Clinical trial results:
Immunogenicity and reactogenicity of concomitantly administered hexavalent and Group B meningococcal vaccines in infancy.

Summary

EudraCT number	2018-003451-38
Trial protocol	GB
Global end of trial date	22 February 2022

Results information

Result version number	v1 (current)
This version publication date	10 September 2022
First version publication date	10 September 2022

Trial information

Trial identification

Sponsor protocol code	OVG2018/05

Additional study identifiers

ISRCTN number	ISRCTN85819697
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Oxford Vaccine Group
Sponsor organisation address	Centre for Clinical Vaccinology and Tropical Medicine, Churchill Hospital, Headington, Oxford, Oxford, United Kingdom, OX3 7LE
Public contact	Professor Matthew Snape, Oxford Vaccine Group, +44 01865611400, matthew.snape@paediatrics.ox.ac.uk
Scientific contact	Professor Matthew Snape, Oxford Vaccine Group, +44 01865611400, matthew.snape@paediatrics.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	25 February 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 April 2021
Global end of trial reached?	Yes
Global end of trial date	22 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the immune response of the Haemophilus influenza type B (Hib) component of the 6in1-IH (Infanrix-Hexa) and 6in1-V (Vaxelis) vaccines when co-administered with 4CMenB in the UK routine immunisation schedule, as measured by blood tests taken at at 5 months of age.

Protection of trial subjects:

All participants received an approved, routine vaccine in a location convenient to them.
Anaesthetic cream, to numb the skin, was provided before the blood samples at 5 and 13 months were taken.
Participants parents were also provided with telephone access to an on-call study team member for urgent clinical queries related to the trial.
Any stress and discomfort is also reduced by using distraction techniques and play assistants accompanying clinical staff on visits.

Background therapy:

All participants in both groups received:
Bexsero (MenB) at 2, 4 and 12 months of age
Rotarix (Rotavirus) orally at 2 and 3 months of age
Prevenar13 (PCV13) at 3 and 12 months of age
Menitorix (Hib/MenC) at 12 months of age
MMR VaxPro or Priorix at 12 months of age

Evidence for comparator:

The study compared the concentrations of antibodies against Haemophilus influenza type B in response to immunisation with either Vaxelis or Infanrix-hexa, to determine if Vaxelis could be used in the UK immunisation schedule alongside 4CMenb (Bexsero). Having the option to use either of the 6 in 1 vaccines is important to ensure all children continue to be immunised even if one vaccine becomes temporarily unavailable.

Actual start date of recruitment	16 July 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 194
Worldwide total number of subjects	194
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)	194
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:

Parents/legal guardians of potential participants were informed of the study through website based advertising and social media. The main method of recruitment, mailouts through National Health Applications and Infrastructure Services who hold the central NHS patient database and the Child Health Information Service an equivalent NHS database.

Pre-assignment

Screening details:

Participants were screened over the phone to conduct an eligibility check. Then during the first visit, participant's eligibility was assessed by a study doctor after medical history was taken and examination performed. A total of 86 participant were excluded (Living out of area, language barriers and having already had 8 week immunisations).

Period 1

Period 1 title	Overall Trial (Overall period) (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

Arm description:

Group 1 received the routine schedule of Infanrix Hexa at 2, 3 and 4 months.
Both groups then received Meningococcal B at 2, 4 and 12 months. Rotavirus at 2 and 3 months. PCV13 at 3 and 12 months. With a Hib-MenC and MMR vaccine at 12 months.

Arm type	Active comparator
Investigational medicinal product name	6 in1 (IH) (Infanrix hexa)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Injection , Intramuscular use

Dosage and administration details:

It is available as a powder and suspension for intramuscular injection with a volume of 0.5ml. It can be given as a 3 dose primary series on the current UK immunisation schedule

Investigational medicinal product name	Meningococcal B
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	Rotavirus
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	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, administered at 3 and 12 months, in line with the routine UK infant immunisation schedule for infants born on or after 1 January 2020.

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	MMR VaxPro or Priorix
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

Arm title	Group 2

Arm description:

Group 2 were also vaccinated following the routine UK infant immunisation schedule, however they were administered 6in1 - Vaxelis rather than Infanrix Hexa. They then also received the additional vaccines: Meningococcal B at 2, 3 and 12 months. Rotavirus at 2 and 3 months. PCV13 at 3 and 12 months. With a Hib-Men C and MMR vaccine at 12 months.

Arm type	Active comparator
Investigational medicinal product name	6 in1 (IH) (Infanrix hexa)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Injection , Intramuscular use

Dosage and administration details:

It is available as a powder and suspension for intramuscular injection with a volume of 0.5ml. It can be given as a 3 dose primary series on the current UK immunisation schedule

Investigational medicinal product name	Meningococcal B
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	Rotavirus
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	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, administered at 3 and 12 months, in line with the routine UK infant immunisation schedule for infants born on or after 1 January 2020.

