INFORMED CONSENT FORM

1. Study Information

Protocol Title:
Investigation and Comparison of the Antibody Response initiated by Recombinant, Cell-Based and Egg-Based Influenza Vaccines

Principal Investigator Contact Details:

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International Sponsor:

Funded by: Sanofi Aventis

2. Purpose of the Research Study

You are invited to participate in this research study because you have received either more or less than 2 influenza vaccines in the last 5 years, and have not received any influenza vaccine for at least 6 months. It is important to us that you first take time to read through and understand the information provided in this sheet. Nevertheless, before you take part in this research study, the study will be explained to you and you will be given the chance to ask questions. After you are properly satisfied that you understand this study, and that you wish to take part in the study, you must sign this informed consent form. You will be given a copy of this consent form to take home with you.

Influenza is the most common vaccine-preventable disease. Although it can be a mild disease, it can also cause very serious illness in otherwise healthy people. Influenza vaccines can be grouped into three categories depending on how they are manufactured (egg-grown, cell-grown and recombinant-protein). In this study, we will be using the egg-grown vaccine Fluarix, the cell-grown vaccine Flucelvax Quadrivalent and the recombinant-protein vaccine Flublok. Unlike egg and cell-based vaccines, the recombinant-protein manufacturing process takes a shorter time and produces a purer antigen. Flucelvax and Flublok are not registered in Singapore, but are widely used overseas. Flublok was approved by U.S. FDA in 2013, although it has never been administered to Singaporean subjects – Singapore was not included in the previous clinical trials. However, given the acceptable safety data generated from the millions of doses of the recombinant vaccine administered in the USA (under the tradename Flublok Quadrivalent), and the fact that this product will be sourced from the US, we consider that the risk/benefit ratio is appropriate for the conduct of a clinical study.

The purpose of this project is to compare the antibody response of people receiving the different vaccine types to see if receiving the recombinant-protein vaccine results in a better

antibody response. This study will recruit 360 subjects from the community over a period of 6 months.

People who are vaccinated against influenza develop antibodies which protect against the virus. When a vaccinated person is exposed to influenza, these antibodies latch onto the virus and remove it from the body. Previous research studies have shown that antibody levels in blood are an indicator of protection against influenza. The immune response to the influenza vaccine in people who receive the vaccine frequently (≥3 influenza vaccinations during the past 5 years) compared with those that don't get the vaccine that frequently (≤1 vaccination during the past 5 years) is not well known. The findings from this study will identify which vaccine provides better antibody levels and overall protection against influenza infections, while also evaluating how these responses differ in people with different vaccination history (frequently vaccinated or infrequently vaccinated).

3. What procedures will be followed in this study

If you agree to take part in this study, the following procedures will occur.

You will be asked to complete this informed consent form documenting you agree to take part in this study. To participate in this study, you must meet the following criteria:

- Aged between 21 and 49 years;
- Able to provide informed consent;
- Have not received influenza vaccine for at least 6 months[1];
- Willing to provide current mobile phone number for SMS reminders during the study period to monitor flu-like illness;
- Willing to provide 4 blood samples;
    - Just prior to vaccination (V1),
    - 14 days post vaccination (V2),
    - 6 months post vaccination (V3) and
    - 12 months post vaccination (V4).
- Willing to self-perform nasal swab if you experience cold or flu-like symptoms during the study period.

1 If you received the influenza vaccine less than 6 months ago you may be enrolled onto the study but your vaccination visit and blood sample collection will be scheduled at least 6 months after the last influenza vaccine dose was administered

You will not be able to participate in this study if you have received immunosuppressive treatment (e.g. cancer treatment, or any other treatment that suppresses your immune system) within the past 6 months, if you feel unwell (e.g., you are currently ill or have a fever above 38°C), if you have had an allergic reaction to the influenza vaccine in the past, or if you cannot recall if you were vaccinated against influenza during more or less than two of the preceding five years.

If you are determined to not be eligible for the study, your participation in the study will end after the screening visit.

3.1. Study schedule

If you decide to take part in this study, you will be randomized to receive one of the three vaccines (Fluarix, Flucelvax or Flublok). Randomisation means assigning you to one of three groups by chance, like tossing a coin or rolling dice.

Participation in the study will involve 4 visits over a 1-year period. Vaccination during study visit 1 will take place at the P.H. Feng Research Centre. All participants will be asked to provide 1 (10 ml) tube of blood (approximately 2 teaspoons) at each visit, taken to measure antibody levels. In order to measure the cellular response further, 1 in 3 of participants will be selected, by randomization at the screening visit, to provide 2 additional 10 ml tubes of blood to measure frequencies and function of antibody producing cells. These selected participants will be required to provide 30 ml of blood at all subsequent visits. Blood collected for research investigations will be de-identified (i.e. coded so that the recipient of your blood sample will not be able to identify you as a donor) before being sent to collaborating laboratories within Singapore and World Health Organization Collaborating Centre for Reference and Research on Influenza (WHOCCRRI) in Melbourne, Australia. You will be asked to complete questionnaires to collect information about you and symptoms if you become unwell.

After you have the vaccine, please monitor for side effects (e.g., headache, fever/chills, muscle pain) and report them to a member of the study team.

Assessment/ Procedure	**Screening[1]**	**Visit 1 (V1) (prior to vaccination)**	**Visit 2 (V2) (14 days post vaccination)**	**Visit 3 (V3) (6 months post vaccination)**	**Visit 4 (V4) (12 months post vaccination)**
Study timeline	Day -28 to 1	Day 1	Day 14-21	Day 120-180	Day 300-360
Approximate time required for each visit (hr)	1	1	0.5	0.5	0.5
Informed Consent	✓				
Collection of demographic information	✓				
Weight and height measurement	✓				
History of seasonal influenza vaccination	✓				
Randomization	✓				
Blood Collection	✓[2]	✓[2]	✓	✓	✓
Vaccination and immediate surveillance (15 min)		✓			
Flu symptom diary		D14-D360			
Swab collection		D14-D360			

Footnotes:

[1] Screening visit may be performed on the same day as Visit 1.
[2] Collection of the first blood sample to occur before vaccination, and may be taken at Screening or Visit 1 if the blood draw is not possible for one reason or another.

3.2. Monitoring flu-like illness

Approximately two weeks after you are vaccinated you will begin receiving weekly SMS and/or email reminders to complete a weekly survey of flu-like illness. If you meet the criteria for flu-like illness, you will be sent daily symptom surveys via SMS and/or email. You will also be asked to perform a COVID-19 antigen rapid test (ART) and inform the study team within 24 hours of your flu-like illness and COVID-19 ART result. You are required to collect respiratory swabs for influenza testing only if the COVID-19 ART is negative.

Detailed instructions on how to collect the swabs, as well as swab kits and COVID-19 ART test kits will be provided upon enrolment to the study. The study team will follow up with you to arrange for collection of the respiratory swabs. Please store the respiratory swabs in the home refrigerator until the study team or an external courier collects them. You will be notified of your influenza test results via text messages.

3.3. Incidental findings

“Incidental findings” are findings that have potential health or reproductive importance to research participants like you/your child and are discovered in the course of conducting the study, but are unrelated to the purposes, objectives or variables of the study. There will not be any incidental findings arising in this research.

4. Your Responsibilities in This Study

If you agree to participate in this study, you should follow the advice given to you by the study team. You should be prepared to undergo all the procedures described in section 3 of this consent form. In addition, you are advised to perform a nasal swab and Antigen Rapid Test (ART) if you experience any cold or flu-like symptoms during the course of the study.

5. What Is Not Standard Care or is Experimental in This Study

Fluarix is licensed in Singapore. Flublok and Flucelvax are licensed in the U.S. but not in Singapore. All the procedures listed in section 3 (e.g. blood collection, self-recording of symptoms in diary, nasal swab collection etc) are performed as part of the study for research purposes and are not part of routine clinical care.

This study will not affect your medical care in the hospital or any benefits you are entitled to.

6. Possible Risks and Side Effects

Blood samples will be collected as part of the study. There are no major risks associated with giving blood. Obtaining blood can cause pain, bleeding, bruising, or swelling at the site of the needle stick. Fainting sometimes occurs and infection rarely occurs.

