Clinical trial results:
Assessment of post booster antibody responses in UK infants given a reduced priming schedule of meningococcal serogroup B and 13 valent pneumococcal conjugate vaccines

Summary

EudraCT number	2015-000817-32
Trial protocol	GB
Global end of trial date	01 June 2021

Results information

Result version number	v1 (current)
This version publication date	11 February 2022
First version publication date	11 February 2022

Trial information

Trial identification

Sponsor protocol code	2015/03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02482636
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford, Clinical Trials and Research Governance (CTRG)
Sponsor organisation address	Boundary Brook House, Oxford, United Kingdom, OX3 7GB
Public contact	Oxford Vaccine Group, University of Oxford, 44 1865611400, info@ovg.ox.ac.uk
Scientific contact	Oxford Vaccine Group, University of Oxford, 44 1865611400, info@ovg.ox.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 October 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Technical - To assess geometric mean concentrations (GMC) of serotype specific pneumococcal antibody responses measured in the blood sample taken after the final infant vaccinations, usually at 13 months of age, following two or three doses of 13 valent pneumococcal conjugate vaccine (PCV13) at 3 and 12 months or at 2, 4, and 12 months of age

Lay - To assess how much antibody can be detected in the blood sample taken a month after the final infant vaccinations, usually taken at 13 months of age, after two or three doses of the routinely used pneumococcal vaccine, called Prevenar13.

Protection of trial subjects:

The blood sampling may be uncomfortable but the clinical study staff are very experienced at drawing blood samples and not more than two attempts will be made. Finger or heel (in infants) prick may be attempted if venepuncture proves difficult.
For infants under 3 months of age, oral sucrose solution (such as Sweet-Ease®) may be offered to minimise discomfort (subject to local practice/preference). The parents will be asked if she/he wishes to feed the infant during the procedure to minimise discomfort. An anaesthetic cream (such as EMLA®, Denela or Ametop®), cryogenic spray may be offered for infants one month or older. As per JCVI recommendation, parents will be advised to give their baby three doses of paracetamol (infant formula) prophylactically in the 24 hours after each primary MenB vaccination.
Any stress and discomfort is also reduced by using distraction techniques.
Every effort will be made to protect the participants' identity. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

Background therapy:

All participants receive:
Bexsero (MenB) at 2, 4 and 12 months of age
Infanrix/IPV/Hib at 2,3 and 4 month
MenC conjugate vaccination at 12 months given as the combined Hib/MenC conjugate vaccine, Menitorix
Rotarix orally at 2 and 3 months
Infants may receive one of 2 licensed MMR vaccines depending on local availability and parental consent: Priorix or MMR®II (live attenuated vaccines that protects against measles, mumps and rubella) at 13 months
Infant doses of paracetamol are also provided to families to give following the MenB vaccinations at 2 and 4 months of age.

Evidence for comparator:

The Department of Heath JCVI has recommended that the Bexsero vaccine, designed to protect against meningococcal B and other serogroups not covered by the MenC conjugate vaccine, may be cost effective if given as a 2+1 schedule and if the current MenC conjugate vaccine dose given at 3 months is removed. There are no published immunogenicity data for Bexsero when given at 2, 4 and 12 months (the ages at which a 2+1 schedule would be implemented in the UK) and with concomitant Infanrix/IPV/Hib. The MenC conjugate vaccine currently given for primary immunisation at 3 months of age is a tetanus based conjugate which was shown to enhance the response to the Hib component of Infanrix/IPV/Hib. Removal of MenC conjugate vaccine from the infant schedule would raise uncertainty as to the adequacy of the Hib response to Infanrix/IPV/Hib.
Another uncertainty about the 2+1 Bexsero schedule is that it would be given at the same appointments currently used for PCV13 (13 valent pneumococcal conjugate vaccine), thus necessitating 3 injections at the first and third infant visits and just one injection at the second. Past experience has shown that there is reluctance among parents, and some health professionals, to give 3 injections at one visit to a very young infant.
An option is to reduce PCV13 to a 1+1 schedule, giving a single priming dose at 3 months. Though the

immunogenicity of one dose in infancy will be lower than two doses, a prior study with PCV9 showed higher booster responses with fewer priming doses. With the rapidly reducing incidence of PCV13 disease in young children in the UK, and highly effective herd protection, the potentially increased risk of an invasive pneumococcal infection between 4 and 12 months in a child who has only received one dose of PCV13 instead of two will be very low and unlikely to outweigh the cost savings from reducing the number of PCV13 doses from 3 to 2.
This study includes two arms defined by their PCV13 schedule as 1+1 or 2+1.

Actual start date of recruitment	22 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 213
Worldwide total number of subjects	213
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	213
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Healthy infants aged up to 13 weeks, due to receive their primary vaccinations as per the UK immunisation schedule with the exception of PCV13, were recruited via child health database mailouts in Oxfordshire and via GP surgeries in Gloucestershire and Hertfordshire, and were assesses for eligibility between 22/09/2015 and 1/11/2017.