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	MMR VaxPro or Priorix
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

Number of subjects in period 1	Group 1	Group 2
Started	98	96
Completed	91	89
Not completed	7	7
Moved out of area	3	3
Consent withdrawn by subject	3	3
Recruited to another study	-	1
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Group 1
Reporting group description:	
Group 1 received the routine schedule of Infanrix Hexa at 2, 3 and 4 months. Both groups then received Meningococcal B at 2, 4 and 12 months. Rotavirus at 2 and 3 months. PCV13 at 3 and 12 months. With a Hib-MenC and MMR vaccine at 12 months.	
Reporting group title	Group 2
Reporting group description:	
Group 2 were also vaccinated following the routine UK infant immunisation schedule, however they were administered 6in1 - Vaxelis rather than Infanrix Hexa. They then also received the additional vaccines: Meningococcal B at 2, 3 and 12 months. Rotavirus at 2 and 3 months. PCV13 at 3 and 12 months. With a Hib-Men C and MMR vaccine at 12 months.	

Reporting group values	Group 1	Group 2	Total
Number of subjects	98	96	194
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)	98	96	194
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 Infanrix Hexa/Vaxelis dose			
Units: days			
median	60	60	
full range (min-max)	57.2 to 63	57 to 63	-
Gender categorical Units: Subjects			
Female	50	52	102
Male	48	44	92

End points

End points reporting groups

Reporting group title	Group 1

Reporting group description:

Group 1 received the routine schedule of Infanrix Hexa at 2, 3 and 4 months.
Both groups then received Meningococcal B at 2, 4 and 12 months. Rotavirus at 2 and 3 months. PCV13 at 3 and 12 months. With a Hib-MenC and MMR vaccine at 12 months.

Reporting group title	Group 2

Reporting group description:

Group 2 were also vaccinated following the routine UK infant immunisation schedule, however they were administered 6in1 - Vaxelis rather than Infanrix Hexa. They then also received the additional vaccines: Meningococcal B at 2, 3 and 12 months. Rotavirus at 2 and 3 months. PCV13 at 3 and 12 months. With a Hib-Men C and MMR vaccine at 12 months.

Primary: Anti-PRP (Hib) IgG concentrations when co-administered with 4CMenB

End point title	Anti-PRP (Hib) IgG concentrations when co-administered with 4CMenB

End point description:

Compare the immunogenicity of the Haemophilus influenza type B (Hib) component of 6 in 1(IH) (Infanrix hexa) and 6 in 1(V) (Vaxelis) when co-administered with 4CMenB in the UK routine immunisation schedule at 5 months of age. Assess the anti-PRP (Hib) IgG concentrations at 5 months of age as measured by ELISA.

End point type	Primary

End point timeframe:

5 months of age

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	85		
Units: U/ml				
geometric mean (confidence interval 95%)	0.87 (0.66 to 1.16)	20.34 (14.58 to 28.37)		

Statistical analyses

Statistical analysis title	Statistical analyses title: Two-sided t-test

Statistical analysis description:

Two-sided t-test for superiority of Hex-V compared to Hex-IH in anti-PRP IgG GMCs at 5 month of age

Comparison groups	Group 2 v Group 1

Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Geometric mean ratio
Point estimate	23.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	15.11
upper limit	35.78

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited local and systemic adverse events post 5 days of any immunisation.

Adverse event reporting additional description:

All AEs that occur within 5 days of a vaccination visit and all SAEs (excluding those defined in the protocol as not requiring reporting) that occur during the study that are observed by the Investigator or reported by the participant's parent/guardian, will be recorded on the CRF, whether or not attributed to trial vaccines.

Assessment type	Systematic

Dictionary used

Dictionary name	Protocol
Dictionary version	V4.0

Reporting groups

Reporting group title	Group 1

Reporting group description:

Group 1 received the routine schedule of Infanrix Hexa at 2, 3 and 4 months.
Both groups then received Meningococcal B at 2, 4 and 12 months. Rotavirus at 2 and 3 months. PCV13 at 3 and 12 months. With a Hib-MenC and MMR vaccine at 12 months.

Reporting group title	Group 2

Reporting group description:

Group 2 were also vaccinated following the routine UK infant immunisation schedule, however they were administered 6in1 - Vaxelis rather than Infanrix Hexa. They then also received the additional vaccines: Meningococcal B at 2, 3 and 12 months. Rotavirus at 2 and 3 months. PCV13 at 3 and 12 months. With a Hib-Men C and MMR vaccine at 12 months.

Serious adverse events	Group 1	Group 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 98 (7.14%)	9 / 96 (9.38%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Head injury	Additional description: Head injury and respiratory tract infection		
subjects affected / exposed	0 / 98 (0.00%)	1 / 96 (1.04%)	
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	4 / 98 (4.08%)	4 / 96 (4.17%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Viral infection			
subjects affected / exposed	1 / 98 (1.02%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 98 (0.00%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Croup			
subjects affected / exposed	0 / 98 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary tract infection with unilateral ureteric dilatation			
subjects affected / exposed	0 / 98 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pyrexia	Additional description: Post immunisation fever		
subjects affected / exposed	1 / 98 (1.02%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis	Additional description: Tonsillitis and gastro-esophageal reflux disease		
subjects affected / exposed	1 / 98 (1.02%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	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	Group 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	96 / 98 (97.96%)	96 / 96 (100.00%)	
General disorders and administration site conditions			

Irritability			
subjects affected / exposed	91 / 98 (92.86%)	94 / 96 (97.92%)	
occurrences (all)	91	94	
Drowsiness			
subjects affected / exposed	84 / 98 (85.71%)	82 / 96 (85.42%)	
occurrences (all)	84	82	
Change in appetite/feeding			
subjects affected / exposed	74 / 98 (75.51%)	73 / 96 (76.04%)	
occurrences (all)	74	73	
Fever	Additional description: Fever ≥ 37.6°C		
subjects affected / exposed	47 / 98 (47.96%)	38 / 96 (39.58%)	
occurrences (all)	47	38	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	63 / 98 (64.29%)	66 / 96 (68.75%)	
occurrences (all)	63	66	
Vomiting			
subjects affected / exposed	53 / 98 (54.08%)	52 / 96 (54.17%)	
occurrences (all)	53	52	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 April 2019	Edits made to the Protocol, Participant Information booklet and the Health Professional Letter to reflect a change in immunisation schedule for the Pneumococcal conjugate vaccine (PCV)13. This vaccine will be administered at 3 and 12 months rather than at 2, 4 and 12 months as is routinely given. This anticipated change in UK infant immunisation schedule is planned for 2019 (see attached cover letter for additional details). IMP name error in the Initial IRAS form submission One of the investigational medicinal product (IMP) for this study is 6 in 1(IH) (Infanrix hexa) vaccine which protects against diphtheria, tetanus, poliovirus, whooping cough (pertussis), hepatitis B and haemophilus influenza B (Hib). We have however noted that in the IMP section of the initial IRAS application form that was submitted, in error we wrote and described the components of the 5in1 vaccine (commercially known as INFANRIX-IPV+Hib, which does not contain the Hepatitis B component) instead of Infanrix Hexa
22 July 2019	Amendments to an existing REC approved documents: Ametop and EMLA Instructions (over 1 year) documents using revised and updated templates, Recruitment Text To request addition of new study documents: EMLA Instructions 3 months - 11 months EMLA Instructions Animation Video EMLA Instructions Animation Script
06 January 2020	Protocol amendment: -Change of wording of sentence regarding PCV13 administration timings from 'This reflects the imminent change in the UK infant immunisation schedule' to 'This reflects the change in the routine UK infant immunisation schedule for infants born on or after 1 January 2020.' - Change in wording of a sentence in Section 8.6 to clarify when finger or heel prick would be appropriate to attempt if venepuncture is unsuccessful in participants. Participant Information Booklet - Change of wording of sentence regarding PCV administration timings from "*PCV 13 will be administered at 3 and 12 months, instead of 2, 4 and 12 months as routinely given at the time of the study start date (May 2019). This reflects a change in the UK infant immunisation schedule planned for 2019." To "*PCV 13 will be administered at 3 and 12 months, this reflects the change in the routine UK infant immunisation schedule for infants born on or after 1 January 2020." To request addition of new study document: - Parent PCV13 Update Letter
17 August 2020	Adjusted sample size and power calculations changes on the study protocol: After reviewing the current disruption on clinical activities by COVID-19 and the urgency to obtain the data for policy making in the UK, the study team decided to evaluate the study power based on the recruitment up to the time this was paused for the COVID-19 pandemic, and decided to increase the type I error from two-sided 5% (one-sided 2.5%) to one-sided 5%. The current study recruitment has achieved the planned power based on the adjusted type I error. Therefore, the study CI, sponsor and funder group has decided not to resume recruiting and continue with a sample size of 194 participants.

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.

Recruitment paused due to the COVID-19 pandemic, the current study recruitment (194) had achieved the planned power based on the adjusted type I error. Secondary objectives and results will be reported in the finalised publication in due course.

Notes: