Clinical trial results:
A pilot study of the impact of BCG administration on the immunogenicity of serogroup C meningococcal conjugate vaccine in healthy infants

Summary

EudraCT number	2013-003488-71
Trial protocol	GB
Global end of trial date	27 June 2018

Results information

Result version number	v1 (current)
This version publication date	19 April 2019
First version publication date	19 April 2019

Trial information

Trial identification

Sponsor protocol code	OVG-2013/04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02002156
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Oxford Vaccine Group and Jenner Institute, CCVTM, Churchill Hospital, Oxford, United Kingdom, OX3 7LE
Public contact	Oxford Vaccine Group, University of Oxford, 44 1865611400, andrew.pollard@paediatrics.ox.ac.uk
Scientific contact	Oxford Vaccine Group, University of Oxford, 44 1865611400, andrew.pollard@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	21 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 May 2016
Global end of trial reached?	Yes
Global end of trial date	27 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To characterise the impact of BCG immunisation given at birth or 3 months of age on the initial response to infant serogroup C meningococcal vaccine (MenC).

Protection of trial subjects:

Ethical, Legal and Management Protection: Every effort was made to ensure that parents or guardians giving informed consent were able to understand fully the nature of the study including the risks,burdens, benefits and implications that taking part had for their child. The study involved the collection of blood samples that would not normally be part of routine care. In order to minimise any discomfort, local anaesthetic cream was offered to numb the skin prior to the sample being collected. The members of the study team undertaking venepuncture had specific training and experience in this technique. With the parent/guardians agreement two attempts at blood sampling were made and if unsuccessful a further visit was arranged by the study team.
Strict inclusion and exclusion criteria applied to the enrolment of each study participant.
The study complied with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so ensuring that the participant's anonymity was maintained throughout the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 November 2013
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: 28
Worldwide total number of subjects	28
EEA total number of subjects	28

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	28
Infants and toddlers (28 days-23 months)	0
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:

This study required that participants were enrolled as soon as possible after birth. Study information was provided before rather than after birth wherever practically possible, at visits to hospital and/or community-based antenatal clinics and ultrasound appointments, or sent by post.

Pre-assignment

Screening details:

No pre-screening was performed for this trial. Following consent at the first trial visit, screening was restricted to confirmation of eligibility, review of medical history and medical examination.

Period 1

Period 1 title	Visit 1 Enrolment and Randomisation
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The trial was not blinded after randomisation had been completed.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1

Arm description:

BCG administered at V1

Arm type	Experimental
Investigational medicinal product name	Bacillus Calmette-Guérin (BCG)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intradermal use

Dosage and administration details:

The BCG vaccine was given according to current UK guidelines. Wherever possible, BCG was administered into the left upper arm at the insertion of the deltoid muscle as detailed in these guidelines. The tip of the shoulder was avoided because of the increased risk of keloid formation at this site.

The dose administered was 0.05 mL for children under 12 months, 0.1 mL for children 12 months and older.

Arm title	Group 2

Arm description:

BCG administered at visit 3 (3 months)

Arm type	Experimental
Investigational medicinal product name	Bacillus Calmette-Guérin (BCG)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intradermal use

Dosage and administration details:

The BCG vaccine was given according to current UK guidelines. Wherever possible, BCG was administered into the left upper arm at the insertion of the deltoid muscle as detailed in these

guidelines. The tip of the shoulder was avoided because of the increased risk of keloid formation at this site.

The dose administered was 0.05 mL for children under 12 months, 0.1 mL for children 12 months and older.

Arm title	Group 3
Arm description:	
Control - BCG offered at visit 7 (13 months)	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Group 1	Group 2	Group 3
Started	10	9	9
Completed	10	9	9

Period 2	
Period 2 title	Follow up visits (2-7)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1

Arm description:

BCG administered at V1
All participants in the three groups in this trial followed the same visit schedule, part from the BCG administration date. The visit schedule was as follows:
Visit 2 and 4(2 and 4 months): Confirmation of ongoing consent, eligibility and collection of interim medical history. Administration of routine schedule vaccines due at 2 and 4 months.
Visit 3, 6 and 7 (3, 12 and 13 months): Confirmation of ongoing consent, eligibility and collection of interim medical history. Administration of routine schedule vaccines due at 3, 12 and 13 months, including MenC. Collection of blood samples.
Visit 5 (5 months): Confirmation of ongoing consent, eligibility and collection of interim medical history. Collection of blood samples.