Pre-assignment

Screening details:

376 infants were assessed for eligibility and 163 infants were excluded before randomisation. Infants with bleeding disorders, at risk of invasive pneumococcal disease, or with a history of allergic reactions to any of the vaccine components were excluded. 213 eligible infants were enrolled.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1 (2+1 PCV13)

Arm description:

PCV13 schedule 2+1; both arms receive Bexsero 2+1 and Infanrix/IPV/Hib with one MenC conjugate vaccination at 12 months given as the combined Hib/MenC conjugate vaccine, Menitorix

Arm type	Active comparator
Investigational medicinal product name	PCV13
Investigational medicinal product code	
Other name	Prevenar13
Pharmaceutical forms	Solution for injection
Routes of administration	Injection , Intramuscular use

Dosage and administration details:

13 valent pneumococcal conjugate vaccine (PCV13) IM 0.5ml at 2, 4 and 12 months

Investigational medicinal product name	DTaP/IPV/Hib
Investigational medicinal product code	
Other name	Infanrix-IPV-Hib
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Injection , Intramuscular use

Dosage and administration details:

DTaP/IPV/Hib vaccine IM 0.5ml at 2, 3 and 4 months

Investigational medicinal product name	Rotavirus vaccine
Investigational medicinal product code	
Other name	Rotarix
Pharmaceutical forms	Oral suspension in pre-filled oral applicator
Routes of administration	Oral use

Dosage and administration details:

Rotavirus vaccine oral 1.5ml at 2 and 3 months

Investigational medicinal product name	4CMenB
Investigational medicinal product code	
Other name	Bexsero
Pharmaceutical forms	Solution for injection
Routes of administration	Injection , Intramuscular use

Dosage and administration details: 4-component Meningococcal B (4CMenB) vaccine IM 0.5ml given at 2, 4 and 12 months	
Investigational medicinal product name	Meningococcal C/Hib vaccine
Investigational medicinal product code	
Other name	Menitorix
Pharmaceutical forms	Powder and solvent for solution for injection in cartridge
Routes of administration	Injection , Intramuscular use
Dosage and administration details: Meningococcal C/Hib vaccine IM 0.5ml at 12 months	
Investigational medicinal product name	Measles/Mumps/Rubella (MMR) vaccine
Investigational medicinal product code	
Other name	Priorix or MMR II
Pharmaceutical forms	Powder and solvent for solution for injection in pre-filled syringe
Routes of administration	Injection , Intramuscular use
Dosage and administration details: Measles/Mumps/Rubella (MMR) vaccine IM 0.5ml at 13 months - Priorix or MMR II vaccine - depending on local availability and parental consent.	
Arm title	Group 2 (1+1 PCV13)
Arm description: PCV13 schedule 1+1; both arms receive Bexsero and Infanrix/IPV/Hib with one MenC conjugate vaccination at 12 months given as the combined Hib/MenC conjugate vaccine, Menitorix	
Arm type	Active comparator
Investigational medicinal product name	PCV13
Investigational medicinal product code	
Other name	Prevenar13
Pharmaceutical forms	Solution for injection
Routes of administration	Injection , Intramuscular use
Dosage and administration details: 13 valent pneumococcal conjugate vaccine (PCV13) IM 0.5ml at 3 and 12 months (instead of current routine schedule of 2,4 and 12 months)	
Investigational medicinal product name	DTaP/IPV/Hib
Investigational medicinal product code	
Other name	Infanrix-IPV-Hib
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Injection , Intramuscular use
Dosage and administration details: DTaP/IPV/Hib vaccine IM 0.5ml at 2, 3 and 4 months	
Investigational medicinal product name	Rotavirus vaccine
Investigational medicinal product code	
Other name	Rotarix
Pharmaceutical forms	Oral suspension in pre-filled oral applicator
Routes of administration	Oral use
Dosage and administration details: Rotavirus vaccine oral 1.5ml at 2 and 3 months	
Investigational medicinal product name	4CMenB
Investigational medicinal product code	
Other name	Bexsero
Pharmaceutical forms	Solution for injection
Routes of administration	Injection , Intramuscular use
Dosage and administration details: 4-component Meningococcal B (4CMenB) vaccine IM 0.5ml given at 2, 4 and 12 months	

Investigational medicinal product name	Meningococcal C/Hib vaccine
Investigational medicinal product code	
Other name	Menitorix
Pharmaceutical forms	Powder and solvent for solution for injection in cartridge
Routes of administration	Injection , Intramuscular use

Dosage and administration details:

Meningococcal C/Hib vaccine IM 0.5ml at 12 months

Investigational medicinal product name	Measles/Mumps/Rubella (MMR) vaccine
Investigational medicinal product code	
Other name	Priorix or MMR II
Pharmaceutical forms	Powder and solvent for solution for injection in pre-filled syringe
Routes of administration	Injection , Intramuscular use

Dosage and administration details:

Measles/Mumps/Rubella (MMR) vaccine IM 0.5ml at 13 months - Priorix or MMR II vaccine - depending on local availability and parental consent.

Number of subjects in period 1	Group 1 (2+1 PCV13)	Group 2 (1+1 PCV13)
Started	106	107
Completed	101	96
Not completed	5	11
Consent withdrawn by subject	5	11

Baseline characteristics

Reporting groups	
Reporting group title	Group 1 (2+1 PCV13)
Reporting group description:	
PCV13 schedule 2+1; both arms receive Bexsero 2+1 and Infanrix/IPV/Hib with one MenC conjugate vaccination at 12 months given as the combined Hib/MenC conjugate vaccine, Menitorix	
Reporting group title	Group 2 (1+1 PCV13)
Reporting group description:	
PCV13 schedule 1+1; both arms receive Bexsero and Infanrix/IPV/Hib with one MenC conjugate vaccination at 12 months given as the combined Hib/MenC conjugate vaccine, Menitorix	

Reporting group values	Group 1 (2+1 PCV13)	Group 2 (1+1 PCV13)	Total
Number of subjects	106	107	213
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	106	107	213
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Age at first PCV dose			
Units: days			
median	60	91	
full range (min-max)	55 to 88	84 to 114	-
Gender categorical			
Units: Subjects			
Female	46	58	104
Male	60	49	109
Maternal vaccination			
Units: Subjects			
Yes	76	86	162
No	23	18	41
Not known	7	3	10
Age at booster			
Units: day			
median	371	371	
full range (min-max)	359 to 406	366 to 416	-
Interval from last primary PCV dose to blood sample			
Units: day			
median	30	62	
full range (min-max)	21 to 57	50 to 92	-

End points

End points reporting groups

Reporting group title	Group 1 (2+1 PCV13)
Reporting group description:	
PCV13 schedule 2+1; both arms receive Bexsero 2+1 and Infanrix/IPV/Hib with one MenC conjugate vaccination at 12 months given as the combined Hib/MenC conjugate vaccine, Menitorix	
Reporting group title	Group 2 (1+1 PCV13)
Reporting group description:	
PCV13 schedule 1+1; both arms receive Bexsero and Infanrix/IPV/Hib with one MenC conjugate vaccination at 12 months given as the combined Hib/MenC conjugate vaccine, Menitorix	

Primary: Pneumococcal serotype specific GMCs - post booster

End point title	Pneumococcal serotype specific GMCs - post booster
End point description:	
Pneumococcal serotype specific geometric mean concentrations (GMCs) in blood samples following the completion of either a 2, 4 and 12 month schedule of PCV13 vaccination, or only 3 and 12 month PCV13 vaccination	
End point type	Primary
End point timeframe:	
13 months of age	

End point values	Group 1 (2+1 PCV13)	Group 2 (1+1 PCV13)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	86		
Units: concentration µg/mL				
geometric mean (confidence interval 95%)				
serotype 1	3.07 (2.58 to 3.64)	8.92 (7.42 to 10.73)		
serotype 3	0.61 (0.51 to 0.74)	0.62 (0.52 to 0.74)		
serotype 4	2.55 (2.15 to 3.04)	3.43 (2.86 to 4.12)		
serotype 5	1.74 (1.49 to 2.03)	2.11 (1.81 to 2.45)		
serotype 6A	8.62 (7.29 to 10.21)	6.36 (5.34 to 7.58)		
serotype 6B	6.19 (5.10 to 7.50)	2.39 (1.94 to 2.94)		
serotype 7F	3.98 (3.42 to 4.62)	3.36 (2.93 to 3.86)		
serotype 9V	2.34 (2.00 to 2.73)	2.50 (2.16 to 2.88)		
serotype 14	10.49 (8.84 to 12.44)	16.9 (13.54 to 21.08)		
serotype 18C	1.98 (1.70 to 2.30)	1.63 (1.42 to 1.87)		
serotype 19A	8.38 (7.17 to 9.80)	8.83 (7.4 to 10.52)		

serotype 19F	11.12 (9.46 to 13.07)	14.76 (12.54 to 17.37)		
serotype 23F	2.87 (2.38 to 3.46)	1.72 (1.44 to 2.05)		

Statistical analyses

Statistical analysis title	Adjusted p-value
Statistical analysis description:	
Adjusted in regression for sex and interval to blood	
Comparison groups	Group 1 (2+1 PCV13) v Group 2 (1+1 PCV13)
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [1]
Method	Regression, Logistic

Notes:

[1] - Serotype (S) 1: <0.0001; S3: 0.57; S4: 0.047; S5: 0.20; S6A: 0.002; S6B: <0.0001; S7F: 0.059; S9V: 0.85; S14: 0.002; S18C: 0.017; S19A: 0.98; S19F: 0.035; S23F: <0.0001.

Secondary: GMC of serotype specific pneumococcal antibody responses and proportions ≥ 0.35 µg/mL - post primary vaccination

End point title	GMC of serotype specific pneumococcal antibody responses and proportions ≥ 0.35 µg/mL - post primary vaccination
End point description:	
assess GMC of serotype specific pneumococcal antibody responses and proportions ≥ 0.35 µg/mL measured in the blood samples taken at 5 months of age, following one or two doses of 13 valent pneumococcal conjugate vaccine (PCV13) at 3 months or at 2 and 4 months of age	
End point type	Secondary
End point timeframe:	
5 months of age	

End point values	Group 1 (2+1 PCV13)	Group 2 (1+1 PCV13)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	102		
Units: percentage IgG concentr. ≥ 0.35 µg/mL				
geometric mean (confidence interval 95%)				
serotype 1	95.9 (89.8 to 98.9)	74.0 (64.3 to 82.3)		
serotype 3	34.5 (24.5 to 45.7)	39.5 (29.2 to 50.7)		
serotype 4	92.8 (85.7 to 97.0)	64.4 (54.2 to 73.6)		
serotype 5	89.6 (81.7 to 94.9)	39.2 (29.7 to 49.4)		
serotype 6A	84.4 (75.5 to 91.0)	12.9 (7.0 to 21.0)		
serotype 6B	34.0 (24.7 to 44.3)	1.0 (0 to 5.3)		

serotype 7F	97.9 (92.7 to 99.7)	86.1 (77.8 to 92.2)		
serotype 9V	79.4 (70.0 to 86.9)	16.8 (10.1 to 25.6)		
serotype 14	94.8 (88.4 to 98.3)	86.3 (78.0 to 92.3)		
serotype 18C	81.4 (72.3 to 88.6)	33.7 (24.6 to 43.8)		
serotype 19A	91.8 (84.4 to 96.4)	44.1 (34.3 to 54.3)		
serotype 19F	100 (96.3 to 100)	79.2 (70.0 to 86.6)		
serotype 23F	57.7 (47.3 to 67.7)	5.9 (2.2 to 12.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: GMC of serotype specific pneumococcal antibody responses and proportions ≥ 0.35 µg/mL - post booster

End point title	GMC of serotype specific pneumococcal antibody responses and proportions ≥ 0.35 µg/mL - post booster

End point description:

assess GMC of serotype specific pneumococcal antibody responses and proportions ≥ 0.35 µg/mL measured in the blood samples taken at 13 months of age, following one or two doses of 13 valent pneumococcal conjugate vaccine (PCV13) at 3 months or at 2 and 4 months of age and a booster at 12 months of age

End point type	Secondary

End point timeframe:

13 months of age

End point values	Group 1 (2+1 PCV13)	Group 2 (1+1 PCV13)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	86		
Units: percentage IgG concentr. ≥ 0.35 µg/mL				
geometric mean (confidence interval 95%)				
serotype 1	100 (96.0 to 100)	100 (95.8 to 100)		
serotype 3	75.9 (65.5 to 84.4)	78.8 (68.6 to 86.9)		
serotype 4	98.9 (94.0 to 100)	100 (95.8 to 100)		
serotype 5	98.9 (94.0 to 100)	100 (95.8 to 100)		
serotype 6A	100 (96.0 to 100)	100 (95.8 to 100)		
serotype 6B	100 (96.0 to 100)	97.7 (91.9 to 99.7)		

serotype 7F	100 (96.0 to 100)	100 (95.8 to 100)		
serotype 9V	100 (96.0 to 100)	100 (95.8 to 100)		
serotype 14	100 (96.0 to 100)	100 (95.8 to 100)		
serotype 18C	100 (96.0 to 100)	100 (95.8 to 100)		
serotype 19A	100 (96.0 to 100)	100 (95.8 to 100)		
serotype 19F	100 (96.0 to 100)	100 (95.8 to 100)		
serotype 23F	100 (96.0 to 100)	95.3 (88.5 to 98.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: antibody responses to MenB vaccination: % hSBA titres ≥4 - post primary vaccination

End point title	antibody responses to MenB vaccination: % hSBA titres ≥4 - post primary vaccination

End point description:

antibody responses to MenB vaccination using proportions achieving hSBA titres ≥4 for the three main MenB vaccine antigen target strains, 5/99 (NadA), NZ98/254 (PorA) and 44/76-SL (fHbp) in the blood samples taken at 5 months of age

End point type	Secondary

End point timeframe:

5 months

End point values	Group 1 (2+1 PCV13)	Group 2 (1+1 PCV13)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	97		
Units: percentage hSBA titres ≥4				
geometric mean (confidence interval 95%)				
strain 5/99 (NadA)	100 (95.8 to 100)	100 (96.2 to 100)		
strain 44/76-SL (fHbp)	95.3 (88.5 to 98.7)	97.9 (92.7 to 99.7)		
strain NZ98/254 (PorA)	88.5 (79.9 to 94.3)	86.5 (78.0 to 92.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: antibody responses to MenB vaccination: % hSBA titres ≥4 - post booster

End point title	antibody responses to MenB vaccination: % hSBA titres ≥4 - post booster

End point description:

antibody responses to MenB vaccination using proportions achieving hSBA titres ≥4 for the three main MenB vaccine antigen target strains, 5/99 (NadA), NZ98/254 (PorA) and 44/76-SL (fHbp) in the blood samples taken at 13 months of age

End point type	Secondary

End point timeframe:

13 months of age

End point values	Group 1 (2+1 PCV13)	Group 2 (1+1 PCV13)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	80		
Units: percentage hSBA titres ≥4				
geometric mean (confidence interval 95%)				
strain 5/99 (NadA)	100 (95.4 to 100)	100 (95.4 to 100)		
strain 44/76-SL (fHbp)	92.4 (84.2 to 97.2)	93.8 (86.0 to 97.9)		
strain NZ98/254 (PorA)	88.6 (79.5 to 94.7)	92.1 (83.6 to 97.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: antibody responses to MenB vaccination: GMT - post primary vaccination

End point title	antibody responses to MenB vaccination: GMT - post primary vaccination

End point description:

antibody responses to MenB vaccination using GMTs for the three main MenB vaccine antigen target strains, 5/99 (NadA), NZ98/254 (PorA) and 44/76-SL (fHbp) in the blood samples taken at 5 months of age

End point type	Secondary

End point timeframe:

5 months of age

End point values	Group 1 (2+1 PCV13)	Group 2 (1+1 PCV13)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	97		
Units: titre				
geometric mean (confidence interval 95%)				
strain 5/99 (NadA)	528.6 (420.1 to 665.0)	587.3 (476.8 to 723.4)		
strain 44/76-SL (fHbp)	39.5 (29.8 to 52.3)	51.3 (41.9 to 62.8)		
strain NZ98/254 (PorA)	14.1 (10.4 to 19.1)	13.7 (10.4 to 18.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: antibody responses to MenB vaccination: GMT - post booster

End point title	antibody responses to MenB vaccination: GMT - post booster

End point description:

antibody responses to MenB vaccination using GMTs for the three main MenB vaccine antigen target strains, 5/99 (NadA), NZ98/254 (PorA) and 44/76-SL (fHbp) in the blood samples taken at 13 months of age

End point type	Secondary

End point timeframe:

13 months of age

End point values	Group 1 (2+1 PCV13)	Group 2 (1+1 PCV13)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	80		
Units: titre				
geometric mean (confidence interval 95%)				
strain 5/99 (NadA)	1454.5 (1054.5 to 2007.3)	1336.8 (1001.8 to 1784.0)		
strain 44/76-SL (fHbp)	34.0 (24.4 to 47.4)	44.5 (33.1 to 59.8)		
strain NZ98/254 (PorA)	26.6 (18.3 to 38.7)	28.7 (21.2 to 38.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: meningococcal serogroup C rSBA proportion titres ≥8 - post primary

vaccination	
End point title	meningococcal serogroup C rSBA proportion titres ≥8 - post primary vaccination
End point description:	
assess meningococcal serogroup C rSBA: proportion of infants with titres ≥8 from blood samples taken at 5 months of age	
End point type	Secondary
End point timeframe:	
5 months of age	

End point values	Group 1 (2+1 PCV13)	Group 2 (1+1 PCV13)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	95		
Units: percentage titres ≥8				
geometric mean (confidence interval 95%)	2.4 (0.3 to 8.3)	2.1 (0.3 to 7.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: meningococcal serogroup C rSBA proportion titres ≥8 - post booster	
End point title	meningococcal serogroup C rSBA proportion titres ≥8 - post booster
End point description:	
assess meningococcal serogroup C rSBA: proportion of infants with titres ≥8 from blood samples taken at 13 months of age	
End point type	Secondary
End point timeframe:	
13 months of age	

End point values	Group 1 (2+1 PCV13)	Group 2 (1+1 PCV13)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	78		
Units: percentage titres ≥8				
geometric mean (confidence interval 95%)				
MenC	98.7 (93.0 to 100)	97.4 (91.0 to 99.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: meningococcal serogroup C rSBA GMT - post primary vaccination

End point title	meningococcal serogroup C rSBA GMT - post primary vaccination

End point description:

assess meningococcal serogroup C rSBA GMTs from blood samples taken at 5 months of age

End point type	Secondary

End point timeframe:

5 months of age

End point values	Group 1 (2+1 PCV13)	Group 2 (1+1 PCV13)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	95		
Units: titre				
geometric mean (confidence interval 95%)				
MenC	2.2 (1.9 to 2.4)	2.2 (2.0 to 2.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: meningococcal serogroup C rSBA GMT - post booster

End point title	meningococcal serogroup C rSBA GMT - post booster

End point description:

assess meningococcal serogroup C rSBA GMTs from blood samples taken at 13 months of age

End point type	Secondary

End point timeframe:

13 months of age

End point values	Group 1 (2+1 PCV13)	Group 2 (1+1 PCV13)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	78		
Units: titre				
geometric mean (confidence interval 95%)				
MenC	888.3 (640.0 to 1232.8)	540.4 (404.1 to 722.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: antibody responses IgG GMC to Infanrix-IPV-Hib vaccine - post primary vaccination

End point title	antibody responses IgG GMC to Infanrix-IPV-Hib vaccine - post primary vaccination

End point description:

assess antibody responses, by IgG GMC to the tetanus and diphtheria components, as well as IgG GMCs against pertussis components (pertussis toxin (PT), pertactin (PRN), filamentous haemagglutinin (FHA) and fimbrial antigens (fims) 2 and 3), polyribosyl ribitol phosphate-Haemophilus influenzae type b (PRP-Hib) of Infanrix-IPV-Hib vaccine after three doses at 2, 3 and 4 months of age, from the blood sample taken at 5 months of age

End point type	Secondary

End point timeframe:

