Clinical trial results:
FULL TITLE: Pneumococcal Conjugate Vaccine (PCV-13) and Experimental Human Pneumococcal Carriage Study (EHPC) Study.
KEY WORDS: mucosa, innate, cellular, humoral, Streptococcus pneumoniae, pneumococcus, carriage, colonisation, human, lung, antibody, vaccine, T-cells, genome sequencing, conjugate vaccine, protection.

Summary

EudraCT number	2012-005141-20
Trial protocol	GB
Global end of trial date	07 November 2014

Results information

Result version number	v1 (current)
This version publication date	16 May 2019
First version publication date	16 May 2019
Summary attachment (see zip file)	First Human Challenge Testing of a Pneumococcal Vaccine: Double Blind Randomised Control Trial (First Human Challenge Testing of a Pneumococcal Vaccine - Double Blind Randomised Controlled Trial.pdf)

Trial information

Trial identification

Sponsor protocol code	4431

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Royal Liverpool and Broadgreen University Hospital
Sponsor organisation address	Prescott Street, Liverpool, United Kingdom, L7 8XP
Public contact	Heather Rogers, Royal Liverpool and Broadgreen University Hospital Trust, +44 1517063320, rgt@rlbuht.nhs.uk
Scientific contact	Heather Rogers, Royal Liverpool and Broadgreen University Hospital Trust, +44 1517063320, rgt@rlbuht.nhs.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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 November 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 November 2014
Global end of trial reached?	Yes
Global end of trial date	07 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main study aim is to determine whether PCV is protective against pneumococcal carriage in healthy adult volunteers.

Protection of trial subjects:

All participants were given emergency antbiotics (amoxicillin 500mg TDS for 3/7 supply) to be taken if instructed by the research team/ if unwell and unable to contact the research team/ at the end of the study if they were positive for colonization. They were also given a thermometer and an emergency contact card with 24/7 access to the research team.

Background therapy:

All participants were nasally inoculated with 80,000CFU/0.1ml of SPN6B pneumococcal bacteria in each nostril.
All participants underwent research samples including blood, nasal wash and saliva smaples during the screen and follow up period as per protocol.

Evidence for comparator:

The participants were randomly allocated to receive either Pneumococcal Conjugate Vaccine (PCV13) OR Hepatitis A vaccine (Avaxim: Control). The control vaccine was chosen as it contains a similar adjuvant compound and therefore it should cause similar localised reactions however it is not known to affect nasal immunity. The control vaccine is also beneficial to the participant and all participants were offered the full course of Hep A at the end of the study.

Actual start date of recruitment	01 March 2013
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: 99
Worldwide total number of subjects	99
EEA total number of subjects	99

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)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	99
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

100 healthy volunteers were recruited into the study over the 9 month period. Consort statement available in publication online.
T

Pre-assignment

Screening details:

All participants were screened against the inclusion and exclusion criteria. During the screening visit, all participants were given a clinical examination: listen to their heart and lungs, medical history taken (by a research Dr or a delegated person), vital signs monitored, full blood count was taken to ensure that they have an adequate immunity.

Period 1

Period 1 title	Randomisation and vaccination (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Assessor

Blinding implementation details:

Separate unblinding team of nurses administered the vaccine to the participant using sealed envelopes. The unblided team had no further involvement in the trial. All research staff including clinical staff and lab staff were blinded to the randomisation. Unblinding only occured at the end of the study, last subject, last visit once all of the data had been locked down.
Participants were later unblinded by sending a vaccine letter explaining theoir allocation, a copy was also sent to their GP.

Arms

Are arms mutually exclusive?	Yes
Arm title	PCV Intervention

Arm description:

Randomised to receive Pneumococcal Conjugate Vaccine (PCV13)

Arm type	Active comparator
Investigational medicinal product name	Prevenar
Investigational medicinal product code	
Other name	Pneumococcal Conjugate Vaccine PCV13
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

PCV13 one dose given by intramuscular injection by a member of the unblinded nursing team

Arm title	Control: Hepatitis A Vaccine

Arm description:

Hepatitis A vaccine: Avaxim

Arm type	Placebo
Investigational medicinal product name	Avaxim
Investigational medicinal product code	
Other name	Hepatitis A Vaccine
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Avaxim one dose given by intramuscular injection by a member of the unblinded nursing team

Number of subjects in period 1	PCV Intervention	Control: Hepatitis A Vaccine
Started	49	50
Completed	48	48
Not completed	1	2
Consent withdrawn by subject	-	1
Physician decision	-	1
Removed due to anxiety	1	-

Baseline characteristics

Reporting groups	
Reporting group title	PCV Intervention
Reporting group description:	
Randomised to receive Pneumococcal Conjugate Vaccine (PCV13)	
Reporting group title	Control: Hepatitis A Vaccine
Reporting group description:	
Hepatitis A vaccine: Avaxim	

Reporting group values	PCV Intervention	Control: Hepatitis A Vaccine	Total
Number of subjects	49	50	99
Age categorical			
Healthy participants aged 18-50 years old			
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)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	49	50	99
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Age per group as per Intention-to-treat n=99			
Units: years			
arithmetic mean	24.1	23.2	
standard deviation	± 6.1	± 6.9	-
Gender categorical			
Gender reported as male, number (%)			
Units: Subjects			
Female	29	31	60
Male	20	19	39

End points

End points reporting groups

Reporting group title	PCV Intervention
Reporting group description:	
Randomised to receive Pneumococcal Conjugate Vaccine (PCV13)	
Reporting group title	Control: Hepatitis A Vaccine
Reporting group description:	
Hepatitis A vaccine: Avaxim	

Primary: Pneumococcal Colonization at any time point

End point title	Pneumococcal Colonization at any time point
End point description:	
Pneumococcal colonization is determined by the presence of SPN6B pneumococcus in the nasal wash using classical microbiological culture at any time point post nasal inoculation (Day 2, Day 7, Day 14 and Day 21)	
End point type	Primary
End point timeframe:	
Colonization assessed at Day 2, Day 7, Day 14 and Day 21 post nasal inoculation. Primary endpoint is colonization at any of these time points post inoculation	

End point values	PCV Intervention	Control: Hepatitis A Vaccine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48[1]	48[2]		
Units: Number (%)				
Positive	5	23		
Negative	43	25		

Notes:

[1] - One subject withdrew due to anxiety following the randomisation and vaccination

[2] - One subject removed due to a low white cell count.
One subject withdrew consent post vaccination an

Attachments (see zip file)	Publication with tables/First Human Challenge Testing of a

Statistical analyses

Statistical analysis title	Generalized linear model
Statistical analysis description:	
The primary endpoint was analyzed using a generalized linear model with treatment as a single predictor, generating risk ratios and odds ratios together with their 95% confidence intervals (CIs) of being colonized with pneumococcus between the PCV and control groups.	

Comparison groups	PCV Intervention v Control: Hepatitis A Vaccine

Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.0002 [4]
Method	Generalized linear model.
Parameter estimate	Odds ratio (OR)

Notes:

[3] - Generalized linear model. All statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC) and Stata 13 (StataCorp, College Station, TX). All analyses performed by Prof Duolao Wang
[4] - Pneumococcal colonization at any time point between PCV and Control group

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any adverse events would be reported for each participant during the study participation.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	PCV Intervention
Reporting group description: -	
Reporting group title	Avaxim (Control)

Reporting group description: -

Serious adverse events	PCV Intervention	Avaxim (Control)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 49 (0.00%)	0 / 50 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	PCV Intervention	Avaxim (Control)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	
Infections and infestations			
Pyrexia and hospital admission	Additional description: One participant (PCV group, 6B colonized) was admitted to hospital overnight at 48 hours postinoculation complaining of pyrexia lethargy, and sore throat. Diagnosed with tonsillitis and a nontoxigenic Corynebacterium diptheriae was cultured		
subjects affected / exposed	1 / 49 (2.04%)	0 / 50 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 July 2013	Expand unblinded team to include RLUH staff. Participants are offered the complete Hep A course at the end of the study, this is to be arranged between the volunteer and the Well Travelled Clinic. Addition of throat swab at each visit. Add comparison of traditional culture methods with qPCR methods to detect bacteria. Addition of GP questionnaire.
18 December 2013	Take extra blood samples at certain visits. Prolong the time between completing the challenge study and taking part in the bronchoscopy from 2 weeks to no end date. Addition of paired blood sample on the day of the bronchoscopy. FBC full blood count to be taken at pre-vaccine visit AND pre-inoculation visit. Remove saliva samples throughout. Increase overall sample size to allow for higher dropout. Remove the interim analysis after 50 participants to remain blinded until the end of the study. Addition of a GP vaccination letter to inform the GP of the allocation at the end of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26114410