Arm type	Experimental
Investigational medicinal product name	Bacillus Calmette-Guérin (BCG)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intradermal use

Dosage and administration details:

The BCG vaccine was given according to current UK guidelines. Wherever possible, BCG was administered into the left upper arm at the insertion of the deltoid muscle as detailed in these

guidelines. The tip of the shoulder was avoided because of the increased risk of keloid formation at this site.

The dose administered was 0.05 mL for children under 12 months, 0.1 mL for children 12 months and older.

Arm title	Group 2

Arm description:

BCG administered at visit 3 (3 months)
All participants in the three groups in this trial followed the same visit schedule, part from the BCG administration date. The visit schedule was as follows:
Visit 2 and 4(2 and 4 months): Confirmation of ongoing consent, eligibility and collection of interim medical history. Administration of routine schedule vaccines due at 2 and 4 months.
Visit 3, 6 and 7 (3, 12 and 13 months): Confirmation of ongoing consent, eligibility and collection of interim medical history. Administration of routine schedule vaccines due at 3, 12 and 13 months, including MenC. Collection of blood samples.
Visit 5 (5 months): Confirmation of ongoing consent, eligibility and collection of interim medical history. Collection of blood samples.

Arm type	Experimental
Investigational medicinal product name	Bacillus Calmette-Guérin (BCG)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intradermal use

Dosage and administration details:

The BCG vaccine was given according to current UK guidelines. Wherever possible, BCG was administered into the left upper arm at the insertion of the deltoid muscle as detailed in these guidelines. The tip of the shoulder was avoided because of the increased risk of keloid formation at this site.

The dose administered was 0.05 mL for children under 12 months, 0.1 mL for children 12 months and older.

Arm title	Group 3

Arm description:

Control - BCG offered at visit 7 (13 months)
All participants in the three groups in this trial followed the same visit schedule, part from the BCG administration date. The visit schedule was as follows:
Visit 2 and 4(2 and 4 months): Confirmation of ongoing consent, eligibility and collection of interim medical history. Administration of routine schedule vaccines due at 2 and 4 months.
Visit 3, 6 and 7 (3, 12 and 13 months): Confirmation of ongoing consent, eligibility and collection of interim medical history. Administration of routine schedule vaccines due at 3, 12 and 13 months, including MenC. Collection of blood samples.
Visit 5 (5 months): Confirmation of ongoing consent, eligibility and collection of interim medical history. Collection of blood samples.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	Group 1	Group 2	Group 3
Started	10	9	9
Completed	10	8	8
Not completed	0	1	1
Consent withdrawn by subject	-	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Group 1
Reporting group description:	
BCG administered at V1	

Reporting group title	Group 2
Reporting group description:	
BCG administered at visit 3 (3 months)	
Reporting group title	Group 3
Reporting group description:	
Control - BCG offered at visit 7 (13 months)	

Reporting group values	Group 1	Group 2	Group 3
Number of subjects	10	9	9
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	10	9	9
Infants and toddlers (28 days-23 months)	0	0	0
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
Gender categorical Units: Subjects			
Female	6	5	5
Male	4	4	4

Reporting group values	Total		
Number of subjects	28		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	28		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		

Gender categorical Units: Subjects			
Female	16		
Male	12		

End points

End points reporting groups

Reporting group title	Group 1

Reporting group description:

BCG administered at V1

Reporting group title	Group 2

Reporting group description:

BCG administered at visit 3 (3 months)

Reporting group title	Group 3

Reporting group description:

Control - BCG offered at visit 7 (13 months)

Reporting group title	Group 1

Reporting group description:

BCG administered at V1
All participants in the three groups in this trial followed the same visit schedule, part from the BCG administration date. The visit schedule was as follows:
Visit 2 and 4(2 and 4 months): Confirmation of ongoing consent, eligibility and collection of interim medical history. Administration of routine schedule vaccines due at 2 and 4 months.
Visit 3, 6 and 7 (3, 12 and 13 months): Confirmation of ongoing consent, eligibility and collection of interim medical history. Administration of routine schedule vaccines due at 3, 12 and 13 months, including MenC. Collection of blood samples.
Visit 5 (5 months): Confirmation of ongoing consent, eligibility and collection of interim medical history. Collection of blood samples.