5 months of age

End point values	Group 1 (2+1 PCV13)	Group 2 (1+1 PCV13)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	84		
Units: IgG concentration				
geometric mean (confidence interval 95%)				
Anti-diphtheria toxoid IgG IU/ml	0.47 (0.40 to 0.55)	0.32 (0.27 to 0.38)		
Anti-tetanus toxoid IgG IU/ml	1.26 (1.08 to 1.46)	1.38 (1.21 to 1.57)		
Anti-PRP-Hib IgG µg/mL	1.01 (0.72 to 1.41)	0.71 (0.54 to 0.94)		
Anti-PT IgG IU/mL	28.94 (25.43 to 32.93)	26.32 (22.86 to 30.31)		
Anti-PRN IgG IU/mL	44.05 (35.72 to 54.31)	42.08 (34.58 to 51.21)		
Anti-FHA IgG IU/mL	61.78 (53.75 to 71.00)	58.35 (50.57 to 67.32)		
FIM 2 and 3 IgG U/mL	2.71 (2.15 to 3.42)	5.17 (3.93 to 6.80)		

Statistical analyses

No statistical analyses for this end point

Secondary: antibody responses IgG GMC to Infanrix-IPV-Hib vaccine - post booster

End point title	antibody responses IgG GMC to Infanrix-IPV-Hib vaccine - post booster

End point description:

assess antibody responses by IgG GMC to the tetanus and diphtheria components, as well as IgG GMCs against pertussis components (pertussis toxin (PT), pertactin (PRN), filamentous haemagglutinin (FHA) and fimbrial antigens (fims) 2 and 3), polyribosyl ribitol phosphate-Haemophilus influenzae type b (PRP-Hib) of Infanrix-IPV-Hib vaccine after three doses at 2, 3 and 4 months of age, from the blood sample

taken at 13 months of age

End point type	Secondary

End point timeframe:

13 months of age

End point values	Group 1 (2+1 PCV13)	Group 2 (1+1 PCV13)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	74		
Units: IgG concentration				
geometric mean (confidence interval 95%)				
Anti-diphtheria toxoid IgG IU/ml	0.68 (0.58 to 0.81)	0.58 (0.47 to 0.71)		
Anti-tetanus toxoid IgG IU/ml	4.37 (3.28 to 5.84)	3.88 (2.97 to 5.07)		
Anti-PRP-Hib IgG µg/mL	35.77 (26.77 to 47.80)	28.00 (22.00 to 35.64)		
Anti-PT IgG IU/mL	3.19 (2.56 to 3.98)	2.67 (2.16 to 3.28)		
Anti-PRN IgG IU/mL	5.42 (4.22 to 6.98)	3.99 (3.22 to 4.94)		
Anti-FHA IgG IU/mL	12.94 (9.99 to 16.76)	10.57 (8.57 to 13.03)		
FIM 2 and 3 IgG U/mL	1.44 (1.15 to 1.79)	1.31 (1.10 to 1.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: antibody responses proportions above correlates of protection to Infanrix-IPV-Hib vaccine - post primary vaccination

End point title	antibody responses proportions above correlates of protection to Infanrix-IPV-Hib vaccine - post primary vaccination

End point description:

assess antibody responses, presented as percentage of participants with IgG to Diphtheria-toxoid, Tetanus-toxoid and polyribosyl ribitol phosphate (PRP - Hib) above correlates of protection, of Infanrix-IPV-Hib vaccine after three doses at 2, 3 and 4 months of age, from the blood sample taken at 5 months of age

End point type	Secondary

End point timeframe:

5 month of age

End point values	Group 1 (2+1 PCV13)	Group 2 (1+1 PCV13)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	82		
Units: proport. above correlates of protection				
geometric mean (confidence interval 95%)				
Anti-diphtheria toxoid IgG ≥ 0.1 IU/mL	98.5 (92.1 to 100)	95.1 (88.0 to 98.7)		
Anti-diphtheria toxoid IgG ≥ 1 IU/mL	13.2 (6.2 to 23.6)	11.0 (5.1 to 19.8)		
Anti-tetanus toxoid IgG ≥ 0.1 IU/mL	100 (94.8 to 100)	100 (95.6 to 100)		
Anti-tetanus toxoid IgG ≥ 1 IU/mL	65.2 (52.8 to 76.3)	67.1 (55.8 to 77.1)		
Anti PRP-Hib IgG ≥ 0.15µg/mL	93.0 (84.3 to 97.7)	100 (95.6 to 100)		
Anti PRP-Hib IgG ≥ 1 µg/mL	49.3 (37.2 to 61.4)	67.1 (55.8 to 77.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: antibody responses proportions above correlates of protection to Infanrix-IPV-Hib vaccine - post booster

End point title	antibody responses proportions above correlates of protection to Infanrix-IPV-Hib vaccine - post booster

End point description:

assess antibody responses, presented as percentage of participants with IgG to Diphtheria-toxoid, Tetanus-toxoid and polyribosyl ribitol phosphate (PRP - Hib) above correlates of protection, of Infanrix-IPV-Hib vaccine after three doses at 2, 3 and 4 months of age, from the blood sample taken at 13 months of age

End point type	Secondary

End point timeframe:

13 months of age

End point values	Group 1 (2+1 PCV13)	Group 2 (1+1 PCV13)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	74		
Units: proport. above correlates of protection				
geometric mean (confidence interval 95%)				
Anti-diphtheria toxoid IgG ≥ 0.1 IU/mL	100 (95.1 to 100)	94.6 (86.7 to 98.5)		
Anti-diphtheria toxoid IgG ≥ 1 IU/mL	34.2 (23.5 to 46.3)	25.7 (16.3 to 37.2)		
Anti-tetanus toxoid IgG ≥ 0.1 IU/mL	100 (95.1 to 100)	100 (95.1 to 100)		

Anti-tetanus toxoid IgG ≥ 1 IU/mL	89.0 (79.5 to 95.1)	91.9 (83.2 to 97.0)		
Anti PRP-Hib IgG ≥ 0.15µg/mL	100 (95.1 to 100)	100 (95.1 to 100)		
Anti PRP-Hib IgG ≥ 1 µg/mL	98.6 (92.6 to 100)	100 (95.1 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: reactogenicity using a daily health diary for a week following vaccination

End point title	reactogenicity using a daily health diary for a week following vaccination

End point description:

assess reactogenicity using a daily health diary for a week following vaccination at 2, 3, 4 and 12 months of age to record local reactions and systemic symptoms, particularly with reference to the use of paracetamol as indicated when the MenB vaccine, Bexsero, is administered. Temperature will also be recorded and analysed from the iButton system

End point type	Secondary

End point timeframe:

for a week following vaccination at 2, 3, 4 and 12 months of age

End point values	Group 1 (2+1 PCV13)	Group 2 (1+1 PCV13)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	107		
Units: number	106	107		

Attachments (see zip file)	Local and systemic reactions/Local and systemic reactions.jpg

Statistical analyses

No statistical analyses for this end point

Secondary: Pneumococcal serotype specific GMCs - post primary vaccination

End point title	Pneumococcal serotype specific GMCs - post primary vaccination

End point description:

Pneumococcal serotype specific geometric mean concentrations (GMC) in blood samples at 5 months of age (1 month post the primary series of PCV13 vaccination for group 1 and 2 months post the single priming dose for group 2)

End point type	Secondary

End point timeframe:

5 months of age

End point values	Group 1 (2+1 PCV13)	Group 2 (1+1 PCV13)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	102		
Units: concentration µg/mL				
geometric mean (confidence interval 95%)				
serotype 1	1.25 (1.07 to 1.45)	0.57 (0.47 to 0.69)		
serotype 3	0.28 (0.23 to 0.33)	0.27 (0.21 to 0.34)		
serotype 4	1.08 (0.93 to 1.26)	0.43 (0.36 to 0.51)		
serotype 5	0.90 (0.77 to 1.07)	0.29 (0.24 to 0.35)		
serotype 6A	1.25 (1.00 to 1.56)	0.13 (0.11 to 0.15)		
serotype 6B	0.26 (0.20 to 0.33)	0.09 (0.08 to 0.09)		
serotype 7F	2.46 (2.11 to 2.88)	0.81 (0.69 to 0.95)		
serotype 9V	0.73 (0.60 to 0.89)	0.18 (0.16 to 0.21)		
serotype 14	4.19 (3.23 to 5.43)	1.13 (0.90 to 1.40)		
serotype 18C	0.90 (0.73 to 1.11)	0.22 (0.19 to 0.27)		
serotype 19A	1.56 (1.25 to 1.96)	0.33 (0.27 to 0.39)		
serotype 19F	4.54 (3.80 to 5.42)	0.64 (0.54 to 0.76)		
serotype 23F	0.43 (0.34 to 0.54)	0.09 (0.08 to 0.10)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

for a week following each vaccination appointment at 2, 3, 4 and 12 months of age

Adverse event reporting additional description:

Safety data in terms of SAEs, is collected at each visit for the preceding period, with details verified from GP notes. Parents are asked to complete a health diary for the week following each vaccination appointment to document local reactions (redness/swelling/ pain at the injection site) as well as any systemic symptoms and use of paracetamol.

Assessment type	Systematic

Dictionary used

Dictionary name	Protocol
Dictionary version	v6.0

Reporting groups

Reporting group title	Group 1 (2+1 PCV13)

Reporting group description:

PCV13 schedule 2+1 and all participants in both arms receiving Bexsero 2+1 and Infanrix/IPV/Hib with one MenC conjugate vaccination at 12 months given as the combined Hib/MenC conjugate vaccine, Menitorix

Reporting group title	Group 2 (1+1 PCV13)

Reporting group description:

PCV13 schedule 1+1 and all participants at both arms receiving Bexsero and Infanrix/IPV/Hib with one MenC conjugate vaccination at 12 months given as the combined Hib/MenC conjugate vaccine, Menitorix

