2619.
15. Kleijn ED de, Groot R de, Labadie J, Lafeber AB, Dobbelsteen G van den, Alphen L van, Dijken H van, Kuipers B, Omme GW van, Wala M, Juttman R, Rümke HC. Immunogenicity and safety of a hexavalent meningococcal outer-membrane-vesicle vaccine in children of 2-3 and 7-8 years of age. Vaccine 2000; 18: 1456-1466.
16. Rümke HC. Protocol for clinical study: Monovalent RIVM meningococcal OMP vesicle F91 vaccines in toddlers (version 2.1). July 1998; Laboratory for Clinical Vaccine Research, RIVM.
17. Peeters, CCAM, Rümke HC, Sundermann LC, Rouppe van der Voort EM, Meulenbelt J, Schuller M, Kuipers AJ, van der Ley P, Poolman JT. Phase I clinical trial with a hexavalent PorA containing meningococcal outer membrane vesicle vaccine. Vaccine 1996; 14: 1008-1015.
18. Rouppe van der Voort EM, van der Ley P, van der Biezen J, George S, Tunnela O, van Dijken H, Kuipers B, and Poolman JT. Specificity of human bactericidal antibodies against PorA P1.7,16 induced with a hexavalent outer membrane vesicle vaccine. Infect Immun 1996; 64: 2745 - 2751.
19. Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus I. The role of humoral antibodies. J Exp Med 1969; 129: 1307-1326.
20. Frasch CE. Meningococcal vaccines: past, present and future. In: Meningococcal Disease. Ed. By K. Cartwright. Publ.: John Wiley & Sons, England 1995: 245-283.
21. Perkins BA, Jonsdottir K, Briem H, Griffiths E, Plikaytis BD, Høiby EA, Rosenqvist E, Holst J, Nøkleby H, Sotolongo F, Sierra G, Campa HC, Carlone GM, Williams D, Dykes J, Kapczynski D, Tikhomirov E, Wenger JD, Broome CV. Immunogenicity of two efficacious outer membrane protein-based serogroup B meningococcal vaccines among young adults in Iceland. J Infect Dis 1998; 177: 683-691.
22. Microsoft Access version 2.0. Microsoft Corporation; 1989-1994.
23. SPSS for Windows. Release 9.0 (Dec 18 1998). SPSS Inc.; 1989-1999.
24. Lafeber AB Limpt CJP van, Labadie J, Berbers GAM, Rümke HC. Study on the immunogenicity and safety of a booster dose Monovalent RIVM meningococcal OMP vesicle F91 vaccine in children, 2.5 years after vaccination with Hexavalent RIVM meningococcal OMP vesicle vaccine. Study 89 A. RIVM Rapport 2000.
25. Rouppe van der Voort EM, Schuller M, Holst J, De Vries P, Ley P van der, Dobbelsteen G van den, Poolman J. Immunogenicity studies with a genetically enigeered hexavalent PorA ans a wild-type meningococcal group B outer membrane vesicle vaccine in infant cynomolgus monkeys. Vaccine 2000; 18:1334-1343.
26. Tappero JW, Lagos R, Ballesteros AM, Plikaytis B, Williams D, Dykes J, Gheesling LL, Carlone GM, Høiby EA, Holst J, Nøkleby H, Rosenqvist E, Sierra G, Campa C, Sotolongo F, Vega J, Garcia J, Herrera P, Poolman JT, Perkins BA. Immunogenicity of 2 serogroup B outer-membrane protein meningococcal vaccines - A randomized controlled trial in Chile. JAMA 1999; 281 (16) : 1520-1527.

Declaration of quality control

Undersigned states herewith that the research presented in this report has been carried out according to the OECD principles of Good Clinical Practice (GCP) and that this report reflects a complete, correct and reliable overview of the results obtained.

GCP inspections of the experiments and reports submitted to the management research team leader took place on:

Inspection Date	Type of Inspection
10-03-99	GCP Inspection on study site
10-09-99	GCP Inspection afterwards on data trial laboratory
23-09-99	Control of sera in different assays

This report was inspected on 17 October 2000
Inspection of report no.

Quality control officer:

name : M.C. Jongerius
laboratory : Laboratory for Clinical Vaccine Research

Appendix 1 Mailing list

1	Hoofdinspecteur Preventieve en Curatieve Gezondheidszorg
2	Directeur-Generaal Volksgezondheid
3	Inspectie Gezondheidszorg, Inspecteur Infectieziekten
4	Gezondheidsraad, Den Haag voorzitter
5	Gezondheidsraad, Den Haag secretaris werkgroep RVP
6	Medisch Ethische Commissie AZR/EUR, Rotterdam
7-9	Prof. Dr R. de Groot
10-17	GGD Rotterdam en omstreken
18-21	Stichting Thuiszorg Rotterdam
22	Nationaal Referentie Laboratorium Bacteriële Meningitis AMC/RIVM, Amsterdam
23	Depot Nederlandse Publikaties en Nederlandse Bibliografie
24	Directie RIVM
25	Directeur sector Vaccins
26	Directeur sector Volksgezondheidsonderzoek
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30-31	Hoofd LCB
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36-37	Hoofd KRZ
38	Hoofd CIE
39	Hoofd LIS
40	Hoofd LIO
41	Prof. Juhani Eskola, Nat. Inst. Public Health, Helsinki Finland
42	Prof. Keith Cartwright, Public Health Laboratory Gloucester, UK
43	Dr. Ray Borrow, Public Health Laboratory, Manchester, UK
44	Dr. David Salisbury, Dept. of Health, London, UK
45	Dr M.A.E Conyn-van Spaendonck
46	H.E. de Melker
47-58	Leden IGZ infectieziektenoverleg
59-73	Auteurs
74	SBD/Voorlichting en Public Relations
75	Bureau Rapportenregistratie
76	Bibliotheek RIVM
77-91	Bureau Rapportenbeheer
92-125	Reserve

Appendix 2 Participants

Table 2. Participants randomisation

Schedule **Adjuvant**	**2+1**	**3+1**	**Total**	**Sexe**
$Al(OH)_3$	32	35	67	♀ 36 ♂ 31
$AlPO_4$	32	35	67	♀ 40 ♂ 27
Total	**64**	**70**	**134**	
Sexe	♀ 37 ♂ 27	♀ 39 ♂ 31		

Table 3. Participants dropout

Adjuvant	**Schedule**	**UTN**	**Drop-out moment**
$Al(OH)_3$	2+1	187	after vacc.2, only observation adv.reactions day1
$Al(OH)_3$	3+1	199 224	after vacc.1, only observation adv.reactions day1 after vacc.4, only observation adv.reactions day1
$AlPO_4$	2+1	-	-
$AlPO_4$	3+1	184 287 173 277 288	after vacc.1, only observation adv.reactions day1 after vacc.1, only observation adv.reactions day1 before vacc.4 before vacc.4 after vacc.4, only observation adv.reactions day1

Table 4. Exclusion of participants for adverse reactions Per Protocol analyses

Adjuvant	Schedule	UTN	Exclusion for:
$Al(OH)_3$	2+1	124	observation day 1 after vacc.1
		285	observation day 1 after vacc.2
		120, 123, 257	all observations after vacc.3
		106, 124, 129, 142, 154, 178, 189, 210, 217, 279	observation day 1 after vacc.3
$Al(OH)_3$	3+1	136, 149	observation day 1 after vacc.1
		196	observation day 1 after vacc.2
		112, 212	observation day 1 after vacc.3
		112, 114, 153, 212, 221, 225	observation day 1 after vacc.4
$AlPO_4$	2+1	181	observation day 1 after vacc.1
		105, 139, 175, 181, 192, 231, 239	observation day 1 after vacc.3
		171	all observations after vacc.3
$AlPO_4$	3+1	126, 211, 277	observation day 1 after vacc.1
		263	observation day 1 after vacc.2
		250, 258	observation day 1 after vacc.3
		144, 185, 211	observation day 1 after vacc.4
		263	all observations after vacc.4

Table 5. Exclusion of participants for serological Per Protocol analyses

Adjuvant	Schedule	UTN	Exclusion for:
$Al(OH)_3$	2+1	120, 123, 257	blood sample 3, 4 & 5
$Al(OH)_3$	3+1	-	-
$AlPO_4$	2+1	171	blood sample 4 & 5
$AlPO_4$	3+1	263	blood sample 5 & 6
		170*	blood sample 2

***** UTN=170: blood sample 2 is also excluded for the Intention-to-treat analyses because of unaccountable bactericidal activity

Appendix 3 Adverse Reactions

Table 6. Systemic adverse reactions after vaccination 1

	day 1				day 2-3				day 4-7			
	$Al(OH)_3$ N=67		$AlPO_4$ N=67		$Al(OH)_3$ N=66		$AlPO_4$ N=65		$Al(OH)_3$ N=66		$AlPO_4$ N=65	
Reactions	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Fever	2	*3.3	1	*1.6	5	7.6	2	3.1	3	4.5	2	3.1
Headache	0		1	1.5	0		0		0		0	
Drowsiness	3	4.5	10	14.9	6	9.1	7	10.8	4	6.1	2	3.1
Unusual crying	3	4.5	2	3.0	4	6.1	1	1.5	1	1.5	1	1.5
Less appetite	1	1.5	5	7.5	5	7.6	5	7.7	4	6.1	2	3.1
Nausea	1	1.5	1	1.5	0		2	3.1	0		1	1.5
Joint complaints	0		0		0		0		0		0	
Cutaneous symptoms	1	1.5	0		0		1	1.5	0		1	1.5
Medication	1	1.5	1	1.5	4	6.1	1	1.5	1	1.5	2	3.1
Visit doctor or hospital	0		0		0		0		0		1	1.5
Illness in family	1	1.5	0		2	3.0	0		2	3.0	1	1.5
Other	0		0		0		1	1.5	1	1.5	1	1.5

