Informed Consent Form

HOW DO PAST INFLUENZA INFECTIONS AFFECT RESPONSES TO VACCINATION OR INFECTION?

Community Influenza Cohort Sub-study

You have been a part of the study of influenza infection being run by the National Institute of Hygiene and Epidemiology in collaboration with Provincial and District Health Officials and Oxford University. If you are at least 18 years old, we are asking you to consider participating in an additional study sponsored by collaborators from The University of Melbourne, Department of Microbiology and Immunology.

The study seeks to understand how to make better influenza vaccines. Influenza infections or vaccinations can protect us from future influenza infection. After infection or vaccination cells in our blood called **B cells** make **antibodies** that can bind to influenza virus**.** Protective B cells and antibodies can remain in the blood for years and prevent re-infection. However, we may get influenza a number of times because influenza viruses change continually.

During the study so far we have learned that:

- 90% of participants were infected at least once in five years, and 60% were infected more than once.
- Most infections cause little or no illness.
- People normally make antibodies after infection, but the amount varies widely between people.
- Of concern, people often make less antibody with each new influenza infection.
- These findings from Ha Nam have influenced influenza vaccine research world-wide.

We want to work out how past influenza infections affect B cell responses to new influenza viruses so we can develop better ways to vaccinate. We seek your participation, because cohort participants are amongst the few people in the world whose recent past experience of influenza infection is very well known. Participating in the study involves providing blood samples with volumes sufficient to isolate and assess B cells, and several sampling times to determine peak and long-term antibody levels. If you consent to taking part in this study you may be selected for vaccination assessment **or** for natural infection assessment.

Vaccination assessment involves:

1. Immunization against influenza = one dose of licenced influenza vaccine, provided by the study.
2. Providing the following blood samples:
    - 20 ml up to 1 week before vaccination
    - 10 ml 4-days after vaccination
    - 20 ml 7-days after vaccination
    - 10 ml 14-days after vaccination
    - 20 ml 21-days after vaccination
    - 10 ml at least 180 days after vaccination, preferably after 270 days

You will not be asked to provide blood samples as part of usual cohort activities (i.e. one 3 ml blood sample is collected annually), if you provided a blood-sample as part of the sub-study that month.

Infection assessment involves:

1. Providing a 20 ml blood sample the next time samples are collected.
2. In the event that you develop influenza illness in the following two years, you will be asked to provide 20 ml blood samples on days-7 and -21 after illness started, and a 10 ml blood sample at least 180 days after illness started.

Participation

You do not have to take part. It is your decision and the decision of each person in the family. You can continue to participate in the influenza study, if you decide not to participate in this sub-study. You can decide to stop being a part of the study at any time.

What will happen to blood samples?

Blood samples will be tested for evidence of influenza infection and to understand the body's response to influenza. Samples will be tested and stored at the National Institute of Hygiene and Epidemiology, and at the Oxford University Clinical Research Unit, both in Hanoi. Samples will also be sent overseas to the University of Melbourne in Australia, and to Stanford University in the US for special tests that cannot be conducted in Viet Nam. Samples will be stored indefinitely in secure laboratories and freezers. If you decide to withdraw your permission to use your samples in this research project, please write to a study doctor, Annette Fox or Le Quynh Mai, and let her know you are withdrawing your permission for your samples to be stored and used for this or future research (Addresses below).

Genetic Testing: We will characterize "antibody" **genes** used by B cells to indicate whether "old" or "new" virus-specific B cells are responding. "Antibody" genes differ between individual B cells, and do not indicate relationships between people. "Antibody" gene results will not be provided to participants because they are not diagnostic for any disease/illness, and are of no known benefit.

Secondary uses of specimens: With your permission, your blood samples may be shared anonymously with other investigators for related infectious disease research. Such research will be strictly anonymous, in that no identifying information that would link the samples to you is provided to the researcher. An ethics board will review any such research prior to access being given to your samples. This secondary use will in no way compromise this study or the use of your samples as part of this study.

Will information and test results remain confidential?

Yes. All the information collected about participants during the course of the study will be kept confidential. We use participant identification numbers instead of names on all study documents and samples so no one will know whom they belong to. Study results are published and are available on the Internet, and are presented at National and International meetings, but no one will know who the study participants are, and participants are not identified.

Are there any risks or disadvantages of taking part?

Inactivated influenza vaccine may cause mild side effects including localised pain, redness, swelling; mild fever; mild body ache, joint pain, drowsiness or tiredness, lasting for 1–2 days. The risk of having a severe allergic reaction to vaccination is low, but if you have experienced a severe allergic reaction to vaccination in the past you should not be vaccinated. The district immunization programme will give vaccine in case side effects occur.