Serious adverse events	Group 1 (2+1 PCV13)	Group 2 (1+1 PCV13)	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 106 (12.26%)	8 / 107 (7.48%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Mild concussion secondary to fall			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacerated ear requiring sutures			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burns			

subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Congenital Lymphangioma			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Irritability/ALTE			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurodevelopmental delay + feeding difficulties			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Fever related to vaccines			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mild acute gastroenteritis			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal bleeding			

subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchiolitis			
subjects affected / exposed	3 / 106 (2.83%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RSV bronchiolitis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wheezing/respiratory infection			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia, wheezing			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest infection			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Croup			

subjects affected / exposed	1 / 106 (0.94%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Abnormal liver function			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Kidney infection and sepsis			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Tonsillitis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septicaemia			
subjects affected / exposed	2 / 106 (1.89%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Group 1 (2+1 PCV13)	Group 2 (1+1 PCV13)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	106 / 106 (100.00%)	107 / 107 (100.00%)	
General disorders and administration site conditions			
Feeding	Additional description: Diary 1 to 4		
subjects affected / exposed[1]	82 / 95 (86.32%)	75 / 87 (86.21%)	
occurrences (all)	82	75	
Less active	Additional description: Diary 1 to 4		
subjects affected / exposed[2]	82 / 96 (85.42%)	78 / 87 (89.66%)	
occurrences (all)	82	78	
Irritability	Additional description: Diary 1 to 4		
subjects affected / exposed[3]	95 / 96 (98.96%)	81 / 87 (93.10%)	
occurrences (all)	95	81	
Crying	Additional description: Diary 1 to 4		
subjects affected / exposed[4]	88 / 96 (91.67%)	74 / 87 (85.06%)	
occurrences (all)	88	74	
Redness	Additional description: Diary 1 to 4		
subjects affected / exposed[5]	71 / 90 (78.89%)	58 / 81 (71.60%)	
occurrences (all)	71	58	
Swelling	Additional description: Diary 1 to 4		
subjects affected / exposed[6]	51 / 89 (57.30%)	45 / 81 (55.56%)	
occurrences (all)	51	45	
Tenderness	Additional description: Diary 1 to 4		
subjects affected / exposed[7]	67 / 91 (73.63%)	64 / 79 (81.01%)	
occurrences (all)	67	64	
Immune system disorders			
Temperature	Additional description: Diary 1 to 4		
subjects affected / exposed[8]	85 / 97 (87.63%)	78 / 88 (88.64%)	
occurrences (all)	85	78	
Gastrointestinal disorders			
Sickness	Additional description: Diary 1 to 4		
subjects affected / exposed[9]	61 / 96 (63.54%)	55 / 87 (63.22%)	
occurrences (all)	61	55	
Diarrhoea	Additional description: Diary 1 to 4		
subjects affected / exposed[10]	72 / 96 (75.00%)	70 / 87 (80.46%)	
occurrences (all)	72	70	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The number of subjects does not match due to combination of withdrawal and missing diary card data.
[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The number of subjects does not match due to combination of withdrawal and missing diary card data.
[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The number of subjects does not match due to combination of withdrawal and missing diary card data.
[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The number of subjects does not match due to combination of withdrawal and missing diary card data.
[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The number of subjects does not match due to combination of withdrawal and missing diary card data.
[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The number of subjects does not match due to combination of withdrawal and missing diary card data.
[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The number of subjects does not match due to combination of withdrawal and missing diary card data.
[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The number of subjects does not match due to combination of withdrawal and missing diary card data.
[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The number of subjects does not match due to combination of withdrawal and missing diary card data.
[10] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The number of subjects does not match due to combination of withdrawal and missing diary card data.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 October 2015	.The principal investigators have been updated on page 1 .The type of laboratory assays performed for meningococcal serogroup C and W at 5 months of age (secondary objectives and endpoints) have been revised on pages 9,11,18 and 38 .Clarification of the timings to assess antibody responses to Men B, tetanus, diphtheria and pertussis on pages 9,11,18 and 38 .The titre thresholds for different type of assays have been clarified on pages 9, 11, 18 and 38 .Clarification that reactogenicity data will only be collected following immunizations at 2, 3, 4 and 12 months of age on pages 10, 12, 18, 28 and 38 .Clarification of the references used to define the protective levels of antibodies to Men B vaccine and PCV13 on page 28 .Clarification of the laboratory responsible for processing NP swabs on pages 31 and 32 .Removal of functional pertussis antibody studies on page 31 .Clarification of the name of the sample storage facility at PHE on page 32 .Clarification of the data analysis, including an interim analysis on page 40 .Clarification of the location of the Clinical Trial Data Manager on page 41 .The guidelines followed by the study laboratories have been updated on page 43 .Update of references on page45. .Clarification of PHE recruitment methods on page 23.
12 January 2018	.The study has been extended. The final visit (visit 8) will now be when participants are 21-33months of age (instead of 18 months of age). The extension involves an additional visit and a blood test. This will allow an extended description of antibody responses to the vaccines given in this trial, which has been listed as an additional secondary endpoint. .Participants will be recruited from all study areas (Thames Valley, Gloucestershire and Hertfordshire). .The PI for the PHE sites in Gloucestershire and Hertfordshire has also changed.
12 February 2018	.Increase maximal blood volume taken at visit 8 from 5mL to 8mL. .Remove increased body temperature from the temporary exclusion criteria for visit 8. .Change laboratory processes for visit 8, now all samples will be shipped to OVG, spun, frozen and then either stored or sent to other sites for analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Follow up results are confidential and not reported. Paper is in draft, will be published soon and distributed to participants.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29174323

http://www.ncbi.nlm.nih.gov/pubmed/33428870