Vaccine injection into the upper arm may cause transient discomfort. Immediate and potentially life-threatening allergic reactions to the vaccine could be manifested by adverse events such as throat swelling, asthma, or low blood pressure. All participants will be required to wait for 15 minutes after vaccination to document any adverse events.

If you develop flu like symptoms during the study period, you will be asked to self-collect a nasal swab. Instructions on how to do this, as well as a swab kit will be provided upon enrolment to the study. There is minimal risk involved in collecting these swabs, though it can cause some pain and discomfort, especially if the nostril is already sore or irritated due to illness.

7. Possible Benefits from Participating in the Study

We cannot guarantee or promise that you will receive any benefits from this study. This study may be able to provide previously unknown information about influenza antibody levels after vaccination with three different vaccines. This information is useful for influenza vaccination programmes.

You may be less likely to catch influenza or develop complications during the study period as a result of having the vaccine. Results of study procedures: you will be provided with your respiratory sample test results. A member of the study team will be available to discuss the results with you, should you have any questions.

You will be able to discuss any concerns you have about your test results with the PI. Influenza test results are not expected to cause any distress as these are not stigmatized conditions with long term ill- health outcomes.

8. Important Information for Women Subjects

In Singapore, influenza vaccinations are encouraged during pregnancy, therefore pregnant and breast-feeding women will not be excluded from the study.

9. Alternatives to Participation

Your participation in this study is voluntary. Your decision not to take part in this study will not affect your medical care or any benefits you are entitled to.

10. Costs & Payments if Participating in the Study

You will be reimbursed for your time, inconvenience and transportation costs. You will be paid SG$50 for every study visit you complete, including screening visit. You are not expected to incur any expenses as a consequence of participating in this research.

11. Voluntary Participation

Your participation in this study is voluntary. You may stop participating in this study at any time. Your decision not to take part in this study, or to take part and later withdraw, will not affect your medical care or any benefits you are entitled. If you do decide to take part in this study, any biological samples collected will be deemed to be gifted to NCID / Tan Tock Seng Hospital (TTSH) and its collaborating laboratories and will not be returned to you. You will not have any right or claim to the samples at all or any intellectual property rights that may be derived from the use of the samples. If you choose to withdraw from the study at any stage, please inform the Principal Investigator or study team member. However, the information that has been collected in reference to the study matter up until that point will be used as part of the data analysis for this study. You will not have any right or claim to any share in the commercial gain derived from the research (if any). However, you retain your right to ask the Principal Investigator to discard or destroy any remaining biological samples if the sample(s) is individually-identifiable and has not been used for the research, or it has been used for research but it is practicable to discontinue further use of the biological sample(s) for the research. The Study Investigators may stop your participation in the study at any time if they decide that it is in your best interests. They may also do this if you do not follow instructions required to complete the study adequately. In the event of any new information becoming available that may be relevant to your willingness to continue in this study, you will be informed in a timely manner by the Principal Investigator or his/her representative.

12. Compensation for Injury

If you follow the directions of the study team and you are physically injured due to the procedure given under the plan for this study, NCID/TTSH will pay the medical expenses for the treatment of that injury. Payment for management of the normally expected consequences of your treatment will not be provided by the NCID/TTSH. NCID/TTSH without legal commitment will compensate you for the injuries arising from your participation in the study without you having to prove NCID/TTSH is at fault. There are however conditions and limitations to the extent of compensation provided. You may wish to discuss this with the study Principal Investigator. By signing this consent form, you will not waive any of your legal rights or release the parties involved in this study from liability for negligence.

13. Optional consent for the donation of leftover biological samples

This study only recruits participants who can personally give consent to the study and the donation of the leftover samples.

Choosing whether or not to donate your leftover samples for future research is voluntary. It is your choice whether or not to give consent for the storage and use of your samples and information, as described in this Consent Form. Choosing not to donate will not affect your medical care or cause you to lose benefits to which you are entitled.

Even if you decide now that your leftover samples can be stored for future research, you may still change your mind at any time. If this happens, you must tell the Principal Investigator that you have changed your mind.

In such a case, any results that arose from research conducted with the samples before your consent was withdrawn may be retained and used for the research. The reason is to enable a complete and comprehensive evaluation of the research. However, you retain your right to ask the Principal Investigator to discard or destroy any remaining samples that have not been used if the samples can still be linked to your personal identifiers, and it is practicable to discontinue its further use.

The leftover samples donated for future research will be deemed to be gifted to NCID/TTSH and will not be returned to you. You will not have any right or claim to the samples at all or any intellectual property rights that may be derived from the use of the samples.

13.1. Purpose of donating the leftover biological samples

While most of your de-identified biological samples and/or data will be used for this project, the study team may store your leftover samples and/or data subjected to your consent. These leftover samples and/or data may be used for exploratory research to find new scientific information about Influenza viruses and related diseases, which may occur locally or overseas. The samples will not be used for any purpose other than for future research.

13.2. How will your leftover samples and associated information be stored and used?

We will store your leftover samples for the purposes mentioned above until they are all used up. Any information that was collected for the study will also be coded and may be used with your coded leftover samples in future research. We will not attempt to link these back to your personal identifiers. The samples will not be used for restricted human biomedical research involving human-animal combinations. Leftover samples will not be transferred out of Singapore.

You may choose to indicate at the end of this consent document, if you agree or do not agree to having part of your de-identified biological samples and/or data stored indefinitely for future analyses. If you do not agree to the use of your biological samples and/or data for future analyses, the collaborating laboratories will destroy the leftover samples and/or data at the end of this study. Please note that we will not contact you for further consent each time your leftover samples and information are used in future research.

“Incidental Findings” are findings that have potential health or reproductive importance to research participants like you, and are discovered in the course of conducting research, but are unrelated to the purposes, objectives or variables of the research. These findings may affect your current or future life and/ or health insurance coverage.

We do not plan to contact you or your regular doctor with any incidental findings from future research conducted with your leftover samples. This is because research tests are often done using experimental procedures, so the results may not help in making decisions on managing your health.

In the rare case that any incidental findings reveal a condition likely to be life-threatening or grave, and can be avoided or ameliorated, the Principal Investigator/ a qualified healthcare professional will try contact you to ask if you would like to receive the finding. At the point of contact, you can choose to receive or refuse the finding.

If an incidental finding has public health implications (for example, infectious diseases) that are mandated by law to be notified to the relevant authorities, the Principal Investigator/ a qualified healthcare professional will contact you to inform you of the finding, and the implications of the finding.

If you have been communicated on any incidental findings, please seek further medical attention and confirmation of the result(s) in an accredited clinical laboratory. The costs for any care related to this would not be paid for by this research. These costs would be your responsibility.

13.3. Are there any risks from donating your leftover samples for future research?

Other than the initial physical risk from the removal of your biological material as described in Section 6, there are no additional physical risks expected from the collection of your leftover samples.

13.4. Are there any costs or payments if you consent to the donation of your leftover samples for future research?

There will not be any additional reimbursement for the donation of your leftover tissue for future research. You are also not expected to incur any costs from this donation. There will not be any compensation or treatment for injury arising from leftover sample(s) as we do not anticipate any physical injuries from this donation.

14. Confidentiality of Study and Medical Records

Your participation in this study will involve the collection of “Personal Data”. Any biological samples and/or information containing your “Personal Data” that is collected for the purposes described in this Informed Consent Form will not be transferred out of Singapore. “Personal Data” means data about you which makes you identifiable (i) from such data or (ii) from that data and other information which an organisation has or likely to have access. This includes medical conditions, medications, investigations and treatment history. Information and “Personal Data” collected for this study will be kept confidential. Your records, to the extent of the applicable laws and regulations, will not be made publicly available. However, the relevant authorities and authorized representatives of the Sponsor (Sanofi Aventis), the NHG Domain Specific Review Board, Ministry of Health, Health Sciences Authority, associated study research staff and study monitors, will be granted direct access to your original medical records/ study records to check study procedures and data, without making any of your information public. Data collected and entered into the Case Report Forms are the property of NCID/TTSH. In the event of any publication regarding this study, your identity will remain confidential. Research arising in the future, based on your “Personal Data”, will be subject to review by the relevant institutional review board. By signing the Informed Consent Form attached, you (or your legally acceptable representative, if relevant) are authorising (i) the collection, access to, use and storage of your “Personal Data”, and (ii) the disclosure to authorise service providers and relevant third parties. Your biological samples will be de-identified (coded) before it is sent to the local or overseas collaborating laboratories.

By participating in this research study, you are confirming that you have read, understood and consent to the Personal Data Protection Notification available at (https://www.ttsh.com.sg/patients-and-visitors/your-hospital-stay/pages/patients-rights.aspx).

15. Who To Contact if You Have Questions

If you have questions about this research study, in case of any injuries during the course of this study, or if you have any further questions about the donation of your leftover samples for future research, you may contact the Principal Investigator, Dr Barnaby Young, at 6357 7458 (office) or 8133 4132 (mobile).

The study has been reviewed by the NHG Domain Specific Review Board (the central ethics committee) for ethics approval.

If you want an independent opinion to discuss problems and questions, obtain information and offer inputs on your rights as a research subject, you may contact the NHG Domain Specific Review Board Secretariat at 6471-3266. You can also find more information about participating in clinical research, the NHG Domain Specific Review Board and its review processes at www.research.nhg.com.sg.

If you have any complaints or feedback about this research study, you may contact the Principal Investigator or the NHG Domain Specific Review Board Secretariat.

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Email: barnaby_young@ncid.sg
Tel: 6357 7458 (office) / 8133 4132 (mobile)

I voluntarily consent to take part in this research study. I have fully discussed and understood the purpose and procedures of this study. This study has been explained to me in a language that I understand. I have been given enough time to ask any questions that I have about the study, and all my questions have been answered to my satisfaction. I have also been informed of the possible benefits and risks of this study.

By participating in this research study, I confirm that I have read, understood and consent to the TTSH Personal Data Protection Notification.

Consent for the Use of Left-over Biological Specimen and/or Data for Future Research

☐Yes, I agree to donate ☐ left-over **biological specimen**, ☐ **data** for future research

*Please also check **one** of these boxes:*

☐There are no restrictions on the kind of research that may be done with my left-over biological specimen and/or data, with the exception of restricted research involving human-animal combinations

☐ The Investigator may use my left-over biological specimen and/or data for future research as long as the research is related to Influenza virus.

☐No, I do not agree to donate my left-over biological specimen and/or data for future research.

_____	_____	_____
Name of Participant	Signature	Date

Translator Information

The study has been explained to the participant / legally acceptable representative in

_____ by _____

<insert language> *<insert name of translator>*

Witness Statement

I, the undersigned, certify that:

- I am 21 years of age or older.
- To the best of my knowledge, the participant/ the participant's legally acceptable representative signing this informed consent form has the study fully explained in a language understood by him/ her and clearly understands the nature, risks and benefits of his/ her participation in the study.

- I have taken reasonable steps to ascertain the identity of the participant/ the participant's legally acceptable representative giving the consent.
- I have taken steps to ascertain that the consent has been given voluntarily without any coercion or intimidation.

_____	_____	_____
Name of Witness	Signature	Date

1. In accordance with Section 6(d) of the Human Biomedical Research Act and Regulation 25 of the Human Biomedical Research Regulations 2017, appropriate consent must be obtained in the presence of a prescribed witness who is 21 years of age or older, and has mental capacity. The witness must be present during the entire informed consent discussion, and must not be the same person taking the appropriate consent. The witness may be a member of the team carrying out the research.
2. However, if the participant/ the participant's legally acceptable representative is unable to read, and/ or sign and date on the consent form, an impartial witness should be present instead. The impartial witness should not be a member of the study team.

Investigator / Delegated Study Team Member Statement

I, the undersigned, certify that I explained the study to the participant and to the best of my knowledge the participant signing this informed consent form clearly understands the nature, risks and benefits of his / her participation in the study.

_____	_____	_____
Name of Investigator / Delegated Study Team Member / Person administering consent	Signature	Date