* percentages calculated in relation to number of participants for who temperature was measured

Table 7. Systemic adverse reactions after vaccination 2

	day 1				day 2-3				day 4-7			
	$Al(OH)_3$ N=66		$AlPO_4$ N=65		$Al(OH)_3$ N=65		$AlPO_4$ N=65		$Al(OH)_3$ N=65		$AlPO_4$ N=65	
Reactions	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Fever	1	*2.0	3	*5.2	5	7.7	4	6.2	3	4.6	3	4.6
Headache	1	1.5	0		0		1	1.5	0		0	
Drowsiness	2	3.0	9	13.8	7	10.8	9	13.8	5	7.7	4	6.2
Unusual crying	0		0		1	1.5	4	6.2	2	3.1	2	3.1
Less appetite	1	1.5	1	1.5	3	4.6	4	6.2	3	4.6	4	6.2
Nausea	0		0		3	4.6	0		1	1.5	0	
Joint complaints	0		0		0		0		0		0	
Cutaneous symptoms	0		0		0		0		0		0	
Medication	0		0		3	4.6	2	3.1	3	4.6	4	6.2
Visit doctor or hospital	0		0		1	1.5	0		0		2	3.1
Illness in family	1	1.5	0		1	1.5	2	3.1	1	1.5	2	3.1
Other	0		0		2	3.1	3	4.6	2	3.1	3	4.6

* percentages calculated in relation to number of participants for who temperature was measured

Table 8. Systemic adverse reactions after vaccination 3

	day 1				day 2-3				day 4-7			
	$Al(OH)_3$ N=65		$AlPO_4$ N=65		$Al(OH)_3$ N=65		$AlPO_4$ N=65		$Al(OH)_3$ N=65		$AlPO_4$ N=65	
Reactions	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Fever	3	*6.3	1	*1.9	1	1.5	1	1.5	1	1.5	1	1.5
Headache	0		1	1.5	0		0		0		0	
Drowsiness	3	4.6	6	9.2	2	3.1	0		1	1.5	0	
Unusual crying	1	1.5	0		0		0		0		0	
Less appetite	0		2	3.1	2	3.1	0		1	1.5	0	
Nausea	0		0		0		0		1	1.5	0	
Joint complaints	0		0		0		0		0		0	
Cutaneous symptoms	0		0		0		0		0		0	
Medication	0		0		1	1.5	0		0		0	
Visit doctor or hospital	0		0		1	1.5	0		0		0	
Illness in family	0		0		1	1.5	0		1	1.5	0	
Other	0		0		1	1.5	0		1	1.5	0	

* percentages calculated in relation to number of participants for who temperature was measured

Table 9. Systemic adverse reactions after vaccination 4

	day 1				day 2-3				day 4-7			
	$Al(OH)_3$ N=34		$AlPO_4$ N=31		$Al(OH)_3$ N=33		$AlPO_4$ N=30		$Al(OH)_3$ N=33		$AlPO_4$ N=30	
Reactions	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Fever	0		1	*4.2	0		0		0		0	
Headache	0		0		0		0		0		0	
Drowsiness	1	2.9	5	16.1	0		1	3.3	1	3.0	0	
Unusual crying	0		0		0		0		0		0	
Less appetite	1	2.9	1	3.2	0		0		0		0	
Nausea	0		0		0		0		0		0	
Joint complaints	0		0		0		0		0		0	
Cutaneous symptoms	0		0		0		0		0		0	
Medication	0		0		0		0		0		0	
Visit doctor or hospital	0		0		0		0		0		0	
Illness in family	0		0		0		0		0		0	
Other	0		0		0		0		0		0	

* percentage calculated in relation to number of participants for who temperature was measured

Table 10. Local adverse reactions after vaccination 1

	day 1				day 2-3				day 4-7			
	$Al(OH)_3$ N=67		$AlPO_4$ N=67		$Al(OH)_3$ N=66		$AlPO_4$ N=65		$Al(OH)_3$ N=66		$AlPO_4$ N=65	
Reactions	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Redness												
<2.5cm	5	7.5	8	11.9	4	6.1	2	3.1	0		1	1.5
2.5-5cm	0		0		0		2	3.1	0		0	
>5cm	0		0		0		0		0		0	
Swelling												
<2.5cm	5	7.5	3	4.5	5	7.6	0		0		0	
2.5-5cm	0		1	1.5	1	1.5	0		0		0	
>5cm	0		0		0		0		0		0	
Itching												
mild	0		0		0		1	1.5	1	1.5	0	
serious	0		0		0		0		0		0	
very serious	0		0		0		0		0		0	
Pain												
mild	8	11.9	23	34.3	5	7.6	11	16.9	0		0	
serious	0		0		0		1	1.5	0		0	
very serious	0		0		0		0		0		0	
Not using arm												
mild	0		1	1.5	0		2	3.1	0		0	
serious	0		0		0		0		0		0	
very serious	0		0		0		0		0		0	

Table 11. Local adverse reactions after vaccination 2

	day 1				day 2-3				day 4-7			
	$Al(OH)_3$ N=66		$AlPO_4$ N=65		$Al(OH)_3$ N=65		$AlPO_4$ N=65		$Al(OH)_3$ N=65		$AlPO_4$ N=65	
Reactions	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Redness												
<2.5cm	5	7.6	6	9.2	1	1.5	3	4.6	0		0	
2.5-5cm	0		0		0		1	1.5	0		0	
>5cm	0		0		0		0		0		0	
Swelling												
<2.5cm	0		3	4.6	1	1.5	2	3.1	1	1.5	0	
2.5-5cm	0		0		0		2	3.1	0		0	
>5cm	0		0		0		0		0		0	
Itching												
mild	0		0		0		0		0		0	
serious	0		0		0		0		0		0	
very serious	0		0		0		0		0		0	
Pain												
mild	16	24.2	21	32.3	3	4.6	12	18.5	2	3.1	0	
serious	0		0		0		0		0		0	
very serious	0		0		0		0		0		0	
Not using arm												
mild	0		0		0		1	1.5	0		0	
serious	0		0		0		0		0		0	
very serious	0		0		0		0		0		0	

Table 12. Local adverse reactions after vaccination 3

	day 1				day 2-3				day 4-7			
	$Al(OH)_3$ N=65		$AlPO_4$ N=65		$Al(OH)_3$ N=65		$AlPO_4$ N=65		$Al(OH)_3$ N=65		$AlPO_4$ N=65	
Reactions	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Redness												
<2.5cm	1	1.5	5	7.7	1	1.5	2	3.1	1	1.5	1	1.5
2.5-5cm	0		0		0		0		0		0	
>5cm	0		0		0		0		0		0	
Swelling												
<2.5cm	0		2	3.1	1	1.5	1	1.5	0		1	1.5
2.5-5cm	0		0		0		0		0		0	
>5cm	0		0		0		0		0		0	
Itching												
mild	0		1	1.5	0		0		1	1.5	0	
serious	0		0		0		0		0		0	
very serious	0		0		0		0		0		0	
Pain												
mild	18	27.7	22	33.8	1	1.5	8	12.3	0		1	1.5
serious	0		0		0		0		0		0	
very serious	0		0		0		0		0		0	
Not using arm												
mild	0		1	1.5	0		1	1.5	0		1	1.5
serious	0		0		0		0		0		0	
very serious	0		0		0		0		0		0	

Table 13. Local adverse reactions after vaccination 4

	day 1				day 2-3				day 4-7			
	$Al(OH)_3$ N=34		$AlPO_4$ N=31		$Al(OH)_3$ N=33		$AlPO_4$ N=30		$Al(OH)_3$ N=33		$AlPO_4$ N=30	
Reactions	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Redness												
<2.5cm	0		4	12.9	0		2	6.7	0		0	
2.5-5cm	0		0		0		0		0		0	
>5cm	0		0		0		0		0		0	
Swelling												
<2.5cm	2	5.9	2	6.5	0		0		1	3.0	0	
2.5-5cm	0		0		0		0		0		0	
>5cm	0		0		0		0		0		0	
Itching												
mild	0		0		0		0		0		0	
serious	0		0		0		0		0		0	
very serious	0		0		0		0		0		0	
Pain												
mild	17	50.0	10	32.3	0		2	6.7	0		0	
serious	0		0		0		0		0		0	
very serious	0		0		0		0		0		0	
Not using arm												
mild	0		0		0		0		0		0	
serious	0		0		0		0		0		0	
very serious	0		0		0		0		0		0	

Appendix 4 Serology

Table 14. Percentages participants with SBA titre ≥ 1:4

	$Al(OH)_3$						$AlPO_4$					
	2+1			3+1			2+1			3+1		
Study moment	**n**	**N**	**%**	**n**	**N**	**%**	**n**	**N**	**%**	**n**	**N**	**%**
Pré prim. series	0	30	0	0	34	0	0	32	0	0	35	0
Pré second vacc.	0	30	0	1	32	3	0	32	0	0	30	0
Pré third vacc.				17	32	53				22	32	69
Post prim. series	18	29	62	20	34	59	26	32	81	25	32	78
Pré booster	2	31	6	2	33	6	3	32	9	5	31	16
Post booster	26	28	93	31	32	97	27	28	96	29	29	100

Table 15. SBA response in the 2+1-schedules

	$Al(OH)_3$			$AlPO_4$		
Study moment	**N**	**GMT**	**[95%CI]**	**N**	**GMT**	**[95%CI]**
Pré prim. series	30	1.0	-	32	1.0	-
Pré second vacc.	30	1.0	-	32	1.0	[1.0 - 1.1]
Post prim. series	29	5.1	[3.2 - 8.2]	32	8.8	[5.9 - 13.0]
Pré booster	31	1.2	[1.0 - 1.4]	32	1.3	[1.0 - 1.6]
Post booster	28	24.9	[15.2 - 40.8]	28	25.6	[16.8 - 39.1]

Table 16. SBA response in the 3+1-schedules

	$Al(OH)_3$			$AlPO_4$		
Study moment	**N**	**GMT**	**[95%CI]**	**N**	**GMT**	**[95%CI]**
Pré prim. series	34	1.0	-	35	1.0	-
Pré second vacc.	32	1.0	[1.0 - 1.1]	30	1.0	[1.0 - 1.1]
Pré third vacc.	32	*3.0	[2.0 - 4.4]	32	7.8	[4.6 - 13.4]
Post prim. series	34	4.9	[2.9 - 8.4]	32	7.7	[4.8 - 12.1]
Pré booster	33	1.2	[0.9 - 1.5]	31	1.4	[1.1 - 1.9]
Post booster	32	46.2	[29.0 - 73.5]	29	70.5	[44.0 - 113.0]

* significant difference in GMT between $Al(OH)_3$ and $AlPO_4$ ($p<0.05$; Mann-Whitney-U)

Table 17. Percentages participants with rise in SBA titre ≥ 4

	$Al(OH)_3$						$AlPO_4$					
	2+1			3+1			2+1			3+1		
Study moment	**n**	**N**	**%**	**n**	**N**	**%**	**n**	**N**	**%**	**n**	**N**	**%**
Post /pré prim. series	18	28	64	20	33	61	26	32	81	25	32	78
Post booster / pré prim. series	25	27	93	30	31	97	27	28	96	29	29	100
Post / pré booster	26	28	93	30	31	97	27	28	96	29	29	100
Post booster / post prim. series	16	27	59	27	32	84	12	28	43	20	28	71

Table 18. ELISA response in the 2+1-schedules

	$Al(OH)_3$			$AlPO_4$		
Study moment	**N**	**GMT**	**[95%CI]**	**N**	**GMT**	**[95%CI]**
Pré prim. series	29	27	[24 - 31]	32	27	[25 - 29]
Pré second vacc.	29	*129	[96 - 172]	32	244	[187 - 113]
Post prim. series	29	*1636	[1206 - 2219]	31	3537	[2778 - 4502]
Pré booster	30	*184	[137 - 247]	32	479	[348 - 659]
Post booster	28	4726	[3471 - 6434]	27	6644	[4857 - 9087]

Table 19. ELISA response in the 3+1-schedules

	$Al(OH)_3$			$AlPO_4$		
Study moment	**N**	**GMT**	**[95%CI]**	**N**	**GMT**	**[95%CI]**
Pré prim. series	34	28	[25 - 31]	35	28	[25 - 31]
Pré second vacc.	31	*264	[197 - 353]	29	373	[292 - 476]
Pré third vacc.	32	*1569	[1201 - 2051]	31	3090	[2309 - 4132]
Post prim. series	34	*2385	[1751 - 3249]	30	4508	[3524 - 5769]
Pré booster	33	406	[289 - 572]	31	614	[465 - 816]
Post booster	32	*6425	[4867 - 8480]	27	9506	[7112 - 12703]

* significant difference in GMT between $Al(OH)_3$ and $AlPO_4$ ($p<0.05$; Mann-Whitney-U)

Appendix 5 Individual line listings

UTN	Blood Sample	Adjuvantia	Schedule	P1.1,4	H1.5	OMV_ELISA	Exclusion for prot.analyses	Exclusion for ITT.analyses
102	pre prim.series	Al(OH)3	2+1	1	1	25	no	no
102	during prim.series	Al(OH)3	2+1	1	1	39	no	no
102	post prim.series	Al(OH)3	2+1	8	1	1155	no	no
102	pre booster	Al(OH)3	2+1	1	1	205	no	no
102	post booster	Al(OH)3	2+1	32	1	12350	no	no
103	pre prim.series	Al(OH)3	2+1	1	1	25	no	no
103	during prim.series	Al(OH)3	2+1	1	1	151	no	no
103	post prim.series	Al(OH)3	2+1	64	1	2649	no	no
103	pre booster	Al(OH)3	2+1	16	1	949	no	no
103	post booster	Al(OH)3	2+1	256	1	3548	no	no
104	pre prim.series	AlPO4	2+1	1	1	25	no	no
104	during prim.series	AlPO4	2+1	1	1	82	no	no
104	post prim.series	AlPO4	2+1	4	1	2946	no	no
104	pre booster	AlPO4	2+1	1	1	942	no	no
104	post booster	AlPO4	2+1	32	1	7418	no	no
105	pre prim.series	AlPO4	2+1	1	1	25	no	no
105	during prim.series	AlPO4	2+1	1	1	507	no	no
105	post prim.series	AlPO4	2+1	32	1	4029	no	no
105	pre booster	AlPO4	2+1	1	1	306	no	no
105	post booster	AlPO4	2+1	64	1	7413	no	no
106	pre prim.series	Al(OH)3	2+1	1	1	25	no	no
106	during prim.series	Al(OH)3	2+1	1	1	150	no	no
106	post prim.series	Al(OH)3	2+1	1	1	269	no	no
106	pre booster	Al(OH)3	2+1	1	1	87	no	no
106	post booster	Al(OH)3	2+1	4	1	1229	no	no
107	pre prim.series	Al(OH)3	2+1	1	1	25	no	no
107	during prim.series	Al(OH)3	2+1	1	1	132	no	no
107	post prim.series	Al(OH)3	2+1	4	1	1139	no	no
107	pre booster	Al(OH)3	2+1	1	1	106	no	no
107	post booster	Al(OH)3	2+1	32	1	5730	no	no
108	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
108	during prim.series	Al(OH)3	3+1	1	1	528	no	no
108	extra during prim.series (only 3+1)	Al(OH)3	3+1	8	1	2849	no	no
108	post prim.series	Al(OH)3	3+1	32	1	4953	no	no
108	pre booster	Al(OH)3	3+1	1	1	818	no	no
108	post booster	Al(OH)3	3+1	256	1	21632	no	no
109	pre prim.series	AlPO4	3+1	1	1	25	no	no
109	during prim.series	AlPO4	3+1	1	1	320	no	no
109	extra during prim.series (only 3+1)	AlPO4	3+1	4	1	2285	no	no
109	post prim.series	AlPO4	3+1	4	1	3874	no	no
109	pre booster	AlPO4	3+1	1	1	212	no	no
109	post booster	AlPO4	3+1	64	1	7234	no	no
110	pre prim.series	AlPO4	3+1	1	1	88	no	no
110	during prim.series	AlPO4	3+1	1	1	626	no	no
110	extra during prim.series (only 3+1)	AlPO4	3+1	256	1	14175	no	no
110	post prim.series	AlPO4	3+1	64	1	7147	no	no
110	pre booster	AlPO4	3+1	4	1	982	no	no
110	post booster	AlPO4	3+1	1024	1	27363	no	no

UTN	Blood Sample	Adjuvantia	Schedule	P1.1,4	H1.5	OMV_ELISA	Exclusion for prot.analyses	Exclusion for ITT.analyses
111	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
111	during prim.series	Al(OH)3	3+1	missing	missing	missing	no	no
111	extra during prim.series (only 3+1)	Al(OH)3	3+1	4	1	1064	no	no
111	post prim.series	Al(OH)3	3+1	8	1	157	no	no
111	pre booster	Al(OH)3	3+1	1	1	207	no	no
111	post booster	Al(OH)3	3+1	32	1	3067	no	no
112	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
112	during prim.series	Al(OH)3	3+1	1	1	279	no	no
112	extra during prim.series (only 3+1)	Al(OH)3	3+1	8	1	1952	no	no
112	post prim.series	Al(OH)3	3+1	4	1	2643	no	no
112	pre booster	Al(OH)3	3+1	1	1	651	no	no
112	post booster	Al(OH)3	3+1	256	1	14822	no	no
113	pre prim.series	AlPO4	2+1	1	1	25	no	no
113	during prim.series	AlPO4	2+1	1	1	354	no	no
113	post prim.series	AlPO4	2+1	64	1	19880	no	no
113	pre booster	AlPO4	2+1	1	1	1130	no	no
113	post booster	AlPO4	2+1	64	1	21430	no	no
114	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
114	during prim.series	Al(OH)3	3+1	1	1	1041	no	no
114	extra during prim.series (only 3+1)	Al(OH)3	3+1	1	1	1042	no	no
114	post prim.series	Al(OH)3	3+1	1	1	1493	no	no
114	pre booster	Al(OH)3	3+1	1	1	478	no	no
114	post booster	Al(OH)3	3+1	64	1	6153	no	no
115	pre prim.series	AlPO4	3+1	1	1	25	no	no
115	during prim.series	AlPO4	3+1	1	1	176	no	no
115	extra during prim.series (only 3+1)	AlPO4	3+1	8	1	2064	no	no
115	post prim.series	AlPO4	3+1	8	missing	missing	no	no
115	pre booster	AlPO4	3+1	1	1	522	no	no
115	post booster	AlPO4	3+1	64	1	6553	no	no
116	pre prim.series	AlPO4	3+1	1	1	25	no	no
116	during prim.series	AlPO4	3+1	1	1	246	no	no
116	extra during prim.series (only 3+1)	AlPO4	3+1	2	1	missing	no	no
116	post prim.series	AlPO4	3+1	1	1	missing	no	no
116	pre booster	AlPO4	3+1	1	1	602	no	no
116	post booster	AlPO4	3+1	32	1	7510	no	no
117	pre prim.series	AlPO4	2+1	1	1	25	no	no
117	during prim.series	AlPO4	2+1	1	1	364	no	no
117	post prim.series	AlPO4	2+1	16	1	4847	no	no
117	pre booster	AlPO4	2+1	1	1	650	no	no
117	post booster	AlPO4	2+1	16	1	8077	no	no
118	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
118	during prim.series	Al(OH)3	3+1	1	1	109	no	no
118	extra during prim.series (only 3+1)	Al(OH)3	3+1	4	1	1474	no	no
118	post prim.series	Al(OH)3	3+1	8	1	1521	no	no
118	pre booster	Al(OH)3	3+1	1	1	104	no	no
118	post booster	Al(OH)3	3+1	32	1	7803	no	no

UTN	Blood Sample	Adjuvantia	Schedule	P1.1,4	H1.5	OMV_ELISA	Exclusion for prot.analyses	Exclusion for ITT.analyses
119	pre prim.series	AlPO4	2+1	1	1	36	no	no
119	during prim.series	AlPO4	2+1	1	1	318	no	no
119	post prim.series	AlPO4	2+1	8	1	5978	no	no
119	pre booster	AlPO4	2+1	1	1	729	no	no
119	post booster	AlPO4	2+1	16	1	5618	no	no
120	pre prim.series	Al(OH)3	2+1	1	1	25	no	no
120	during prim.series	Al(OH)3	2+1	1	1	43	no	no
120	post prim.series	Al(OH)3	2+1	2	1	1183	yes	no
120	pre booster	Al(OH)3	2+1	1	1	52	yes	no
120	post booster	Al(OH)3	2+1	16	1	5030	yes	no
121	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
121	during prim.series	Al(OH)3	3+1	1	1	missing	no	no
121	extra during prim.series (only 3+1)	Al(OH)3	3+1	4	1	2166	no	no
121	post prim.series	Al(OH)3	3+1	4	1	2365	no	no
121	pre booster	Al(OH)3	3+1	1	1	381	no	no
121	post booster	Al(OH)3	3+1	32	1	2336	no	no
123	pre prim.series	Al(OH)3	2+1	1	1	25	no	no
123	during prim.series	Al(OH)3	2+1	1	1	65	no	no
123	post prim.series	Al(OH)3	2+1	32	1	4296	yes	no
123	pre booster	Al(OH)3	2+1	1	1	174	yes	no
123	post booster	Al(OH)3	2+1	64	1	9413	yes	no
124	pre prim.series	Al(OH)3	2+1	1	1	25	no	no
124	during prim.series	Al(OH)3	2+1	1	1	25	no	no
124	post prim.series	Al(OH)3	2+1	1	1	709	no	no
124	pre booster	Al(OH)3	2+1	1	1	61	no	no
124	post booster	Al(OH)3	2+1	1	1	606	no	no
126	pre prim.series	AlPO4	3+1	1	1	48	no	no
126	during prim.series	AlPO4	3+1	1	1	1187	no	no
126	extra during prim.series (only 3+1)	AlPO4	3+1	4	1	1181	no	no
126	post prim.series	AlPO4	3+1	8	1	3853	no	no
126	pre booster	AlPO4	3+1	1	1	1396	no	no
126	post booster	AlPO4	3+1	256	1	8304	no	no
129	pre prim.series	Al(OH)3	2+1	1	1	25	no	no
129	during prim.series	Al(OH)3	2+1	missing	missing	missing	no	no
129	post prim.series	Al(OH)3	2+1	4	1	824	no	no
129	pre booster	Al(OH)3	2+1	1	1	76	no	no
129	post booster	Al(OH)3	2+1	8	1	2146	no	no
130	pre prim.series	AlPO4	2+1	1	1	25	no	no
130	during prim.series	AlPO4	2+1	1	1	324	no	no
130	post prim.series	AlPO4	2+1	2	1	1767	no	no
130	pre booster	AlPO4	2+1	1	1	227	no	no
130	post booster	AlPO4	2+1	4	1	3184	no	no
131	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
131	during prim.series	Al(OH)3	3+1	4	1	345	no	no
131	extra during prim.series (only 3+1)	Al(OH)3	3+1	missing	missing	missing	no	no
131	post prim.series	Al(OH)3	3+1	4	1	2168	no	no
131	pre booster	Al(OH)3	3+1	1	1	230	no	no
131	post booster	Al(OH)3	3+1	128	1	9304	no	no

UTN	Blood Sample	Adjuvantia	Schedule	P1.1,4	H1.5	OMV_ELISA	Exclusion for prot.analyses	Exclusion for ITT.analyses
135	pre prim.series	AlPO4	3+1	1	1	25	no	no
135	during prim.series	AlPO4	3+1	1	1	536	no	no
135	extra during prim.series (only 3+1)	AlPO4	3+1	64	1	2927	no	no
135	post prim.series	AlPO4	3+1	16	1	4883	no	no
135	pre booster	AlPO4	3+1	2	1	508	no	no
135	post booster	AlPO4	3+1	32	1	7265	no	no
136	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
136	during prim.series	Al(OH)3	3+1	1	1	130	no	no
136	extra during prim.series (only 3+1)	Al(OH)3	3+1	16	1	2186	no	no
136	post prim.series	Al(OH)3	3+1	8	1	1368	no	no
136	pre booster	Al(OH)3	3+1	1	1	152	no	no
136	post booster	Al(OH)3	3+1	256	1	3506	no	no
138	pre prim.series	AlPO4	2+1	1	1	39	no	no
138	during prim.series	AlPO4	2+1	1	1	397	no	no
138	post prim.series	AlPO4	2+1	32	1	5327	no	no
138	pre booster	AlPO4	2+1	16	1	600	no	no
138	post booster	AlPO4	2+1	64	1	7512	no	no
139	pre prim.series	AlPO4	2+1	1	1	25	no	no
139	during prim.series	AlPO4	2+1	1	1	149	no	no
139	post prim.series	AlPO4	2+1	4	1	3074	no	no
139	pre booster	AlPO4	2+1	1	1	145	no	no
139	post booster	AlPO4	2+1	16	1	6553	no	no
142	pre prim.series	Al(OH)3	2+1	1	1	25	no	no
142	during prim.series	Al(OH)3	2+1	1	1	113	no	no
142	post prim.series	Al(OH)3	2+1	8	1	1764	no	no
142	pre booster	Al(OH)3	2+1	1	1	111	no	no
142	post booster	Al(OH)3	2+1	16	1	3265	no	no
144	pre prim.series	AlPO4	3+1	1	1	25	no	no
144	during prim.series	AlPO4	3+1	1	1	90	no	no
144	extra during prim.series (only 3+1)	AlPO4	3+1	2	1	1441	no	no
144	post prim.series	AlPO4	3+1	32	1	9071	no	no
144	pre booster	AlPO4	3+1	1	1	527	no	no
144	post booster	AlPO4	3+1	64	1	18587	no	no
145	pre prim.series	Al(OH)3	2+1	1	1	49	no	no
145	during prim.series	Al(OH)3	2+1	1	1	474	no	no
145	post prim.series	Al(OH)3	2+1	32	1	4324	no	no
145	pre booster	Al(OH)3	2+1	1	1	544	no	no
145	post booster	Al(OH)3	2+1	32	1	8577	no	no
148	pre prim.series	AlPO4	2+1	1	1	25	no	no
148	during prim.series	AlPO4	2+1	1	1	162	no	no
148	post prim.series	AlPO4	2+1	2	1	1052	no	no
148	pre booster	AlPO4	2+1	1	1	113	no	no
148	post booster	AlPO4	2+1	128	1	14314	no	no
149	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
149	during prim.series	Al(OH)3	3+1	1	1	1030	no	no
149	extra during prim.series (only 3+1)	Al(OH)3	3+1	1	1	1247	no	no
149	post prim.series	Al(OH)3	3+1	16	1	3639	no	no
149	pre booster	Al(OH)3	3+1	1	1	759	no	no
149	post booster	Al(OH)3	3+1	64	1	8885	no	no

UTN	Blood Sample	Adjuvantia	Schedule	P1.1,4	H1.5	OMV_ELISA	Exclusion for prot.analyses	Exclusion for ITT.analyses
152	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
152	during prim.series	Al(OH)3	3+1	1	1	142	no	no
152	extra during prim.series (only 3+1)	Al(OH)3	3+1	4	1	1285	no	no
152	post prim.series	Al(OH)3	3+1	4	1	793	no	no
152	pre booster	Al(OH)3	3+1	1	1	78	no	no
152	post booster	Al(OH)3	3+1	16	1	2939	no	no
153	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
153	during prim.series	Al(OH)3	3+1	1	1	655	no	no
153	extra during prim.series (only 3+1)	Al(OH)3	3+1	1	1	3100	no	no
153	post prim.series	Al(OH)3	3+1	64	1	8816	no	no
153	pre booster	Al(OH)3	3+1	1	1	991	no	no
153	post booster	Al(OH)3	3+1	2048	1	42173	no	no
154	pre prim.series	Al(OH)3	2+1	1	1	25	no	no
154	during prim.series	Al(OH)3	2+1	1	1	136	no	no
154	post prim.series	Al(OH)3	2+1	1	1	580	no	no
154	pre booster	Al(OH)3	2+1	1	1	139	no	no
154	post booster	Al(OH)3	2+1	missing	missing	missing	no	no
155	pre prim.series	Al(OH)3	2+1	missing	missing	missing	no	no
155	during prim.series	Al(OH)3	2+1	1	1	155	no	no
155	post prim.series	Al(OH)3	2+1	missing	missing	missing	no	no
155	pre booster	Al(OH)3	2+1	1	1	777	no	no
155	post booster	Al(OH)3	2+1	missing	missing	missing	no	no
158	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
158	during prim.series	Al(OH)3	3+1	1	1	162	no	no
158	extra during prim.series (only 3+1)	Al(OH)3	3+1	1	1	1204	no	no
158	post prim.series	Al(OH)3	3+1	1	1	3060	no	no
158	pre booster	Al(OH)3	3+1	1	1	729	no	no
158	post booster	Al(OH)3	3+1	32	1	4208	no	no
159	pre prim.series	AlPO4	3+1	1	1	60	no	no
159	during prim.series	AlPO4	3+1	1	1	277	no	no
159	extra during prim.series (only 3+1)	AlPO4	3+1	8	1	3589	no	no
159	post prim.series	AlPO4	3+1	16	1	15056	no	no
159	pre booster	AlPO4	3+1	1	1	1719	no	no
159	post booster	AlPO4	3+1	32	1	10994	no	no
161	pre prim.series	AlPO4	3+1	1	1	25	no	no
161	during prim.series	AlPO4	3+1	missing	missing	missing	no	no
161	extra during prim.series (only 3+1)	AlPO4	3+1	2	1	2018	no	no
161	post prim.series	AlPO4	3+1	8	1	3676	no	no
161	pre booster	AlPO4	3+1	1	1	1026	no	no
161	post booster	AlPO4	3+1	32	1	8708	no	no
163	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
163	during prim.series	Al(OH)3	3+1	1	1	438	no	no
163	extra during prim.series (only 3+1)	Al(OH)3	3+1	8	1	1268	no	no
163	post prim.series	Al(OH)3	3+1	64	1	10403	no	no
163	pre booster	Al(OH)3	3+1	1	1	660	no	no
163	post booster	Al(OH)3	3+1	64	1	7287	no	no

