



## Clinical trial results:

**A phase II, multi-centre, open labelled randomised control trial to describe immune & transcriptomic responses to trivalent inactivated vaccine (TIV) & MF59 adjuvanted influenza vaccine (ATIV) in 14 -26 month healthy children.**

### Summary

EudraCT number	2012-002443-26
Trial protocol	GB
Global end of trial date	21 November 2014

### Results information

Result version number	v1 (current)
This version publication date	24 August 2016
First version publication date	24 August 2016

### Trial information

#### Trial identification

Sponsor protocol code	OVG2012/04
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01682369
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Oxford Vaccine Group
Sponsor organisation address	CCTVM, Churchill Hospital, Old Road, Headington, Oxford, United Kingdom, OX3 7LE
Public contact	Professor Andrew J Pollard, University of Oxford, 44 01865857420, andrew.pollard@paediatrics.ox.ac.uk
Scientific contact	Professor Andrew J Pollard, University of Oxford, 44 01865857420, 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:

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## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 November 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 November 2014
Global end of trial reached?	Yes
Global end of trial date	21 November 2014
Was the trial ended prematurely?	No

Notes:

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## General information about the trial

Main objective of the trial:

Infants and young children do not respond as well as adults to the flu vaccines currently available in the UK. Fluad, or ATIV is a different type of influenza vaccine has been available in the European continent for the last decade, and contains an adjuvant known as MF59.

This vaccine has been used extensively in adults, but is not yet licensed for use in children. Previous studies have shown that it does produce an enhanced immune response in children compared with traditional vaccines (TIV), and that it is safe in this age group. However, the specific means by which MF59 influences the immune system are not fully characterised.

This study aims to assess the genes that are 'switched on' in response to immunisation with these two vaccines to better understand how the immune response to these vaccines differs.

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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 three 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.

This is a descriptive study to understand how genetic responses vary at different times following immunisation with two different influenza vaccines. Participants had the advantage of receiving one of the influenza vaccines, which is not part of their routine schedule. Participant involvement will help us to understand these responses and plan future vaccine development.

Participants could withdraw from the study at any time.

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Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	United Kingdom: 90
Worldwide total number of subjects	90
EEA total number of subjects	90

Notes:

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**Subjects enrolled per age group**

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In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	90
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:

Study participants were identified within the local area who were of the appropriate age range via the Child Health Computer Database (CHCH) and/or the National Health Applications and Infrastructure Services (NHAIS) who hold the central NHS patient database. Recruitment was also active via the Oxford Vaccine Group study website.

### Pre-assignment

#### Screening details:

Explanation for the study, obtain written informed consent parent/guardian, randomise/assign participant number, check exclusion/inclusion criteria, physical examination, measure/record axillary temperature, collect blood sample (up to 6.0ml), administer dose (0.25ml) of TIV or ATIV vaccine, observe for 15 mins, issue ruler/thermometer/diary card.

### Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
Arm title	TIV (Group 1)

#### Arm description:

Participants were randomised 1:1:1 into 3 groups (n=15 per group) to receive the TIV vaccine with variable visit windows for blood collection at Visit 3 defined as 1A, 1B and 1C.

V1 = Day 0 (blood test at baseline + vaccination 1st dose)

V2 = Day 28 (vaccination 2nd dose)

V3 = 1A (V2 +1), 1B (V2+3) and 1C (V2+7) blood test

V4 = V2 + 28 days (blood test)

Arm type	Experimental
Investigational medicinal product name	TIV (AGRIPPAL®/BEGRIPAL®)
Investigational medicinal product code	
Other name	trivalent inactivated vaccine (TIV)
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

#### Dosage and administration details:

2 x 0.25ml dose administered at an interval of 26-35 days.

Arm title	ATIV (Group 2)
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#### Arm description:

Participants were randomised 1:1:1 into 3 groups (n=15 per group) to receive the ATIV vaccine with variable visit windows for blood collection at Visit 3 defined as 2A, 2B and 2C.

V1 = Day 0 (blood test at baseline + vaccination 1st dose)

V2 = Day 28 (vaccination 2nd dose)

V3 = 2A (V2 +1), 2B (V2+3) and 2C (V2+7) blood test

V4 = V2 + 28 days (blood test)

Arm type	Experimental
Investigational medicinal product name	ATIV (IMUVAC®)
Investigational medicinal product code	
Other name	adjuvanted influenza vaccine (ATIV)
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

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Dosage and administration details:

2 x 0.25ml dose administered at an interval of 26-35 days.

<b>Number of subjects in period 1</b>	TIV (Group 1)	ATIV (Group 2)
Started	46	44
Completed	46	44

## Baseline characteristics

### Reporting groups

Reporting group title	TIV (Group 1)
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Reporting group description:

Participants were randomised 1:1:1 into 3 groups (n=15 per group) to receive the TIV vaccine with variable visit windows for blood collection at Visit 3 defined as 1A, 1B and 1C.

V1 = Day 0 (blood test at baseline + vaccination 1st dose)

V2 = Day 28 (vaccination 2nd dose)

V3 = 1A (V2 +1), 1B (V2+3) and 1C (V2+7) blood test

V4 = V2 + 28 days (blood test)

Reporting group title	ATIV (Group 2)
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Reporting group description:

Participants were randomised 1:1:1 into 3 groups (n=15 per group) to receive the ATIV vaccine with variable visit windows for blood collection at Visit 3 defined as 2A, 2B and 2C.

V1 = Day 0 (blood test at baseline + vaccination 1st dose)

V2 = Day 28 (vaccination 2nd dose)

V3 = 2A (V2 +1), 2B (V2+3) and 2C (V2+7) blood test

V4 = V2 + 28 days (blood test)

Reporting group values	TIV (Group 1)	ATIV (Group 2)	Total
Number of subjects	46	44	90
Age categorical			
Infants and toddlers (28 days - 23 months)			
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)	46	44	90
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			
Infants and toddlers (28 days - 23 months) both male and females were enrolled into the trial.			
Units: Subjects			
Female	20	15	35
Male	26	29	55

### Subject analysis sets

Subject analysis set title	Data Analysis - TIV
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Subject analysis set type	Per protocol
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Subject analysis set description:

Humoral immunity to influenza (HAI titres), multicytokine production, ELISPOT and transcriptome analysis on blood samples collected at V1, V2, V3 and V4.

Subject analysis set title	Data Analysis - ATIV
Subject analysis set type	Per protocol

Subject analysis set description:

Humoral immunity to influenza (HAI titres), multicytokine production, ELISPOT and transcriptome analysis on blood samples collected at V1, V2, V3 and V4.

Reporting group values	Data Analysis - TIV	Data Analysis - ATIV	
Number of subjects	45	45	
Age categorical			
Infants and toddlers (28 days - 23 months)			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	46	44	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
Infants and toddlers (28 days - 23 months) both male and females were enrolled into the trial.			
Units: Subjects			
Female	20	15	
Male	26	29	

## End points

### End points reporting groups

Reporting group title	TIV (Group 1)
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Reporting group description:

Participants were randomised 1:1:1 into 3 groups (n=15 per group) to receive the TIV vaccine with variable visit windows for blood collection at Visit 3 defined as 1A, 1B and 1C.

V1 = Day 0 (blood test at baseline + vaccination 1st dose)

V2 = Day 28 (vaccination 2nd dose)

V3 = 1A (V2 +1), 1B (V2+3) and 1C (V2+7) blood test

V4 = V2 + 28 days (blood test)

Reporting group title	ATIV (Group 2)
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Reporting group description:

Participants were randomised 1:1:1 into 3 groups (n=15 per group) to receive the ATIV vaccine with variable visit windows for blood collection at Visit 3 defined as 2A, 2B and 2C.

V1 = Day 0 (blood test at baseline + vaccination 1st dose)

V2 = Day 28 (vaccination 2nd dose)

V3 = 2A (V2 +1), 2B (V2+3) and 2C (V2+7) blood test

V4 = V2 + 28 days (blood test)

Subject analysis set title	Data Analysis - TIV
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Subject analysis set type	Per protocol
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Subject analysis set description:

Humoral immunity to influenza (HAI titres), multicytokine production, ELISPOT and transcriptome analysis on blood samples collected at V1, V2, V3 and V4.

Subject analysis set title	Data Analysis - ATIV
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Subject analysis set type	Per protocol
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Subject analysis set description:

Humoral immunity to influenza (HAI titres), multicytokine production, ELISPOT and transcriptome analysis on blood samples collected at V1, V2, V3 and V4.

### Primary: Study Objectives

End point title	Study Objectives <sup>[1]</sup>
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End point description:

End point type	Primary
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End point timeframe:

To describe gene expression profile in response to TIV & ATIV vaccine at each time point.

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: Due to the descriptive nature of the study, formal statistical analysis comparing the two groups has not been performed.

End point values	TIV (Group 1)	ATIV (Group 2)	Data Analysis - TIV	Data Analysis - ATIV
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	46	44	45	45
Units: Differentially expressed genes				
number (not applicable)	564	1449	564	1449



## **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

All AEs occurring in the first 8 days after immunisation (Day 0 to Day 7), and all AEs resulting in an unscheduled visits to a physician or emergency department or withdrawal from the study occurring within 1 month after vaccination.

Adverse event reporting additional description:

All AEs occurring in the first 8 days after immunisation (Day 0 to Day 7), and all AEs resulting in an unscheduled visits to a physician or emergency department or withdrawal from the study occurring within 1 month after vaccination observed by the investigator or reported by the participant's parent or guardian, whether or not attributed to study

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	Protocol
Dictionary version	3.0

### Reporting groups

Reporting group title	TIV (Group 1)
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Reporting group description: -

Reporting group title	ATIV (Group 2)
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Reporting group description: -

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: Non-serious adverse events were recorded only as a secondary objective and are not expected to contribute to future safety evaluations of this vaccine. Therefore non-serious adverse events are not listed in this submission.

Serious adverse events	TIV (Group 1)	ATIV (Group 2)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 45 (2.22%)	1 / 45 (2.22%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Croup and Viral Induced Wheeze	Additional description: An SAE of wheeze commenced 18 days after immunisation with IMUVAC and was not considered related to the IMP. An SAE of croup commenced 14 days after immunisation with Fluad and was not considered related to this IMP.		
subjects affected / exposed	1 / 45 (2.22%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	TIV (Group 1)	ATIV (Group 2)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 November 2012	Substantial Amendment 1: the amendment covered a change to V2.0 of the protocol because of on-going difficulties sourcing the control TIV vaccine Agrippal. The Protocol has been amended to allow for the possibility of an additional control vaccine (Imuvac), depending on vaccine availability at the start of enrolment. In addition a further information booklet and Health professional letter has been created to explain the study with use of the Imuvac vaccine. A letter/ Compliments slip has also been created to explain the changes to parents.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26755593>