Taking blood from a vein in your arm by needle stick can be unpleasant, and can cause momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are remotely possible, but have not occurred during collection of over 7500 blood samples to date. A trained technician will take the blood and the amount of blood being taken is considered to be completely safe..

Genetic information from your DNA is unique to you, and there is a potential risk that someone could identify you, or learn something about you, by conducting genetic tests. These risks may also affect members of your family. We will protect your privacy and confidential information by labeling your samples only with a code number. While we hope this will prevent any potential loss of privacy or confidentiality, a risk remains. Genetic material may have uses unrelated to research, and will not be released for such uses without your consent unless required by law. You should discuss your willingness for DNA to be assessed in this study with your family and ask the study doctor about any questions or concerns you may have.

What are the possible benefits of taking part?

You may receive free influenza vaccination and influenza illness assessment and treatment at the Commune Health Centre for any episodes of a flu-like illness that occur whilst you are participating in the study. The Commune Health Centre has been upgraded as part of the study and now provides access to an improved health care facility. Participants will be reimbursed for the time they spend to provide swab and blood samples: 60000 VND/swab collection; 160000 VND per blood donation if only one donation annually or 200000 VND/blood donation if required to provide multiple post-vaccination or post-infection samples.

What if I still have questions?

Please telephone the study coordinator who should be able to answer any further questions you have. Tel 35764320.

Required ethics information and statements

Principle investigator: Annette Fox, telephone +61 383443384.

Full project title: "How do cross-reactive memory B cells affect influenza vaccine titers"

Funded by the Australian National Health and Medical Research Council, AUD$798,048.80 over four years.

This research project has been approved by the Human Research Ethics Committee of The University of Melbourne. If you have any concerns or complaints about the conduct of this research project, which you do not wish to discuss with the research team, you should contact the Manager, Human Research Ethics, Office for Research Ethics and Integrity, University of Melbourne, VIC 3010. Tel: +61 3 8344 2073 or Fax: +61 3 9347 6739 or Email: HumanEthics-complaints@unimelb.edu.au. All complaints will be treated confidentially. In any correspondence please provide the name of the research team or the name or ethics ID number of the research project.

Informed Consent Form

HOW DO PAST INFLUENZA INFECTIONS AFFECT RESPONSES TO VACCINATION OR INFECTION?

Community Influenza Cohort Sub-study

Thank you for reading this and thinking about joining this project. Please ask the study staff if you have any questions. If you agree to be in the study, please sign below (one page per person).

- I have read the participant information sheet for this study, and I have been informed about the purpose, possible risks and benefits of taking part in this study.
- I have had a chance to discuss this information with study staff, and have received answers that I understand to all my questions.
- I am aged 18 years, and I freely agree to take part in the study that involves receiving one dose of influenza vaccine and providing blood samples before and after vaccination

  AND / OR
- I am aged 18 years, and agree to additional investigations that require at least one 20 ml blood sample, and three additional blood samples if I have an influenza illness during the study period
- I consent to study staff collecting and processing information about my health and using this information for future medical research about respiratory infections.
- I agree that blood and other samples from me may be stored and further tests on these samples may be undertaken in the future to further the understanding of respiratory infections in Viet Nam. Researchers outside Viet Nam may do these tests.
- I agree that samples from me may be used to search for genes related to infectious diseases and immune responses. I understand that identification of other genetic diseases is not part of this study.
- I freely agree that I will take part in this study.
- I understand that I may withdraw from this study at any time, and that if I do leave the study it will not affect my future care. If I decide to leave the study, I agree that the information collected about me up to the point when I withdraw, may continue to be used.
- I have been given a copy of this form to keep.

Participant Number H [__] [__] [__]/ S [__] [__] **Name of participant _____**

By signing/marking my name here, I confirm what is written above

x_____	x_____	___/____/_____
Signature of Participant	Full Name	Date of Signature

I, the undersigned, have fully explained the relevant information of this program to the person named above and will provide her/him with a copy of this signed and dated informed consent form.

x_____	x_____	___/____/_____
Investigator/Designee Signature	Full Name	Date of Signature

If the person giving consent cannot read the form themselves, a witness must be present and sign here:
I was present throughout the entire informed consent process with the participant. This form was read accurately to the volunteer, all questions from the volunteer were answered and the volunteer has agreed to take part in the research.

x_____	x_____	___/____/_____
Witness Signature	Full Name	Date of Signature