# 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.<br>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<br>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<br>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.<br>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).<br>IMP name error in the Initial IRAS form submission<br>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<br>year) documents using revised and updated templates, Recruitment Text<br>To request addition of new study documents:<br>EMLA Instructions 3 months - 11 months<br>EMLA Instructions Animation Video<br>EMLA Instructions Animation Script |
| 06 January 2020 | Protocol amendment:<br>-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<br>routine UK infant immunisation schedule for infants born on or after 1 January 2020.'<br>- 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.<br>Participant Information Booklet<br>- 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<br>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."<br>To request addition of new study document:<br>- 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: