Clinical trial results:
The Effect of Live Attenuated Influenza Vaccine (LAIV) on Experimental Human Pneumococcal Colonisation (EHPC) Study

Summary

EudraCT number	2014-004634-26
Trial protocol	GB
Global end of trial date	29 September 2017

Results information

Result version number	v1 (current)
This version publication date	18 May 2019
First version publication date	18 May 2019
Summary attachment (see zip file)	Effect of Live Attenuated Influenza Vaccine on Pneumococcal Carriage (Effect of Live Attenuated Influenza Vaccine on Pneumococcal Carriage.pdf) Effect of Live Attenuated Influenza Vaccine on Pneumococcal Carriage Biovax (Biovax paper.pdf)

Trial information

Trial identification

Sponsor protocol code	4896

Additional study identifiers

ISRCTN number	ISRCTN16993271
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Liverpool School of Tropical Medicine/Royal Liverpool Hospital
Sponsor organisation address	Daulby Street, Liverpool, United Kingdom, L7 8XP
Public contact	Dr Helen Hill, Liverpool School of Tropical Medicine, +44 01517029338, helen.hill@lstmed.ac.uk
Scientific contact	Professor Daniela Ferreira (Scientific) Dr Jamie Rylance (Clinical), Liverpool School of Tropical Medicine, +44 0151702 9338, daniela.ferriera@lstmed.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	29 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 September 2017
Global end of trial reached?	Yes
Global end of trial date	29 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To define the effect of Live Attenuated Influenza Vaccine (LAIV) on pneumococcal colonisation using the Experimental Human Pneumococcal Carriage (EHPC) Model in order to assess the potential effects of mass influenza vaccination including colonisation acquisition, density and duration.

Protection of trial subjects:

An Independent Data Safety Monitoring Committee provide oversight to the trial monitoring safety reports consistent with requirements of pharmacovigilance reporting requirements by the MHRA and NHS National Research ethics Service.

For the duration of the trial participants report adverse events and Serious Adverse Events consistent with both the MHRA and National Research Ethics Service pharmacovigilance reporting requirements.Participants follow up was consistent with the Experimental Human Pneumococcal Carriage safety guidelines. A respiratory clinician is available day and night. Post-inoculation participants contact the team to reported symptoms and their temperature daily >7 days. Participants are assessed by a clinician in the event of symptoms. A safety information sheet is provided to participants.

Background therapy:

This study design includes:
Participants being inoculated nasally with Streptococcus Pneumoniae then comparing being randomised to either the intervention Live Attenuated Influenza Spray plus IM placebo or control Quadrivalent Inactivated Influenza Vaccine (intramuscular) plus nasal placebo to determine carriage.

Study 1 Immunise first (antecedent) Study: vaccinate then inoculate
Study 1 Colonise first (concurrent) Study: inoculate then vaccinate

To blind the participants the control group are administered an intramuscular quadrivalent inactivated influenza vaccine (QIV) with a saline placebo to blind the route of administration

Evidence for comparator:

There are 2 types of influenza vaccines currently available, a quadrivalent live attenuated influenza vaccine (LAIV) which is administered as a nasal spray and a quadrivalent inactivated influenza vaccine (QIV) administered as an intramuscular injection.
Quadrivalent LAIV and QIV contain four influenza strains, 2 influenza A (H1N1 and H3N2) and 2 influenza B. Both are licensed for the prevention of influenza in the UK.

Although LAIV has been proven to be safe and effective in numerous trials, no trial has assessed its potential impact on other nasopharyngeal pathogens.

Actual start date of recruitment	26 August 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: 335
Worldwide total number of subjects	335
EEA total number of subjects	335

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)	335
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Healthy volunteers aged 18 to 50 years recruited in a single centre within the National Health Service in Liverpool, UK over the period of 18 months .

Pre-assignment

Screening details:

Screened day -7
348 screened study 1 n=142 study 2 n= 206 (excluded unable to attend 9 appointments, GP health history not available/ineligible (e.g allergy to antibiotics/concomitant medication)
335 randomised (excludes 13 screen fails including acute infection, abnormal vital signs or FBC)
331 vaccinated
323 vaccinated and inoculated

Period 1

Period 1 title	Study 1 and 2 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Assessor, Subject

Blinding implementation details:

The clinical research team, participants and laboratory scientists were blinded. An independent blinding team administered the vaccine. During vaccination participants wore a blindfold and received both an intramuscular and a nasal dose pairing the vaccine with a placebo (for example the LAIV vaccine (nasal) with an intramuscular placebo or the QIV vaccine (intramuscular with a nasal spray placebo).
Blinding the participant aimed to remove bias when reporting symptoms.

Arms

Are arms mutually exclusive?	Yes
Arm title	Study 1 and 2 Intervention:

Arm description:

Live Attenuated Influenza Vaccine (LAIV) given as a nasal spray with a placebo intramuscular injection of saline.
After 3 days participants were inoculated nasally Streptococcus pneumoniae 6B wild type

Arm type	Experimental
Investigational medicinal product name	Live Attenuated Influenza Vaccine
Investigational medicinal product code	EU/1/13/887/004
Other name	Fluenz or Fluarix
Pharmaceutical forms	Nasal spray, suspension
Routes of administration	Intranasal use , Nasal use

Dosage and administration details:

Dose 0.2ml (0.1ml per nostril)

Arm title	Control:

Arm description:

Inoculate with Streptococcus Pneumoniae then after 3 days immunise with Quadrivalent Inactivated Influenza Vaccination administered by intramuscular injection Fluarix Tetra, GlaxoSmithKline, UK paired with a placebo nasal spray using saline administered via a Mad Nasal LMA Nasal Atomizer

Arm type	Active comparator
Investigational medicinal product name	Quadrivalent Inactivated Influenza Vaccination Fluarix Tetra (IM)
Investigational medicinal product code	PL 10592/0302
Other name	Fluarix Tetra, GlaxoSmithKline, UK
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:
0.5 ml intramuscular injection paired with a saline nasal spray

Number of subjects in period 1	Study 1 and 2 Intervention:	Control:
Started	167	168
Randomised	165	166
Completed	128	152
Not completed	39	16
Physician decision	3	4
Lost to follow-up	5	4
Natural Carriage	10	8
Protocol deviation	21	-

Baseline characteristics

Reporting groups	
Reporting group title	Study 1 and 2

Reporting group description:

These data combine:
Study 1 : intervention and control
Study 2 : intervention and control

Reporting group values	Study 1 and 2	Total	
Number of subjects	335	335	
Age categorical			
Healthy adults			
Units: Subjects			
Study 1	137	137	
Study 2	198	198	
Age continuous			
median age in years			
Units: years			
arithmetic mean	20		
full range (min-max)	18 to 48	-	
Gender categorical			
Female (59%)			
Units: Subjects			
Study 1	137	137	
Study 2	198	198	

Subject analysis sets	
Subject analysis set title	Study 1 Intervention
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Healthy volunteers are randomised to be vaccinated with the Live Attenuated Influenza Vaccine (nasal spray) and a intramuscular injection of a saline placebo followed by nasal inoculation aiming to collonise with Streptococcus Pneumoniae.

Subject analysis set title	Study 1 Control
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Healthy volunteers are randomised to be vaccinated with the Quadrivalent Inactivated Influenza Vaccine FLuarix and a nasal spray saline placebo followed by nasal inoculation aiming to collonise with Streptococcus Pneumoniae.

Subject analysis set title	Study 2 Intervention
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Healthy volunteers are inoculated nasally aiming to collonise with Streptococcus Pneumoniae then after three days randomised to be vaccinated with the Live Attenuated Influenza Vaccine (nasal spray) and a intramuscular injection of a saline placebo

Subject analysis set title	Study 2 Control
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Healthy volunteers are inoculated nasally aiming to achieve carriage of Streptococcus Pneumoniae then after three days vaccinated with the Quadrivalent Inactivated Influenza Vaccine Fluarix Tetra (IM) plus a placebo nasal saline spray.

Reporting group values	Study 1 Intervention	Study 1 Control	Study 2 Intervention
Number of subjects	55	62	73
Age categorical			
Healthy adults			
Units: Subjects			
Study 1	55	62	0
Study 2	0	0	73
Age continuous			
median age in years			
Units: years			
arithmetic mean	20	20	20
full range (min-max)	18 to 48	18 to 48	18 to 46
Gender categorical			
Female (59%)			
Units: Subjects			
Study 1	32	36	0
Study 2	0	0	40

Reporting group values	Study 2 Control		
Number of subjects	90		
Age categorical			
Healthy adults			
Units: Subjects			
Study 1	0		
Study 2	90		
Age continuous			
median age in years			
Units: years			
arithmetic mean	20		
full range (min-max)	18 to 46		
Gender categorical			
Female (59%)			
Units: Subjects			
Study 1	0		
Study 2	49		

End points

End points reporting groups

Reporting group title	Study 1 and 2 Intervention:

Reporting group description:

Live Attenuated Influenza Vaccine (LAIV) given as a nasal spray with a placebo intramuscular injection of saline.
After 3 days participants were inoculated nasally Streptococcus pneumoniae 6B wild type

Reporting group title	Control:

Reporting group description:

Inoculate with Streptococcus Pneumoniae then after 3 days immunise with Quadrivalent Inactivated Influenza Vaccination administered by intramuscular injection Fluarix Tetra, GlaxoSmithKline, UK paired with a placebo nasal spray using saline administered via a Mad Nasal LMA Nasal Atomizer

Subject analysis set title	Study 1 Intervention
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Healthy volunteers are randomised to be vaccinated with the Live Attenuated Influenza Vaccine (nasal spray) and a intramuscular injection of a saline placebo followed by nasal inoculation aiming to collonise with Streptococcus Pneumoniae.

Subject analysis set title	Study 1 Control
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Healthy volunteers are randomised to be vaccinated with the Quadrivalent Inactivated Influenza Vaccine FLuarix and a nasal spray saline placebo followed by nasal inoculation aiming to collonise with Streptococcus Pneumoniae.

Subject analysis set title	Study 2 Intervention
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Healthy volunteers are inoculated nasally aiming to collonise with Streptococcus Pneumoniae then after three days randomised to be vaccinated with the Live Attenuated Influenza Vaccine (nasal spray) and a intramuscular injection of a saline placebo

Subject analysis set title	Study 2 Control
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Healthy volunteers are inoculated nasally aiming to achieve carriage of Streptococcus Pneumoniae then after three days vaccinated with the Quadrivalent Inactivated Influenza Vaccine Fluarix Tetra (IM) plus a placebo nasal saline spray.

Primary: Study 1 Immunise First (antecedent)

End point title	Study 1 Immunise First (antecedent)

End point description:

Study 1 Immunise First
Primary outcome: Study 1 - Primary outcome: detection of pneumococcal bacteria in the nasal wash sample at any time point after inoculation by classical microbiology.

Primary end point is the occurrence of pneumococcal colonisation determined by the presence of pneumococcus in NW at each time point post inoculation (days 2, 7, 9, 14, 22 and 29

End point type	Primary

End point timeframe:

Presence of carriage of Streptococcus Pneumoniae at any time point

End point values	Study 1 Intervention	Study 1 Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	62		
Units: Pneumococcal Carriage rate				
Study 1 Classical Microbiology	25	24		

Statistical analyses

Statistical analysis title	Study 1 Immunise First Primary Outcome
Comparison groups	Study 1 Control v Study 1 Intervention
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.46
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	2.77
Variability estimate	Standard deviation

Notes:

[1] - 202 participants consented, of which 142 were screened, 137 were vaccinated, 130 were inoculated, and 117 participants entered the modified ITT analysis (n=55 LAIV, n=62 control)

Comparison of the primary endpoint showed similar overall carriage rates in LAIV participants and controls (25/55 [45.5%] vs 24/62 [38.7%], OR=1.32, p=0.46).

Primary: Study 2 Colonise First (concurrent)

End point title	Study 2 Colonise First (concurrent)

End point description:

Primary outcome:

Primary end point was AUC bacterial density to day 14 by conventional microbiology.

End point type	Primary

End point timeframe:

Primary outcome of Streptococcus Pneumoniae at any time point following inoculation until day 14

End point values	Study 2 Intervention	Study 2 Control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	73	90		
Units: Subjects				
Study 2 Classical Microbiology	36	45		

Statistical analyses

Statistical analysis title	Study 2 Primary Outcome

Statistical analysis description:

316 participants consented, 206 were screened, 198 were inoculated and 194 vaccinated. Data from 163 participants entered the modified ITT.

There was no significant difference in the primary endpoint of AUC carriage density by conventional microbiology to day 14, (mean±SD 20.93±14.07 and 26.10±14.41 in LAIV and controls respectively, p=0.11)

Comparison groups	Study 2 Intervention v Study 2 Control
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.11
Method	Mixed models analysis
Parameter estimate	Risk difference (RD)
Point estimate	5.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.08
upper limit	11.41
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded until 30 days after inoculation per participant for the duration of the study

Adverse event reporting additional description:

Pharmacovigilance reporting was consistent with MHRA and National Research Ethics Service. There were no Serious Adverse events reported. Participants with respiratory or ENT symptoms were assessed by the study clinician and no adverse events were assessed as related. Symptom data was assessed at each study visit (average 8 visits)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Live Attenuated Influenza Vaccine and placebo
Reporting group description: -	
Reporting group title	Quadrivalent inactivated Influenza Vaccination and placebo

Reporting group description: -

Serious adverse events	Live Attenuated Influenza Vaccine and placebo	Quadrivalent inactivated Influenza Vaccination and placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 165 (0.00%)	0 / 166 (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: 1 %

Non-serious adverse events	Live Attenuated Influenza Vaccine and placebo	Quadrivalent inactivated Influenza Vaccination and placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 165 (1.82%)	5 / 166 (3.01%)	
Ear and labyrinth disorders			
Otitis externa	Additional description: LAIV 1 participant QIV 2 participants (one with previous history)		
subjects affected / exposed	1 / 165 (0.61%)	2 / 166 (1.20%)	
occurrences (all)	1	2	
Eye disorders			

Conjunctivitis	Additional description: 2 participants reported eye infection treated with chloramphenicol		
subjects affected / exposed	0 / 165 (0.00%)	2 / 166 (1.20%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract infection	Additional description: A common event during the winter participants those with possible causality were were reviewed by a clinician. The following were treated with amoxicillin but subsequent microbiology:. QIV Influenza B LAIV Subsequently i) rhinovirus 2) NAD		
subjects affected / exposed	2 / 165 (1.21%)	1 / 166 (0.60%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 April 2014	Amendment 1 Change of Chief Investigator to Professor Neil French. Sponsor- addition of Co-sponsor with NHS Site. Samples: additional blood samples Exclusion criterior clarified.
30 April 2015	Amendment 2 Trial Oversight ; formalisation of roles for DSMG, TSC and TMG. Participants samples: minor change to bloods, and nasal samples Exlcusion criterior clarified.
16 December 2015	Amendment 3: IMP: MHRA and Public Health England confirmed FLumist may be administered nasally due to Fluenz shoratge.
13 September 2016	Amendment 4 Statistical Analysis plan revised based on advice by the Trial Steering Group for the concurrent study (inoculate then vaccinate) from % carriage rates to area under the curve with an increase in sample size to 156. Summary of Poroduct Characteristics: updated Fluarix Tetra and Fluenz. Minor changes to participant information, symptom log and sampling.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported