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STELLAR

STudying Early-Life Live Attenuated influenza virus immune Responses

Full Title: In-depth analysis of the nasal mucosa and systemic immune response in Influenza-vaccinated children

Study Information Booklet

We are inviting children aged 2 to 5 to take part in a study which will investigate how the yearly nasal influenza vaccine effects the immune system within the nose. A better understanding of the exact mechanisms of the immune systems response within the nose will allow better strategies for developing tests, treatments and vaccines for children going forward.

Before you decide that you would like your child to take part in this study, it is important for you to understand what the study is about and what participation would it involve. Please take time to read the information carefully and discuss it with others if you wish. If you have any questions, please contact the study team. Thank you for taking the time to consider volunteering for this study.

Contact the local study team at: Oxford Vaccine Group Tel: 01865 611 400 Email: info@ovg.ox.ac.uk

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Contents

Summary

- This study will compare the protective response to infections (also called an immune responses) in the nose to the protective response in the blood following vaccination with a safe and effective nasal influenza vaccine.
- The nasal live-attenuated influenza virus vaccine is a licensed vaccine on the routine schedule yearly between ages 2 and 17 years old.
- We aim to vaccinate up to 40 children aged between 2 and 5 years old from September 2024 onwards (vaccination possible until the day before the child's 6th birthday).
- Children will have two study visits over a 1-month period in autumn or winter. This will take place in the child's home or another convenient location.
- Children will be immunised with live-attenuated influenza virus vaccine (LAIV) in their own home (or a convenient location) on the first visit. 'Live-attenuated' means the vaccine contains a live virus, which has been weakened so it does not cause infection in healthy people.
- On each of the two visits we plan to obtain a small blood sample and a nasal swab. The blood sample volume with be equivalent to about two teaspoons at each visit and we will use a local anaesthetic cream to numb the skin for blood tests.
- Children will also have nasal fluid (nasosorption) and saliva collected at both visits and additionally will be asking you to take samples at home on 8 days between the two visits. We will train parents in these simple procedures as their first study visit and guidance documents will be provided.
- These home samples will be stored in your freezer until the end of the study, or earlier if convenient, in which they will be collected by the study team (or by a courier).

Why has my child been invited to take part?

You have been approached as your child is in the age range for this study and lives in one of the study areas. If you have received this invitation through the post, it has been mailed to you by the Child Health Information Service, or another equivalent NHS database. Please note that the Oxford Vaccine Group has not been given your child's name or address.

What is this study about?

Lower respiratory tract infections caused by viruses and bacteria account for a substantial burden of disease and death throughout the world.

New nasal vaccines are being developed which show great promise.

1. They are less painful/distressing and so are easier to give than injected vaccines

2. They can be just as good at stopping infection
3. They are often even better at stopping the spread of respiratory diseases than regular vaccines (This protects the people around the children too especially the elderly and vulnerable as children are often the means of disease spread to these groups.)
4. They can prevent colonisation (bugs living there without illness) of the nasal cavity

The nasal influenza vaccine is an effective, well tolerated vaccine given to children between ages 2 and 17 each year. It effectively stimulates an immune response in the nose and reduces infection and transmission of influenza. The exact mechanisms of the immune response within the nose following nasal vaccination are not well understood - particularly in children. This study hopes to gain a better understanding of the protective responses that are induced by this vaccine within the nose. This will allow researchers to develop better tests, treatments and vaccines for children going forward.

Can my child take part?

Children must be aged between 2 and 5 years old (aged two years or more, and not yet turned six years old) when the day of vaccination in the study. Children who have already received an influenza vaccine for the coming winter period cannot enrol in the study.

Children with some medical conditions are not able to take part. These include impaired immunity, asthma/wheeze requiring inhaled or oral steroid use and severe allergic reactions to certain chemicals (including sucrose and gelatine); other serious conditions may also preclude participation.

If the child cannot take part in this study, the reasons for this will be explained and discussed with the parent.

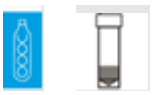
What happens in the study?

If you decide to take part in this study, our study team are available to answer your questions and make an appointment to see you and your child.

During the first visit, the study team will discuss the study with you and answer your questions. If you decide to participate in the study, and your child is eligible to do so, we will ask you to complete a consent form.

What happens at each study visit is summarised in the following table, and then described in more detail.

Table 1: Timeline of the study and clinic visits

Procedure (Day of study)	Day 0 (Visit 1*)	Home Sampling (Days 1, 2, 3, 4, 6, 9, 14 & 21)	Day 28 (Visit 2)
Informed consent			
Check well for vaccination including an armpit temperature			
Vaccination			
Nasal fluid ('Nasosorption') and Saliva Samples	 (Training on how to collect)		
Blood and Nasal Cell Samples			

* Visit 1 - the consent process and procedures may occur on different days on parental request or to support study recruitment. If different, then Day 0 will refer to the vaccination visit)

This study involves two study visits over approximately 29 days. All study visits will be conducted in your own home, or in another convenient location.

The study includes:

- Immunisation with the nasal influenza vaccine
- Completion of a symptom diary on the day of vaccination and for the following 28 days
- Two blood and nasal cell samples at days 0 and 28
- Following some training at Day 0, nasal fluid samples and saliva samples will be collected by parents/guardians (following appropriate training on days 0, 1, 2, 3, 4, 6, 9, 14, 21 and 28. This will be captured as part of the diary that will be completed.
- Reminder text/email messaging reminders may be sent on other days when sampling is due).

Before the final visit (Day 28), you will receive a phone call from the study team to confirm your appointment date and confirm that you are still willing and able to continue in the study.

Day 0 (visit 1)

At the **first study visit**, we will discuss the study in detail including the reasons for doing this study, the vaccination, the study procedures and risks and benefits to taking part in the study. We will go through the consent process in detail. You will be given as much time as needed to consider the information discussed.

If you proceed with the consent process on this day, we will proceed to asking inclusion and exclusion criteria and if eligible, collect the required samples

We will ask you some questions about your child's medical history, including medications. We will record details such as date of birth. If necessary, a medical examination will be done by a study doctor. We check that your child hasn't yet received the flu vaccine this flu season. We will check your child's temperature and ensure that they are fit to receive their vaccine. In some situations, it is necessary to delay vaccination, for example, if your child has:

- a fever (temperature of ≥38.0°C) in the previous 72 hours
- received any other vaccine in the previous 2 weeks
- planned elective surgery, admission to hospital or any other procedure that may require a general anaesthetic within the study period

If your child is well and you remain happy to proceed with the study, your child will have some nasal fluid taken with a blotting-paper-like device (nasosorption sampling). They will also have a saliva sample taken by chewing on a little sponge designed for saliva sampling. These are both very straightforward, and you will be taught the processes in order to conduct further samples on later days. You can also contact the study team if you have any questions.

The samples of nasal cells from inside the nostril will be collected using a small swab. A blood sample will be taken on Day 0 (visit 1), this will be to assess their baseline immune status. At this visit, we will take a maximum of 10 mL of blood (~ 2 teaspoons).

In order to make the process of obtaining a blood sample as well tolerated as possible, we use an anaesthetic cream and/or spray to help numb the skin and a play assistant will attend these visits and will be there to distract your child if needed. If necessary, we may ask to make a second attempt if unsuccessful at the first attempt. If there are difficulties obtaining the blood sample, we may reschedule your visits to another day or use an alternative method of a finger prick. This would be discussed with you if needed and would be your decision.

We will lastly give the nasal influenza vaccine. It is administered as a little spray up each nostril. Children breathe normally during this process and generally tolerate it very well. This is given routinely at this age in the routine UK immunisation schedule. Study staff will observe your child for 15 minutes after the vaccination.

Home sampling

Between Day 0 and Day 28, parents will conduct home "nasosorption" and saliva sampling as per the above schedule (Table 1). You will place a nasosorption strip inside the nostril of your child for approximately up to 2 minutes (or as long as tolerated or until it is soaked through). The samples will be labelled with a number unique to your child, we would ask for you to add the time and date of sampling to this label and record the duration it was tolerated for the child. You may receive a reminder message on each day this is due to occur. If for some reason a sample is not obtained on the day we have specifically asked for it to be obtained, we would ask for you to complete that sample as soon as it is feasible to do so. We would kindly request that you keep and store the samples in your freezer along with a temperature logger that we will provide, you will be shown how to use this temperature logger at Day 0. As part of a daily electronic diary (e-diary, more details below) we will be asking for you to complete the details of sampling on there.

We will also ask you to complete a short symptom e-diary daily for your child between Day 0 and Day 28. We would expect mild viral symptoms to occur in many participants for the first few days following the vaccination. However, as we are looking to characterise the nasal immunity responses following infection, it is important to know if the participating children experience any other symptoms of respiratory illness so that we can include this in our analyses.

We will therefore provide you with access to an e-diary to record any symptoms your child may have in the days between the two visits, including the day of the vaccination. A paper version of the diary may be provided as a back-up. We will explain how to complete this diary. We will give you a thermometer to record your child's temperature and ask you to use this and record if your child has a fever you become concerned about this. We will ask you to record any medications given to your child. This will be explained and shown in person on your 1st visit.

Whilst your child is in the study, parents will have 24-hour telephone access to a study doctor, should they have any concerns.

You will be asked to contact the study team if your child is admitted to hospital at any point during the study.

You can also contact the study team if you have any questions.

Day 28 (Visit 2)

At the **final visit** – approximately 28 days after vaccination, we will enquire about any medical problems since the first visit. We will again check that you are happy to proceed with the study.

Your child will again have nasal cells and a blood sample (10 mL; ~ 2 teaspoons) taken to assess their immune response as described above. We will also obtain a final nasosorption and salivary sample and collect the samples you have stored from the home sampling timepoints, if not previously

collected. We will collect any documentation associated with the study that is due back such as sample logs or if the paper copy of the symptom diary was used.

Do I have to take part?

No, taking part in research is voluntary. If you decide you would like your child to take part in the study and later you change your mind, you can withdraw them from the study at any time. You don't have to give a reason. If you withdraw them from the study, no further data will be collected and we will keep your child's samples, unless you request that they are destroyed. We may offer follow up checks to children who withdraw from the study, if there are any concerns about their health.

Your child's routine medical care would still continue as usual if your child does not participate in the study, or if they withdraw from the study.

What are the benefits of taking part?

By taking part in this study, your child will receive their routine influenza vaccination in your home.

You will be contributing to on-going important research into the workings of children's immune systems.

Your child will receive a **hero certification** following their participation. Participants will receive a 20 GBP voucher as a thank you for taking part in the study, at the end of the study.

What are the potential risks of taking part?

Vaccines (like any medicine) can sometimes cause side effects. The most common side effects reported from the vaccine given in this study are irritability, crying, fatigue, fever, reduced appetite and vomiting. A severe allergic reaction (anaphylaxis) after vaccination is extremely rare (with a risk of less than one in a million). The study nurses and doctors are trained and equipped to treat anaphylaxis; they will observe your child for 15 minutes after vaccination. Most children will get very few to no side effects from the vaccine.

Blood sampling may cause temporary bruising or tenderness. The nasal swabs are very small and soft and unlikely to cause any harm or discomfort, however as with anything inserted into the nose – there is a small chance that this could result in a nosebleed.

Who is organising this study?

The study is sponsored by the University of Oxford. The study is being coordinated by the Oxford Vaccine Group, including scientists, doctors, nurses and play assistants, who investigate infectious diseases and vaccines.

Funding has been received from the European Union and the UK Research and Innovation. The funder will have no influence on study decisions or the results from the study.

What will happen to the samples obtained in the study?

Samples will be processed at Oxford Vaccine Group and stored securely at Oxford Vaccine Group laboratory. Samples may be sent to researchers in other laboratories in the UK and overseas for analysis and storage (in this case, if at all, they would likely go to our collaborators in Switzerland, but they may go elsewhere). Samples will be labelled with a unique number, not your child's name.

We might look at how certain genes involved in the immune system are working in some of the participants, but these will not be able to identify the individual.

We may also ask you whether part of the samples, remaining after the study tests have been done, may be stored in the Oxford Vaccine Group library of samples ("Biobank"). If you agree to this, we will provide you with the relevant information booklet and ask you to sign a separate consent form. If you decide to consent to Biobank, then storing samples for genetic analysis is an option. Otherwise, your left-over samples will be destroyed after the end of the study. You can opt out of having samples stored in the Biobank and still take part in the study.

What will happen to the information collected in the study?

An online screening questionnaire is used to determine your child's eligibility. For those participants who proceed to take part in the study, the data from the screening questionnaire will be kept with their study records. For those who do not proceed to participate in the study, all answers from the screening questionnaire will be kept until the end of the study recruitment period and then will be deleted. Responsible members of the University of Oxford, regulatory authorities and the relevant NHS Trust(s) may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations.

Your child will be given a study number, which will be used on study paperwork and all samples. Any paper notes will be held securely at the study site. With your permission, we may need to obtain information from your child's medical records to confirm medical history or vaccinations received. We will inform your child's GP practice and/or health visitor that your child is taking part in the study and that we will be giving one of the routine vaccinations. The services responsible for recording all childhood vaccines given in the UK will be informed of the vaccine your child has received in this study.

General Data Protection Regulation (GDPR) requires that we state the legal basis for processing information about you. Medical research is regarded as "a task in the public interest". The University of Oxford is the 'data controller' and is responsible for looking after your information and using it properly. We will be using information from you and your child's medical records in order to undertake this study.

We will use as little personally identified information as possible. It will not be possible to identify your child in any publication or report.

We will store the research data and any research documents with personal information, such as consent forms, securely for up to 25 years after the end of the study, or as per national regulatory requirements. Your email address is required for the electronic diaries, in order for them to function. Only designated site staff and the data manager(s) will have access to view your email address and you will need to consent to this

The Oxford Vaccine Group will use you and your child's name and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your child's care, and to oversee the quality of the study. Individuals from the Oxford Vaccine Group and regulatory organisation may look at your child's medical and research records to check the accuracy of the research study. The only people in the Oxford Vaccine Group or University of Oxford who will have access to information that identifies you and your child will be people who need to contact you about the study, or the care of your child, or to monitor/audit the data collection process. The people who analyse the information collected and the samples will not be able to identify your child and will not be able to find out your child's name or your contact details. If you withdraw from the study, we will keep the information about your child that we have already obtained, including blood samples and symptom diary data, but if you prefer you can request for the samples to be destroyed (if they have not already been analysed).

We may contact you about future studies if you have indicated this on the consent form. We will retain a copy of your consent form securely until such time as your details are removed from our database. We will keep the consent form, and your details separate from one another and any research data.

If you have consented to your child taking part in future studies, we will continue to store your child's details (name and date of birth) and your contact details in a password protected database archived on a university server with restricted access indefinitely or until the study team feel that it would no longer be required, at which point it will be deleted.

If you have not consented to your child taking part in future studies, your child and your contact details will be destroyed after 25 years or as per national regulatory requirements.

We will keep your contact details confidentially to inform you about the results of the research. Once the research has been published, we will only keep your child's date of birth and name, to allow us

to identify your child should you make an enquiry about the study. Files will be confidentially destroyed when storage is no longer required.

Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited so that the research is reliable and accurate. Further information about your rights with respect to your personal data is available at https://compliance.web.ox.ac.uk/individual-rights You can find out more about how we use your information by contacting the Oxford Vaccine Group either by telephone on 01865 611 400 or by emailing info@ovg.ox.ac.uk

What happens at the end of the study?

We will provide the published data on our website; a summary of this will be sent to you with a link, to enable you to access the full information.

Who has reviewed this research study?

A Research Ethics Committee must review all research studies of this sort. This project has been reviewed by South Central-Hampshire B Research Ethics Committee (REC reference: 24/SC/0251) and given a favourable opinion. The Oxford Vaccine Centre Patient and Public Involvement group has reviewed the main participant-facing documents associated with this study (study information booklet, consent form, lay summary, invitation letter and advertising materials).

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 this study, you should contact your local study team at 01865 611 400 and info@ovg.ox.ac.uk. You may also contact the University of Oxford RGEA (Research Governance and Ethics Assurance) at rgea.sponsor@admin.ox.ac.uk
The investigators recognise the important contribution that volunteers make to medical research, and will make every effort to ensure your safety and wellbeing. The University of Oxford, as the research sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your taking part in this study. If something does go wrong, you are harmed during the research, and this is due to someone's negligence, then you may have grounds for a legal action for compensation. While the Sponsor will cooperate with any claim, you may wish to seek independent legal advice to ensure that you are properly represented in pursuing any complaint. The study doctor can advise you of further clinical action and refer you to a doctor within the NHS for treatment, if necessary.

In summary, what would happen if I would like my child to take part in the study?

- We would make an appointment to see you and your child at your home (or a convenient location)
- At this visit we would discuss the study with you and answer any questions.
- If you are happy to participate in the study, we would ask you to sign a consent form.

What should I do now if I am interested in taking part?

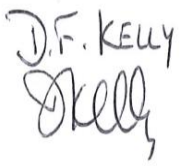
You do not need to make a final decision straight away. If you are interested in your child taking part in this study or have any questions, you can:

- Complete the online screening questionnaire: https://www.ovg.ox.ac.uk/studies/stellar or,
- Contact the research team by the 01865 611 400 or info@ovg.ox.ac.uk or,
- Complete the reply slip and post it to us using the pre-paid envelope provided with your Invitation letter.
- If your response reaches us after the study has finished recruitment, we will let you know.

A postcard reminder may be posted to you by the Child Health Information Service (or another equivalent NHS database), as described above. If we do not hear from you after this, we will assume that you do not want to take part.

Thank you for taking the time to read this information sheet and for considering taking part in this study.

Yours Faithfully,



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