UTN	Blood Sample	Adjuvantia	Schedule	P1.1,4	H1.5	OMV_ELISA	Exclusion for prot.analyses	Exclusion for ITT.analyses
164	pre prim.series	Al(OH)3	2+1	1	1	25	no	no
164	during prim.series	Al(OH)3	2+1	1	1	89	no	no
164	post prim.series	Al(OH)3	2+1	2	1	1295	no	no
164	pre booster	Al(OH)3	2+1	1	1	148	no	no
164	post booster	Al(OH)3	2+1	8	1	2950	no	no
166	pre prim.series	AlPO4	3+1	1	1	25	no	no
166	during prim.series	AlPO4	3+1	1	1	1848	no	no
166	extra during prim.series (only 3+1)	AlPO4	3+1	64	1	30322	no	no
166	post prim.series	AlPO4	3+1	8	1	21225	no	no
166	pre booster	AlPO4	3+1	1	1	1112	no	no
166	post booster	AlPO4	3+1	64	1	29978	no	no
170	pre prim.series	AlPO4	3+1	1	1	25	no	no
170	during prim.series	AlPO4	3+1	2	2	457	yes	yes
170	extra during prim.series (only 3+1)	AlPO4	3+1	16	1	5162	no	no
170	post prim.series	AlPO4	3+1	64	1	10195	no	no
170	pre booster	AlPO4	3+1	4	1	2146	no	no
170	post booster	AlPO4	3+1	512	1	40833	no	no
171	pre prim.series	AlPO4	2+1	1	1	25	no	no
171	during prim.series	AlPO4	2+1	1	1	235	no	no
171	post prim.series	AlPO4	2+1	16	1	2988	no	no
171	pre booster	AlPO4	2+1	2	1	894	yes	no
171	post booster	AlPO4	2+1	missing	missing	missing	yes	no
173	pre prim.series	AlPO4	3+1	1	1	25	no	no
173	during prim.series	AlPO4	3+1	1	1	328	no	no
173	extra during prim.series (only 3+1)	AlPO4	3+1	1	1	789	no	no
173	post prim.series	AlPO4	3+1	1	1	1079	no	no
173	pre booster	AlPO4	3+1	missing	missing	missing	no	no
173	post booster	AlPO4	3+1	missing	missing	missing	no	no
174	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
174	during prim.series	Al(OH)3	3+1	1	1	246	no	no
174	extra during prim.series (only 3+1)	Al(OH)3	3+1	32	1	9362	no	no
174	post prim.series	Al(OH)3	3+1	16	1	5827	no	no
174	pre booster	Al(OH)3	3+1	1	1	327	no	no
174	post booster	Al(OH)3	3+1	128	1	17024	no	no
175	pre prim.series	AlPO4	2+1	1	1	25	no	no
175	during prim.series	AlPO4	2+1	2	1	540	no	no
175	post prim.series	AlPO4	2+1	32	1	9582	no	no
175	pre booster	AlPO4	2+1	2	1	1601	no	no
175	post booster	AlPO4	2+1	128	1	23109	no	no
176	pre prim.series	Al(OH)3	2+1	1	1	25	no	no
176	during prim.series	Al(OH)3	2+1	1	1	381	no	no
176	post prim.series	Al(OH)3	2+1	4	1	1515	no	no
176	pre booster	Al(OH)3	2+1	1	1	178	no	no
176	post booster	Al(OH)3	2+1	32	1	7242	no	no
178	pre prim.series	Al(OH)3	2+1	missing	missing	missing	no	no
178	during prim.series	Al(OH)3	2+1	1	1	143	no	no
178	post prim.series	Al(OH)3	2+1	1	1	818	no	no
178	pre booster	Al(OH)3	2+1	1	1	95	no	no
178	post booster	Al(OH)3	2+1	16	1	4463	no	no

UTN	Blood Sample	Adjuvantia	Schedule	P1.1,4	H1.5	OMV_ELISA	Exclusion for prot.analyses	Exclusion for ITT.analyses
179	pre prim.series	AlPO4	2+1	1	1	25	no	no
179	during prim.series	AlPO4	2+1	1	1	217	no	no
179	post prim.series	AlPO4	2+1	16	1	2996	no	no
179	pre booster	AlPO4	2+1	1	1	200	no	no
179	post booster	AlPO4	2+1	128	1	14985	no	no
181	pre prim.series	AlPO4	2+1	1	1	25	no	no
181	during prim.series	AlPO4	2+1	1	1	839	no	no
181	post prim.series	AlPO4	2+1	16	1	6251	no	no
181	pre booster	AlPO4	2+1	4	1	3475	no	no
181	post booster	AlPO4	2+1	missing	missing	missing	no	no
183	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
183	during prim.series	Al(OH)3	3+1	1	1	159	no	no
183	extra during prim.series (only 3+1)	Al(OH)3	3+1	32	1	9005	no	no
183	post prim.series	Al(OH)3	3+1	8	1	5487	no	no
183	pre booster	Al(OH)3	3+1	1	1	1047	no	no
183	post booster	Al(OH)3	3+1	32	1	8186	no	no
184	pre prim.series	AlPO4	3+1	1	1	25	no	no
184	during prim.series	AlPO4	3+1	missing	missing	missing	no	no
184	extra during prim.series (only 3+1)	AlPO4	3+1	missing	missing	missing	no	no
184	post prim.series	AlPO4	3+1	missing	missing	missing	no	no
184	pre booster	AlPO4	3+1	missing	missing	missing	no	no
184	post booster	AlPO4	3+1	missing	missing	missing	no	no
185	pre prim.series	AlPO4	3+1	1	1	45	no	no
185	during prim.series	AlPO4	3+1	1	1	601	no	no
185	extra during prim.series (only 3+1)	AlPO4	3+1	8	1	3270	no	no
185	post prim.series	AlPO4	3+1	32	1	5658	no	no
185	pre booster	AlPO4	3+1	8	1	1935	no	no
185	post booster	AlPO4	3+1	64	1	6348	no	no
186	pre prim.series	AlPO4	2+1	1	1	25	no	no
186	during prim.series	AlPO4	2+1	1	1	248	no	no
186	post prim.series	AlPO4	2+1	4	1	2183	no	no
186	pre booster	AlPO4	2+1	1	1	356	no	no
186	post booster	AlPO4	2+1	4	1	1794	no	no
187	pre prim.series	Al(OH)3	2+1	1	1	25	no	no
187	during prim.series	Al(OH)3	2+1	1	1	55	no	no
187	post prim.series	Al(OH)3	2+1	missing	missing	missing	no	no
187	pre booster	Al(OH)3	2+1	missing	missing	missing	no	no
187	post booster	Al(OH)3	2+1	missing	missing	missing	no	no
189	pre prim.series	Al(OH)3	2+1	1	1	25	no	no
189	during prim.series	Al(OH)3	2+1	1	1	127	no	no
189	post prim.series	Al(OH)3	2+1	16	1	2257	no	no
189	pre booster	Al(OH)3	2+1	1	1	162	no	no
189	post booster	Al(OH)3	2+1	32	1	2280	no	no
192	pre prim.series	AlPO4	2+1	1	1	25	no	no
192	during prim.series	AlPO4	2+1	1	1	1026	no	no
192	post prim.series	AlPO4	2+1	2	1	1328	no	no
192	pre booster	AlPO4	2+1	1	1	263	no	no
192	post booster	AlPO4	2+1	32	1	10696	no	no