Reporting group title	Group 2

Reporting group description:

BCG administered at visit 3 (3 months)
All participants in the three groups in this trial followed the same visit schedule, part from the BCG administration date. The visit schedule was as follows:
Visit 2 and 4(2 and 4 months): Confirmation of ongoing consent, eligibility and collection of interim medical history. Administration of routine schedule vaccines due at 2 and 4 months.
Visit 3, 6 and 7 (3, 12 and 13 months): Confirmation of ongoing consent, eligibility and collection of interim medical history. Administration of routine schedule vaccines due at 3, 12 and 13 months, including MenC. Collection of blood samples.
Visit 5 (5 months): Confirmation of ongoing consent, eligibility and collection of interim medical history. Collection of blood samples.

Reporting group title	Group 3

Reporting group description:

Control - BCG offered at visit 7 (13 months)
All participants in the three groups in this trial followed the same visit schedule, part from the BCG administration date. The visit schedule was as follows:
Visit 2 and 4(2 and 4 months): Confirmation of ongoing consent, eligibility and collection of interim medical history. Administration of routine schedule vaccines due at 2 and 4 months.
Visit 3, 6 and 7 (3, 12 and 13 months): Confirmation of ongoing consent, eligibility and collection of interim medical history. Administration of routine schedule vaccines due at 3, 12 and 13 months, including MenC. Collection of blood samples.
Visit 5 (5 months): Confirmation of ongoing consent, eligibility and collection of interim medical history. Collection of blood samples.

Subject analysis set title	MenC IgG (Primary Objective)
Subject analysis set type	Per protocol

Subject analysis set description:

MenC-specific IgG at 8 weeks following the dose of MenC vaccine (i.e. at 20 weeks of age if no delay in the schedule).
(The log10-transformed MenC-specific lgG was summarised by the subjects and each group at 20 weeks of age. The exponentiated differences between log10-transformed group means was compared and presented as geometric mean ratios/titres with associated 95% confidence intervals)

Primary: MenC-specific IgG at 8 weeks following the dose of MenC vaccine

End point title	MenC-specific IgG at 8 weeks following the dose of MenC vaccine[1]

End point description:

End point type	Primary

End point timeframe:

MenC-specific IgG at 8 weeks following the dose of MenC vaccine

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All comparisons were considered exploratory and hypothesis-generating as this is an under powered study. Results were interpreted with appropriate caution due to the large degree of variation expected with small studies.
Statistical testing of hypotheses was not conducted as this is a small pilot study.

All results will be available in the trial publication which will be publicly available.

End point values	Group 1	Group 2	Group 3	Group 1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	9	9	9
Units: Titre	10	9	9	10

End point values	Group 2	Group 3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: Titre	9	9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Solicited adverse events to the trial vaccines were not collected for this trial, as all vaccines are licensed and were used in accordance with their marketing authorisation.
SAEs were collected throughout the trial period.

Assessment type	Systematic

Dictionary used

Dictionary name	Protocol
Dictionary version	Current ap

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Solicited adverse events to the trial vaccines were not collected for this trial, as all vaccines are licensed and were used in accordance with their marketing authorisation.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 December 2013	Documents were amended to make it clearer that the study invitation is only for babies who would not normally receive a BCG vaccine. We modified the recruitment text short and long, and updated the parent information booklet accordingly. A document was added to give to parents which outlines what samples are taken at each visit, for each of the three groups. Recruitment text documents were updated.
24 February 2014	Exploratory objective wording in the protocol was clarified around the analyses of monocyte and lymphotcyte ratios and removal of a duplicated sentence regarding MenC SBA. A correction to the site of a vaccination was also made to the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported