OXFORD VACCINE GROUP

ADITEC FLU 2 STUDY:
Understanding the genetic basis for immune responses to flu vaccines in children and adults

Information Booklet
(Child and Parent)

We would like to invite your child to take part in a study of vaccines against the flu virus. Parents are also invited to take part in this study. The study is being run by the Oxford Vaccine Group, part of the University of Oxford.

Before you decide whether to take part, it is important for you to understand what the study is about and what participation would involve. Please take time to read the information carefully, and discuss with others if you wish.

If anything is unclear or you would like further information please contact the study team – details below.

Thank you for taking the time to consider taking part in this study.

Contact Details
Oxford Vaccine Group
Centre for Clinical Vaccinology and Tropical Medicine
Churchill Hospital
Oxford, OX3 7LE

Tel/Fax: 01865 857420
Email: info@ovg.ox.ac.uk
Website: www.ovg.ox.ac.uk
Dear Parent/Legal Guardian,

The Oxford Vaccine Group would like to invite you and your child to take part in a study that aims to understand the genetic responses after immunisation with a new flu vaccine. This booklet outlines the study and what it would involve if you and your child were to take part. This study is being sponsored by the University of Oxford. Approval for this study has been gained from the South West Research Ethics Committee and the Medicines and Healthcare Products Regulatory Agency (MHRA).

**What is the Oxford Vaccine Group?**

The Oxford Vaccine Group is part of the University of Oxford and is an independent research team of doctors, nurses and play assistants. We carry out research studies of new and improved vaccines for babies, young children, teenagers and adults and teach doctors and nurses about immunisations. In the past five years alone, over 7,000 participants in the Thames Valley area have taken part in our research studies.

**Why have we been invited to take part in this vaccine study?**

You have been approached because your child is within the age range for the study and you live in an area where the study is being carried out. This letter has been posted to you by the Child Health Database, who hold the central NHS patient database. Please note that the Oxford Vaccine Group has not been given your names or address. Taking part in this study is voluntary and if you do not want or do not want your child to participate you do not have to reply to this invitation.

**What is this study about?**

Influenza or ‘flu’ is a respiratory illness which is caused by infection with influenza viruses. Fortunately most people who catch flu have a relatively mild illness, but a few people become very unwell and may even die. Potentially vulnerable people include young children, the elderly, pregnant women and adults with underlying health conditions, such as heart or lung disease.
In 2013 the Department of Health introduced a flu vaccine that could be squirted into the nostrils (intranasal), for all children aged two and three years, protecting against four types or strains of flu. Flu vaccination is also recommended for adults over the age of 65 years, all adults and children (age 6 months to 18 years) with specific chronic health problems and for pregnant women. The vaccines used for immunisation are updated every year to match three or four of the most commonly circulating strains.

Although the new intranasal flu vaccine is better at protecting children aged two years and over against the flu compared to the traditional injected vaccines, infants and young children under two years are unable to have this vaccine. A different type of flu vaccine has been available in the European continent for over a decade, which contains an adjuvant (something which helps stimulate the body’s immune response to immunisations) known as MF59, which is an oil-based substance, and protects against three strains of influenza. This vaccine (Fluad®, Gripguard® (France), Chiromas® (Spain)) has been administered to over 85 million adults over 65 years of age.

MF59 containing influenza vaccines have also been administered to over 5000 children in previous studies, which have shown enhanced immune responses in children compared with traditional vaccines, and that the vaccine is safe in this age group. However, currently the vaccine is not licensed for use in children.

The reason for this new study is to gain a better understanding of the how this vaccine is stimulating the immune system. We know that when children’s immune systems respond to infections or vaccines, specific ‘immune response’ genes are activated or ‘switched on’, and that different types of immune responses result when different genes are activated. This is called gene expression. We are also interested to assess the difference in response between children and adults. To do this we would enrol children and adults to receive the MF59 adjuvanted trivalent influenza vaccine (ATIV) and look at which genes are activated when participants receive the vaccine, and how the activated genes correspond to the immune system response. We would also be assessing for any reactions such as fever following immunisation.
Previous research has shown that there is a wide variation in gene expression seen in individuals of different race. This variation can make results difficult to interpret. To ensure that the background gene expression is as consistent as possible we are only enrolling Caucasian children (approximately 70% of children in Oxfordshire) and adults.

We hope the information gained from this study will enable quicker development of vaccines against influenza and other diseases in the future.

**What does the study involve?**

This study would enrol 90 children aged 13 to 24 months and 30 adults aged 18 to 65 years, and consists of 5-6 visits over a 2-4 month period. Parents of children taking part in the study are able to be enrolled in the adult group of the study if interested, but this is not required for your child to participate. Adults who are not parents of children in the study are also able to be enrolled in the adult group. The visits would be conducted at your home and at the first visit the study would be explained and you would be given the chance to ask any questions you may have. Each child enrolled in the study would receive two doses of the ATIV flu vaccine four weeks apart and adults would receive one dose (these are the recommended doses for ATIV in healthy children and adults). Children enrolled in the study would be allocated to one of three study groups based on availability for visits. We would aim for the adults in the study who are parents of child participants to have most of their visits at the same time as their child’s.
The diagram below summarises the study design for the children enrolled:

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Screening, Consent, Group Allocation</th>
<th>Blood Test</th>
<th>ATIV Dose 1</th>
<th>Blood Test</th>
<th>No visit</th>
<th>ATIV Dose 2</th>
<th>Blood Test</th>
<th>No visit</th>
<th>Blood Test</th>
<th>No visit</th>
<th>Blood Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2</td>
<td>Screening, Consent, Group Allocation</td>
<td>No visit</td>
<td>ATIV Dose 1</td>
<td>No visit</td>
<td>Blood Test</td>
<td>ATIV Dose 2</td>
<td>Blood Test</td>
<td>No visit</td>
<td>Blood Test</td>
<td>No visit</td>
<td>Blood Test</td>
</tr>
<tr>
<td>Group 3</td>
<td>Screening, Consent, Group Allocation</td>
<td>No visit</td>
<td>ATIV Dose 1</td>
<td>No visit</td>
<td>No visit</td>
<td>Blood Test</td>
<td>ATIV Dose 2</td>
<td>No visit</td>
<td>Blood Test</td>
<td>Blood Test</td>
<td>Blood Test</td>
</tr>
</tbody>
</table>

The diagram below summarises the study design for the adults enrolled:

<table>
<thead>
<tr>
<th>Group 4 (Adults)</th>
<th>Screening Consent</th>
<th>Blood Test</th>
<th>ATIV</th>
<th>Blood Test</th>
<th>Blood Test</th>
<th>Blood Test</th>
<th>Blood Test</th>
</tr>
</thead>
</table>

In order to assess the genetic and immune response to the vaccine all children would have a blood test four weeks after the second vaccine dose and two additional blood tests performed in the days surrounding either the first or second immunisation. For each blood test in children we would take up to 6.5ml of blood (approximately one teaspoonful). Local anaesthetic cream would be used to minimise the discomfort of the blood test in children and we would use trained staff members to help distract your child during this procedure.
Adults would have four blood tests of up to 9.5ml: one prior to immunisation and three blood tests within the 28 days following the vaccine.

The study staff would explain how to use an electronic online diary for recording any reactions to the vaccines. In this diary we would ask parents/participants to record daily temperatures and any reactions, such as injection site redness or swelling for four days starting from the day of immunisation. We would also ask parents/participants to record general health and behaviour in the two days before the immunisations to help assess the baseline health status of participants. The diary would be checked by a study team member.

**Who can take part in the study?**

Before enrolment into the study, a doctor would examine you and ask some questions to ensure that the child/adult could be included.

Reasons that children or adults would not be able to take part in the study include:

- Non-Caucasian
- Any previous flu vaccination (children) or current season (2015/2016) flu vaccination (adults)
- Immunisation with another vaccine within three weeks prior to visit 1 (ATIV immunisation dose 1)
- Previous confirmed influenza infection or treated with anti-flu medication (children)
- History of egg allergy
- Problems with the immune system or other serious medical conditions
- Bleeding disorders
- Receiving steroid tablets/syrup (e.g. for asthma) or other immunosuppressant medications for more than one week within the three months prior to visit 1 (steroid inhalers or creams are allowed)
- Recent blood transfusion or blood product (within three months prior to visit 1)
- Current participation in another clinical trial
- Not being available for all the study visits or having internet access
• Not having received the routine UK immunisation schedule (children)
• Pregnancy (adults)

**What are the advantages of taking part in the study?**

Participants would have the advantage of receiving a flu vaccine which they would not usually be offered and which has evidence for helping make strong immune response against flu viruses. Importantly, involvement in this study would help us understand these responses and plan future vaccine development.

**What are the risks and side effects of taking part in the study?**

The ATIV vaccine containing MF59 has been licensed and used in adults over the age of 65 years for many years. Although the experience with young adults and children has been limited, recent studies involving more than 4000 children aged 6-72 months in Europe have raised no safety concerns for use in children and that the side effects of ATIV are similar to the traditional influenza vaccine available to children over six months of age and adults.

Common reactions that may be observed in up to three out of every 10 people are tenderness, redness, swelling and hardness at the injection site. Fever following vaccination is seen in approximately one out of every 10 children. Less common reactions for children are a change in eating habits, sleepiness, persistent crying, irritability, swelling of lymph nodes (‘glands’), muscle or joint pain. Very rare (less than 1 in 1000) reactions may include vomiting, diarrhoea, rash, cough and a congested nose. In adults, headache, nausea, vomiting, tiredness, muscle or joint pain have been reported. We expect these events to be generally mild and to resolve within a few days.

Other very rare events that have been seen with routine flu vaccines include seizures and temporary bleeding disorders. In the past, Guillian-Barré syndrome (a rare disorder of nerves) has been associated with flu vaccines but the relationship remains uncertain, with some studies suggesting a possible link but others not finding it.
One large study in the UK found that influenza-like illness itself was associated with an increased risk of the Guillain-Barré syndrome but there was no link with the seasonal influenza vaccines, suggesting that vaccination might actually protect against the disorder by preventing flu. There has been an increase in the number of cases of narcolepsy (a sleep disorder which causes sudden daytime sleepiness) reported in Finland and Sweden in children receiving Pandemrix (a vaccine that was used against ‘swine flu’). Following these reports, the use of this vaccine has now been stopped. There are no reports of this disorder being linked to the ATIV vaccine to be used in this study.

An immediate type anaphylaxis reaction (severe allergic reaction resulting in a rash, swelling of the body and breathing difficulty) may occur in approximately one in a million people receiving a vaccine. This can happen following any vaccination and is not specific to influenza vaccines. The study team will observe participants for 15 minutes following the vaccination as this is the time most such reactions are expected to happen. The study teams carry adrenaline (medicine to treat anaphylaxis reactions) and are trained to administer it should such a reaction occur.

Following the blood tests participants may experience temporary soreness and bruising. In children this discomfort will be minimised by the use of a local anaesthetic cream.

**What happens to the blood samples?**

Blood samples obtained in the study would be processed in the lab at Oxford Vaccine Group to look at how different types of white blood cells respond following immunisation. Blood samples will also be shipped to a laboratory in Europe for further testing of immune responses and to the USA to study the genetic changes following vaccination. All blood samples would be labelled with study codes and initials but not the participant’s name, so are completely anonymous when shipped outside the UK or processed in the laboratory.

If you chose to take part in this study, we will be asking for your separate permission to store components of your child’s/your blood, including DNA, in a collection of samples called a BioBank.
Details of this would be explained in a separate booklet provided to you after enrolment into this study, and you are free to say no to this and continue to take part in the study.

**What happens when the study stops?**

When the study finishes, your child/you will continue to be looked after by their/your GP for general care. We will notify your GP that your child’s/your participation in the study is complete.

**Is there someone I can contact during the study?**

We provide all participants/participant’s parents with a 24-hour telephone number to enable you to contact one of our study team should you have any concerns.

**Who else would be told about my child’s/my involvement in the study?**

Your child’s/your participation would remain confidential and if the results of the study were published, participants would not be identified. With your permission we would inform participant’s GP, and for child participants - health visitor and child health department, that you/your child were enrolled in this study and that we had administered the flu vaccine. We may also require access to healthcare records/vaccination history of participants. Participant’s personal information collected throughout the study will be stored at Oxford Vaccine Group, including any study records with participant’s name and address.

In order to ensure that the study is being conducted correctly, the following groups may inspect the study records and participant’s medical records, without violating your child's/your confidentiality:

- Monitors hired to check that the study is being conducted to a high standard
- Responsible members of the University of Oxford and/or NHS Trust may be given access to data for monitoring and/or audit of the study to ensure we are complying with regulations
- The Medicines and Healthcare products Regulatory Agency (MHRA), who regulate all medicines and vaccines in the United Kingdom.
By signing the consent form for this study, you would be giving permission for these groups to look at your child’s/your medical records; however they would not be able to remove any information that identified your child/you from the premises of the Oxford Vaccine Group.

**What happens if I say ‘no’?**

Taking part in research is voluntary. If you decided not to participate, this would not affect your child’s/your routine care in any way. You are also free to change your mind at any time without giving any reason. If you decide not to take part in this study you should follow any advice from your GP or local health authority regarding vaccination against flu.

**What will happen if we or either of us doesn’t want to carry on with the study?**

You are also free to change your mind at any point during the study and withdraw yourself/your child at any time without giving an explanation. We would analyse the samples we have already taken up to the point you withdraw unless you instruct us otherwise.

**What will happen to the results of the research study?**

We plan to publish the results in a medical journal that will be accessible to the public. This will not contain any information that might allow the readers to identify participants who took part in the study. At the end of the study, we will write to all participants with information to enable them to access to the published results.

**Who is funding the research?**

The study is funded by Advanced Immunisation Technologies (ADITEC). ADITEC is a collaborative research programme initiated in 2011 with an aim to contribute information to develop improved immunisation technologies for future vaccines.

**Who reviewed the study?**

All research is looked at by an independent group of people, called a Research Ethics Committee to protect the safety, rights, well-being and dignity of individuals. This study has
been reviewed and given favourable opinion by the South Central – Hampshire A Research Ethics Committee (Ref: 15/SC/0387).

What will happen if we or either of us don’t want to carry on with the study?

You are also free to change your mind at any point during the study and withdraw yourself at any time without giving an explanation. We would analyse the samples we have already taken up to the point you withdraw unless you instruct us otherwise.

What if I wish to complain?

If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact the Oxford Vaccine Group on 01865 857420 or email info@ovg.ox.ac.uk. You can also contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224 or email the head of CTRG, Heather House ctrg@admin.ox.ac.uk

What else do I need to know?

The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that your child or you suffer any harm as a direct consequence of your participation in this study. Should any information become available during the course of the study that may affect your/your child’s participation, you would be informed as soon as possible.

So, in summary, what would happen if I decide to take part in the study?

- For child participants, we would administer two doses of the ATIV vaccine and take three blood samples up to 6.5ml at 5-6 visits over a period of 2-4 months.
- For adult participants, we would administer one dose of the ATIV vaccine and take four blood samples up to 9.5ml over 6 visits.
- You would have 24-hour telephone access to our study team should you have any concerns following vaccination.
What do I do now?

You do not need to make a final decision straight away. Please contact us by:

- e-mail info@ovg.ox.ac.uk
- Telephone/fax 01865 857420
- Website: www.ovg.ox.ac.uk/recruiting-studies

Alternatively you can complete the attached form and return it in the reply-paid envelope provided.

Members of the research team will be happy to discuss the study with you and answer any questions you may have.

A postcard reminder would be posted to you by the Child Health Department in two weeks’ time. If we do not hear from you after this, we will assume that you do not want to take part in the study. If you do not wish to receive invitations of this kind in the future, please contact the NIHR CRN: Thames Valley and South Midlands – Primary Care team on: tvp.crp@nhs.net.

Thank you for considering taking part in this study.

Yours sincerely,

[Signatures]

Professor Andrew Pollard
Chief Investigator
Professor of Paediatric
Honorary Consultant
Paediatrician

Dr Smiti Bihari
Paediatric Clinical Research Fellow

Rachel White
Lead Research Nurse
### OXFORD VACCINE GROUP

**ADITEC FLU STUDY 2:**
Understanding the genetic basis for immune responses to flu vaccines in children and adults

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**Reply Slip**

I am interested in the below taking part in this study (please tick all that apply):

- [ ] Child
- [ ] Children
- [ ] Adult(s)

### Your details

<table>
<thead>
<tr>
<th>Name</th>
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<tbody>
<tr>
<td>Your address</td>
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<td>Phone number(s)</td>
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<tr>
<td>Home &amp; Mobile (and best time to call)</td>
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<tr>
<td>Email address</td>
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</tr>
</tbody>
</table>

Please indicate preferred method of contact please tick

- [ ] Email
- [ ] Phone

### Your child’s details

<table>
<thead>
<tr>
<th>Name</th>
<th></th>
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<tbody>
<tr>
<td>Date of birth</td>
<td></td>
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<tr>
<td>Sex (please circle)</td>
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</tr>
<tr>
<td>Male/ Female</td>
<td></td>
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<tr>
<td>GP Name and Surgery</td>
<td></td>
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☐ Please contact me, I would like to know more about the study. I realise this is not a commitment to taking part in the study

OR ☐ I do not wish to be included in this study.

*All reasonable attempts will be made to prevent sending you a reminder postcard. To enable us to identify you and remove the correct person from the mailings a name, DOB and address is required to ensure reminders are not sent. Reminders are sent two weeks after this letter, there is a possibility that your response and the postcard reminder will cross in the post.*