UTN	Blood Sample	Adjuvantia	Schedule	P1.1,4	H1.5	OMV_ELISA	Exclusion for prot.analyses	Exclusion for ITT.analyses
193	pre prim.series	AlPO4	3+1	1	1	25	no	no
193	during prim.series	AlPO4	3+1	1	missing	missing	no	no
193	extra during prim.series (only 3+1)	AlPO4	3+1	128	1	5069	no	no
193	post prim.series	AlPO4	3+1	32	1	2555	no	no
193	pre booster	AlPO4	3+1	16	1	413	no	no
193	post booster	AlPO4	3+1	64	missing	missing	no	no
194	pre prim.series	AlPO4	3+1	1	1	25	no	no
194	during prim.series	AlPO4	3+1	1	1	412	no	no
194	extra during prim.series (only 3+1)	AlPO4	3+1	4	1	2108	no	no
194	post prim.series	AlPO4	3+1	8	1	3207	no	no
194	pre booster	AlPO4	3+1	1	1	856	no	no
194	post booster	AlPO4	3+1	16	1	4824	no	no
195	pre prim.series	AlPO4	2+1	1	1	25	no	no
195	during prim.series	AlPO4	2+1	1	1	221	no	no
195	post prim.series	AlPO4	2+1	8	1	2577	no	no
195	pre booster	AlPO4	2+1	1	1	169	no	no
195	post booster	AlPO4	2+1	16	1	3991	no	no
196	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
196	during prim.series	Al(OH)3	3+1	missing	missing	missing	no	no
196	extra during prim.series (only 3+1)	Al(OH)3	3+1	4	1	3051	no	no
196	post prim.series	Al(OH)3	3+1	8	1	3674	no	no
196	pre booster	Al(OH)3	3+1	1	1	1453	no	no
196	post booster	Al(OH)3	3+1	128	1	27135	no	no
197	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
197	during prim.series	Al(OH)3	3+1	1	1	419	no	no
197	extra during prim.series (only 3+1)	Al(OH)3	3+1	8	1	3422	no	no
197	post prim.series	Al(OH)3	3+1	2	1	2030	no	no
197	pre booster	Al(OH)3	3+1	1	1	380	no	no
197	post booster	Al(OH)3	3+1	32	1	4290	no	no
198	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
198	during prim.series	Al(OH)3	3+1	1	1	140	no	no
198	extra during prim.series (only 3+1)	Al(OH)3	3+1	1	1	573	no	no
198	post prim.series	Al(OH)3	3+1	1	1	1310	no	no
198	pre booster	Al(OH)3	3+1	1	1	225	no	no
198	post booster	Al(OH)3	3+1	64	1	4683	no	no
199	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
199	during prim.series	Al(OH)3	3+1	missing	missing	missing	no	no
199	extra during prim.series (only 3+1)	Al(OH)3	3+1	missing	missing	missing	no	no
199	post prim.series	Al(OH)3	3+1	missing	missing	missing	no	no
199	pre booster	Al(OH)3	3+1	missing	missing	missing	no	no
199	post booster	Al(OH)3	3+1	missing	missing	missing	no	no
200	pre prim.series	Al(OH)3	2+1	1	1	25	no	no
200	during prim.series	Al(OH)3	2+1	missing	missing	missing	no	no
200	post prim.series	Al(OH)3	2+1	missing	missing	missing	no	no
200	pre booster	Al(OH)3	2+1	1	1	82	no	no
200	post booster	Al(OH)3	2+1	16	1	4088	no	no

UTN	Blood Sample	Adjuvantia	Schedule	P1.1,4	H1.5	OMV_ELISA	Exclusion for prot.analyses	Exclusion for ITT.analyses
201	pre prim.series	AlPO4	3+1	1	1	25	no	no
201	during prim.series	AlPO4	3+1	2	1	548	no	no
201	extra during prim.series (only 3+1)	AlPO4	3+1	4	1	3323	no	no
201	post prim.series	AlPO4	3+1	4	1	1734	no	no
201	pre booster	AlPO4	3+1	1	1	258	no	no
201	post booster	AlPO4	3+1	64	1	9448	no	no
202	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
202	during prim.series	Al(OH)3	3+1	1	1	479	no	no
202	extra during prim.series (only 3+1)	Al(OH)3	3+1	1	1	717	no	no
202	post prim.series	Al(OH)3	3+1	1	1	642	no	no
202	pre booster	Al(OH)3	3+1	1	1	81	no	no
202	post booster	Al(OH)3	3+1	8	1	2075	no	no
203	pre prim.series	AlPO4	2+1	1	1	25	no	no
203	during prim.series	AlPO4	2+1	1	1	165	no	no
203	post prim.series	AlPO4	2+1	2	1	2017	no	no
203	pre booster	AlPO4	2+1	1	1	250	no	no
203	post booster	AlPO4	2+1	2	1	3662	no	no
205	pre prim.series	AlPO4	2+1	1	1	56	no	no
205	during prim.series	AlPO4	2+1	1	1	850	no	no
205	post prim.series	AlPO4	2+1	8	1	3883	no	no
205	pre booster	AlPO4	2+1	1	1	477	no	no
205	post booster	AlPO4	2+1	64	1	16466	no	no
207	pre prim.series	AlPO4	3+1	1	1	25	no	no
207	during prim.series	AlPO4	3+1	1	1	386	no	no
207	extra during prim.series (only 3+1)	AlPO4	3+1	2	1	959	no	no
207	post prim.series	AlPO4	3+1	16	1	5657	no	no
207	pre booster	AlPO4	3+1	2	1	622	no	no
207	post booster	AlPO4	3+1	32	1	2673	no	no
209	pre prim.series	AlPO4	2+1	1	1	25	no	no
209	during prim.series	AlPO4	2+1	1	1	218	no	no
209	post prim.series	AlPO4	2+1	16	1	4098	no	no
209	pre booster	AlPO4	2+1	4	1	3690	no	no
209	post booster	AlPO4	2+1	32	1	6731	no	no
210	pre prim.series	Al(OH)3	2+1	1	1	25	no	no
210	during prim.series	Al(OH)3	2+1	1	1	missing	no	no
210	post prim.series	Al(OH)3	2+1	32	1	3184	no	no
210	pre booster	Al(OH)3	2+1	4	1	584	no	no
210	post booster	Al(OH)3	2+1	32	1	3928	no	no
211	pre prim.series	AlPO4	3+1	1	1	25	no	no
211	during prim.series	AlPO4	3+1	1	1	873	no	no
211	extra during prim.series (only 3+1)	AlPO4	3+1	2	1	3871	no	no
211	post prim.series	AlPO4	3+1	1	1	4813	no	no
211	pre booster	AlPO4	3+1	1	1	1193	no	no
211	post booster	AlPO4	3+1	32	1	10788	no	no
212	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
212	during prim.series	Al(OH)3	3+1	1	1	191	no	no
212	extra during prim.series (only 3+1)	Al(OH)3	3+1	4	1	1337	no	no
212	post prim.series	Al(OH)3	3+1	8	1	4313	no	no
212	pre booster	Al(OH)3	3+1	1	1	1520	no	no
212	post booster	Al(OH)3	3+1	32	1	5181	no	no

UTN	Blood Sample	Adjuvantia	Schedule	P1.1,4	H1.5	OMV_ELISA	Exclusion for prot.analyses	Exclusion for ITT.analyses
214	pre prim.series	Al(OH)3	3+1	missing	missing	missing	no	no
214	during prim.series	Al(OH)3	3+1	1	1	79	no	no
214	extra during prim.series (only 3+1)	Al(OH)3	3+1	1	1	586	no	no
214	post prim.series	Al(OH)3	3+1	1	1	715	no	no
214	pre booster	Al(OH)3	3+1	1	1	190	no	no
214	post booster	Al(OH)3	3+1	16	1	2226	no	no
215	pre prim.series	AlPO4	3+1	1	1	25	no	no
215	during prim.series	AlPO4	3+1	1	1	613	no	no
215	extra during prim.series (only 3+1)	AlPO4	3+1	4	1	1964	no	no
215	post prim.series	AlPO4	3+1	4	1	2728	no	no
215	pre booster	AlPO4	3+1	1	1	136	no	no
215	post booster	AlPO4	3+1	64	1	6021	no	no
216	pre prim.series	Al(OH)3	2+1	1	1	104	no	no
216	during prim.series	Al(OH)3	2+1	1	1	802	no	no
216	post prim.series	Al(OH)3	2+1	8	1	3818	no	no
216	pre booster	Al(OH)3	2+1	1	1	missing	no	no
216	post booster	Al(OH)3	2+1	8	1	3771	no	no
217	pre prim.series	Al(OH)3	2+1	1	1	25	no	no
217	during prim.series	Al(OH)3	2+1	1	1	113	no	no
217	post prim.series	Al(OH)3	2+1	4	1	1749	no	no
217	pre booster	Al(OH)3	2+1	1	1	278	no	no
217	post booster	Al(OH)3	2+1	64	1	9072	no	no
219	pre prim.series	AlPO4	3+1	1	1	25	no	no
219	during prim.series	AlPO4	3+1	1	1	430	no	no
219	extra during prim.series (only 3+1)	AlPO4	3+1	32	1	9220	no	no
219	post prim.series	AlPO4	3+1	32	1	7198	no	no
219	pre booster	AlPO4	3+1	1	1	606	no	no
219	post booster	AlPO4	3+1	512	1	8398	no	no
221	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
221	during prim.series	Al(OH)3	3+1	1	1	154	no	no
221	extra during prim.series (only 3+1)	Al(OH)3	3+1	8	1	3361	no	no
221	post prim.series	Al(OH)3	3+1	1	1	2463	no	no
221	pre booster	Al(OH)3	3+1	1	1	500	no	no
221	post booster	Al(OH)3	3+1	32	1	5407	no	no
222	pre prim.series	Al(OH)3	2+1	1	1	25	no	no
222	during prim.series	Al(OH)3	2+1	1	1	76	no	no
222	post prim.series	Al(OH)3	2+1	8	1	1475	no	no
222	pre booster	Al(OH)3	2+1	1	1	130	no	no
222	post booster	Al(OH)3	2+1	128	1	5053	no	no
223	pre prim.series	AlPO4	3+1	1	1	25	no	no
223	during prim.series	AlPO4	3+1	missing	missing	missing	no	no
223	extra during prim.series (only 3+1)	AlPO4	3+1	missing	missing	missing	no	no
223	post prim.series	AlPO4	3+1	1	1	2689	no	no
223	pre booster	AlPO4	3+1	1	1	161	no	no
223	post booster	AlPO4	3+1	128	1	missing	no	no
224	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
224	during prim.series	Al(OH)3	3+1	1	1	130	no	no
224	extra during prim.series (only 3+1)	Al(OH)3	3+1	4	1	1598	no	no
224	post prim.series	Al(OH)3	3+1	1	1	1728	no	no
224	pre booster	Al(OH)3	3+1	1	1	2112	no	no
224	post booster	Al(OH)3	3+1	missing	missing	missing	no	no

UTN	Blood Sample	Adjuvantia	Schedule	P1.1,4	H1.5	OMV_ELISA	Exclusion for prot.analyses	Exclusion for ITT.analyses
225	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
225	during prim.series	Al(OH)3	3+1	1	1	290	no	no
225	extra during prim.series (only 3+1)	Al(OH)3	3+1	1	1	1107	no	no
225	post prim.series	Al(OH)3	3+1	64	1	8644	no	no
225	pre booster	Al(OH)3	3+1	2	1	2620	no	no
225	post booster	Al(OH)3	3+1	32	1	6624	no	no
229	pre prim.series	AlPO4	3+1	1	1	25	no	no
229	during prim.series	AlPO4	3+1	1	1	158	no	no
229	extra during prim.series (only 3+1)	AlPO4	3+1	1	1	1054	no	no
229	post prim.series	AlPO4	3+1	1	1	1843	no	no
229	pre booster	AlPO4	3+1	1	1	402	no	no
229	post booster	AlPO4	3+1	512	1	23454	no	no
230	pre prim.series	Al(OH)3	2+1	1	1	25	no	no
230	during prim.series	Al(OH)3	2+1	1	1	96	no	no
230	post prim.series	Al(OH)3	2+1	16	1	2382	no	no
230	pre booster	Al(OH)3	2+1	1	1	165	no	no
230	post booster	Al(OH)3	2+1	128	1	10221	no	no
231	pre prim.series	AlPO4	2+1	1	1	25	no	no
231	during prim.series	AlPO4	2+1	1	1	244	no	no
231	post prim.series	AlPO4	2+1	2	1	1845	no	no
231	pre booster	AlPO4	2+1	1	1	386	no	no
231	post booster	AlPO4	2+1	32	1	500	no	no
232	pre prim.series	Al(OH)3	2+1	1	1	39	no	no
232	during prim.series	Al(OH)3	2+1	1	1	160	no	no
232	post prim.series	Al(OH)3	2+1	2	1	1389	no	no
232	pre booster	Al(OH)3	2+1	1	1	340	no	no
232	post booster	Al(OH)3	2+1	64	1	7926	no	no
236	pre prim.series	Al(OH)3	3+1	1	1	71	no	no
236	during prim.series	Al(OH)3	3+1	1	1	158	no	no
236	extra during prim.series (only 3+1)	Al(OH)3	3+1	2	1	1765	no	no
236	post prim.series	Al(OH)3	3+1	1	1	1329	no	no
236	pre booster	Al(OH)3	3+1	1	1	165	no	no
236	post booster	Al(OH)3	3+1	16	1	3527	no	no
237	pre prim.series	AlPO4	2+1	1	1	25	no	no
237	during prim.series	AlPO4	2+1	1	1	88	no	no
237	post prim.series	AlPO4	2+1	4	1	2487	no	no
237	pre booster	AlPO4	2+1	1	1	143	no	no
237	post booster	AlPO4	2+1	32	1	6951	no	no
238	pre prim.series	AlPO4	3+1	1	1	25	no	no
238	during prim.series	AlPO4	3+1	1	1	277	no	no
238	extra during prim.series (only 3+1)	AlPO4	3+1	16	1	4337	no	no
238	post prim.series	AlPO4	3+1	8	1	6968	no	no
238	pre booster	AlPO4	3+1	1	1	1147	no	no
238	post booster	AlPO4	3+1	32	1	12494	no	no
239	pre prim.series	AlPO4	2+1	1	1	25	no	no
239	during prim.series	AlPO4	2+1	1	1	413	no	no
239	post prim.series	AlPO4	2+1	8	1	3267	no	no
239	pre booster	AlPO4	2+1	1	1	472	no	no
239	post booster	AlPO4	2+1	16	missing	missing	no	no

UTN	Blood Sample	Adjuvantia	Schedule	P1.1,4	H1.5	OMV_ELISA	Exclusion for prot.analyses	Exclusion for ITT.analyses
240	pre prim.series	Al(OH)3	3+1	1	1	57	no	no
240	during prim.series	Al(OH)3	3+1	1	1	2193	no	no
240	extra during prim.series (only 3+1)	Al(OH)3	3+1	missing	missing	missing	no	no
240	post prim.series	Al(OH)3	3+1	1	1	2791	no	no
240	pre booster	Al(OH)3	3+1	missing	missing	missing	no	no
240	post booster	Al(OH)3	3+1	2	1	4032	no	no
243	pre prim.series	Al(OH)3	3+1	1	1	44	no	no
243	during prim.series	Al(OH)3	3+1	1	1	165	no	no
243	extra during prim.series (only 3+1)	Al(OH)3	3+1	1	1	369	no	no
243	post prim.series	Al(OH)3	3+1	1	1	1911	no	no
243	pre booster	Al(OH)3	3+1	1	1	79	no	no
243	post booster	Al(OH)3	3+1	64	1	9456	no	no
244	pre prim.series	AlPO4	3+1	1	1	25	no	no
244	during prim.series	AlPO4	3+1	1	1	457	no	no
244	extra during prim.series (only 3+1)	AlPO4	3+1	8	1	4794	no	no
244	post prim.series	AlPO4	3+1	missing	missing	missing	no	no
244	pre booster	AlPO4	3+1	1	1	736	no	no
244	post booster	AlPO4	3+1	64	1	13369	no	no
245	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
245	during prim.series	Al(OH)3	3+1	1	1	151	no	no
245	extra during prim.series (only 3+1)	Al(OH)3	3+1	1	1	1242	no	no
245	post prim.series	Al(OH)3	3+1	4	1	3762	no	no
245	pre booster	Al(OH)3	3+1	1	1	346	no	no
245	post booster	Al(OH)3	3+1	32	1	5485	no	no
246	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
246	during prim.series	Al(OH)3	3+1	1	1	187	no	no
246	extra during prim.series (only 3+1)	Al(OH)3	3+1	1	1	752	no	no
246	post prim.series	Al(OH)3	3+1	2	1	2152	no	no
246	pre booster	Al(OH)3	3+1	1	1	508	no	no
246	post booster	Al(OH)3	3+1	64	1	7073	no	no
250	pre prim.series	AlPO4	3+1	1	1	25	no	no
250	during prim.series	AlPO4	3+1	1	1	587	no	no
250	extra during prim.series (only 3+1)	AlPO4	3+1	2	1	815	no	no
250	post prim.series	AlPO4	3+1	8	1	3993	no	no
250	pre booster	AlPO4	3+1	1	1	162	no	no
250	post booster	AlPO4	3+1	64	1	9224	no	no
251	pre prim.series	Al(OH)3	2+1	1	1	25	no	no
251	during prim.series	Al(OH)3	2+1	1	1	99	no	no
251	post prim.series	Al(OH)3	2+1	1	1	775	no	no
251	pre booster	Al(OH)3	2+1	1	1	196	no	no
251	post booster	Al(OH)3	2+1	16	1	7704	no	no
252	pre prim.series	AlPO4	2+1	1	1	64	no	no
252	during prim.series	AlPO4	2+1	1	1	570	no	no
252	post prim.series	AlPO4	2+1	32	1	7240	no	no
252	pre booster	AlPO4	2+1	1	1	996	no	no
252	post booster	AlPO4	2+1	128	1	10246	no	no

UTN	Blood Sample	Adjuvantia	Schedule	P1.1,4	H1.5	OMV_ELISA	Exclusion for prot.analyses	Exclusion for ITT.analyses
253	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
253	during prim.series	Al(OH)3	3+1	1	1	333	no	no
253	extra during prim.series (only 3+1)	Al(OH)3	3+1	4	1	844	no	no
253	post prim.series	Al(OH)3	3+1	64	1	9499	no	no
253	pre booster	Al(OH)3	3+1	1	1	413	no	no
253	post booster	Al(OH)3	3+1	32	1	20487	no	no
254	pre prim.series	AlPO4	2+1	1	1	25	no	no
254	during prim.series	AlPO4	2+1	1	1	152	no	no
254	post prim.series	AlPO4	2+1	8	1	5789	no	no
254	pre booster	AlPO4	2+1	1	1	932	no	no
254	post booster	AlPO4	2+1	16	1	11337	no	no
255	pre prim.series	AlPO4	2+1	1	1	25	no	no
255	during prim.series	AlPO4	2+1	1	1	152	no	no
255	post prim.series	AlPO4	2+1	8	1	8532	no	no
255	pre booster	AlPO4	2+1	1	1	649	no	no
255	post booster	AlPO4	2+1	16	1	7650	no	no
256	pre prim.series	Al(OH)3	3+1	1	1	93	no	no
256	during prim.series	Al(OH)3	3+1	1	1	249	no	no
256	extra during prim.series (only 3+1)	Al(OH)3	3+1	1	1	1422	no	no
256	post prim.series	Al(OH)3	3+1	1	1	1856	no	no
256	pre booster	Al(OH)3	3+1	1	1	123	no	no
256	post booster	Al(OH)3	3+1	4	1	2718	no	no
257	pre prim.series	Al(OH)3	2+1	1	missing	missing	no	no
257	during prim.series	Al(OH)3	2+1	1	1	170	no	no
257	post prim.series	Al(OH)3	2+1	16	1	2584	yes	no
257	pre booster	Al(OH)3	2+1	1	1	245	yes	no
257	post booster	Al(OH)3	2+1	32	1	6605	yes	no
258	pre prim.series	AlPO4	3+1	1	1	25	no	no
258	during prim.series	AlPO4	3+1	1	1	654	no	no
258	extra during prim.series (only 3+1)	AlPO4	3+1	32	1	5090	no	no
258	post prim.series	AlPO4	3+1	64	1	10235	no	no
258	pre booster	AlPO4	3+1	8	1	2285	no	no
258	post booster	AlPO4	3+1	512	1	19279	no	no
259	pre prim.series	AlPO4	2+1	1	1	25	no	no
259	during prim.series	AlPO4	2+1	1	1	47	no	no
259	post prim.series	AlPO4	2+1	1	1	824	no	no
259	pre booster	AlPO4	2+1	1	1	120	no	no
259	post booster	AlPO4	2+1	64	1	9834	no	no
260	pre prim.series	Al(OH)3	2+1	1	1	25	no	no
260	during prim.series	Al(OH)3	2+1	1	1	152	no	no
260	post prim.series	Al(OH)3	2+1	16	1	8761	no	no
260	pre booster	Al(OH)3	2+1	1	1	444	no	no
260	post booster	Al(OH)3	2+1	64	1	17064	no	no
263	pre prim.series	AlPO4	3+1	1	1	25	no	no
263	during prim.series	AlPO4	3+1	1	1	240	no	no
263	extra during prim.series (only 3+1)	AlPO4	3+1	2	1	2201	no	no
263	post prim.series	AlPO4	3+1	16	1	4079	no	no
263	pre booster	AlPO4	3+1	1	1	436	yes	no
263	post booster	AlPO4	3+1	missing	missing	missing	yes	no

UTN	Blood Sample	Adjuvantia	Schedule	P1.1,4	H1.5	OMV_ELISA	Exclusion for prot.analyses	Exclusion for ITT.analyses
266	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
266	during prim.series	Al(OH)3	3+1	1	1	864	no	no
266	extra during prim.series (only 3+1)	Al(OH)3	3+1	16	1	4427	no	no
266	post prim.series	Al(OH)3	3+1	16	1	5602	no	no
266	pre booster	Al(OH)3	3+1	4	1	1457	no	no
266	post booster	Al(OH)3	3+1	64	1	10990	no	no
267	pre prim.series	AlPO4	3+1	1	1	25	no	no
267	during prim.series	AlPO4	3+1	1	1	253	no	no
267	extra during prim.series (only 3+1)	AlPO4	3+1	32	1	4192	no	no
267	post prim.series	AlPO4	3+1	8	1	2742	no	no
267	pre booster	AlPO4	3+1	1	1	182	no	no
267	post booster	AlPO4	3+1	32	1	7743	no	no
269	pre prim.series	Al(OH)3	2+1	1	1	25	no	no
269	during prim.series	Al(OH)3	2+1	1	1	58	no	no
269	post prim.series	Al(OH)3	2+1	1	1	939	no	no
269	pre booster	Al(OH)3	2+1	1	1	74	no	no
269	post booster	Al(OH)3	2+1	2	1	773	no	no
270	pre prim.series	AlPO4	2+1	1	1	25	no	no
270	during prim.series	AlPO4	2+1	1	1	82	no	no
270	post prim.series	AlPO4	2+1	8	1	missing	no	no
270	pre booster	AlPO4	2+1	1	1	268	no	no
270	post booster	AlPO4	2+1	8	1	3246	no	no
271	pre prim.series	AlPO4	2+1	1	1	25	no	no
271	during prim.series	AlPO4	2+1	1	1	88	no	no
271	post prim.series	AlPO4	2+1	64	1	5299	no	no
271	pre booster	AlPO4	2+1	1	1	877	no	no
271	post booster	AlPO4	2+1	missing	missing	missing	no	no
272	pre prim.series	AlPO4	3+1	1	1	25	no	no
272	during prim.series	AlPO4	3+1	1	1	246	no	no
272	extra during prim.series (only 3+1)	AlPO4	3+1	8	1	4016	no	no
272	post prim.series	AlPO4	3+1	4	1	4120	no	no
272	pre booster	AlPO4	3+1	1	1	583	no	no
272	post booster	AlPO4	3+1	128	1	17416	no	no
273	pre prim.series	AlPO4	2+1	1	1	25	no	no
273	during prim.series	AlPO4	2+1	1	1	259	no	no
273	post prim.series	AlPO4	2+1	16	1	4162	no	no
273	pre booster	AlPO4	2+1	1	1	723	no	no
273	post booster	AlPO4	2+1	missing	missing	missing	no	no
274	pre prim.series	AlPO4	3+1	1	1	25	no	no
274	during prim.series	AlPO4	3+1	1	1	168	no	no
274	extra during prim.series (only 3+1)	AlPO4	3+1	8	1	3512	no	no
274	post prim.series	AlPO4	3+1	2	1	3900	no	no
274	pre booster	AlPO4	3+1	1	1	561	no	no
274	post booster	AlPO4	3+1	4	1	2334	no	no
275	pre prim.series	AlPO4	2+1	1	1	25	no	no
275	during prim.series	AlPO4	2+1	1	1	323	no	no
275	post prim.series	AlPO4	2+1	32	1	2985	no	no
275	pre booster	AlPO4	2+1	2	1	726	no	no
275	post booster	AlPO4	2+1	16	1	5028	no	no

UTN	Blood Sample	Adjuvantia	Schedule	P1.1,4	H1.5	OMV_ELISA	Exclusion for prot.analyses	Exclusion for ITT.analyses
276	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
276	during prim.series	Al(OH)3	3+1	1	1	94	no	no
276	extra during prim.series (only 3+1)	Al(OH)3	3+1	1	1	691	no	no
276	post prim.series	Al(OH)3	3+1	1	1	792	no	no
276	pre booster	Al(OH)3	3+1	1	1	290	no	no
276	post booster	Al(OH)3	3+1	missing	missing	missing	no	no
277	pre prim.series	AlPO4	3+1	1	1	60	no	no
277	during prim.series	AlPO4	3+1	1	1	214	no	no
277	extra during prim.series (only 3+1)	AlPO4	3+1	1	1	3027	no	no
277	post prim.series	AlPO4	3+1	2	1	9231	no	no
277	pre booster	AlPO4	3+1	missing	missing	missing	no	no
277	post booster	AlPO4	3+1	missing	missing	missing	no	no
278	pre prim.series	Al(OH)3	2+1	1	1	25	no	no
278	during prim.series	Al(OH)3	2+1	1	1	131	no	no
278	post prim.series	Al(OH)3	2+1	2	1	489	no	no
278	pre booster	Al(OH)3	2+1	1	1	63	no	no
278	post booster	Al(OH)3	2+1	64	1	8634	no	no
279	pre prim.series	Al(OH)3	2+1	1	1	25	no	no
279	during prim.series	Al(OH)3	2+1	1	1	406	no	no
279	post prim.series	Al(OH)3	2+1	2	1	7706	no	no
279	pre booster	Al(OH)3	2+1	1	1	291	no	no
279	post booster	Al(OH)3	2+1	missing	missing	missing	no	no
281	pre prim.series	AlPO4	2+1	1	1	25	no	no
281	during prim.series	AlPO4	2+1	1	1	264	no	no
281	post prim.series	AlPO4	2+1	8	1	3566	no	no
281	pre booster	AlPO4	2+1	1	1	376	no	no
281	post booster	AlPO4	2+1	16	1	4914	no	no
282	pre prim.series	Al(OH)3	3+1	1	1	25	no	no
282	during prim.series	Al(OH)3	3+1	1	1	211	no	no
282	extra during prim.series (only 3+1)	Al(OH)3	3+1	1	1	1488	no	no
282	post prim.series	Al(OH)3	3+1	128	1	2520	no	no
282	pre booster	Al(OH)3	3+1	32	1	449	no	no
282	post booster	Al(OH)3	3+1	64	1	2818	no	no
283	pre prim.series	AlPO4	2+1	1	1	25	no	no
283	during prim.series	AlPO4	2+1	1	1	130	no	no
283	post prim.series	AlPO4	2+1	4	1	3669	no	no
283	pre booster	AlPO4	2+1	1	1	280	no	no
283	post booster	AlPO4	2+1	16	1	5105	no	no
285	pre prim.series	Al(OH)3	2+1	1	1	25	no	no
285	during prim.series	Al(OH)3	2+1	1	1	192	no	no
285	post prim.series	Al(OH)3	2+1	8	1	2034	no	no
285	pre booster	Al(OH)3	2+1	1	1	392	no	no
285	post booster	Al(OH)3	2+1	16	1	5634	no	no
287	pre prim.series	AlPO4	3+1	1	1	25	no	no
287	during prim.series	AlPO4	3+1	missing	missing	missing	no	no
287	extra during prim.series (only 3+1)	AlPO4	3+1	missing	missing	missing	no	no
287	post prim.series	AlPO4	3+1	missing	missing	missing	no	no
287	pre booster	AlPO4	3+1	missing	missing	missing	no	no
287	post booster	AlPO4	3+1	missing	missing	missing	no	no

UTN	Blood Sample	Adjuvantia	Schedule	P1.1,4	H1.5	OMV_ELISA	Exclusion for prot.analyses	Exclusion for ITT.analyses
288	pre prim.series	AlPO4	3+1	1	1	25	no	no
288	during prim.series	AlPO4	3+1	1	1	251	no	no
288	extra during prim.series (only 3+1)	AlPO4	3+1	64	1	4793	no	no
288	post prim.series	AlPO4	3+1	16	1	2693	no	no
288	pre booster	AlPO4	3+1	1	1	826	no	no
288	post booster	AlPO4	3+1	missing	missing	missing	no	no
290	pre prim.series	AlPO4	3+1	1	1	25	no	no
290	during prim.series	AlPO4	3+1	1	1	357	no	no
290	extra during prim.series (only 3+1)	AlPO4	3+1	16	1	3851	no	no
290	post prim.series	AlPO4	3+1	4	1	2528	no	no
290	pre booster	AlPO4	3+1	1	1	576	no	no
290	post booster	AlPO4	3+1	16	1	2147	no	no
291	pre prim.series	Al(OH)3	2+1	1	1	25	no	no
291	during prim.series	Al(OH)3	2+1	1	1	290	no	no
291	post prim.series	Al(OH)3	2+1	8	1	2687	no	no
291	pre booster	Al(OH)3	2+1	2	1	383	no	no
291	post booster	Al(OH)3	2+1	128	1	9040	no	no