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TECHNICAL REPORT

Pilot protocol for influenza vaccine effectiveness against laboratory-confirmed influenza infections using healthcare worker cohorts

Version 1.0

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For questions or requests for support in implementing the protocol, please email vpd.vpd@ecdc.europa.eu and/or adminepidemio@epiconcept.fr

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Contents

Abbreviations

ARI	Acute respiratory infection
COVID-19	Coronavirus disease 2019
EEA	European Economic Area
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
EU	European Union
GISAID	Global Initiative on Sharing Avian Influenza Data
IPC	Infection prevention and control
ILI	Influenza-like illness
RSV	Respiratory syncytial virus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
PCR	Polymerase chain reaction
PPE	Personal protective equipment
VC	Vaccination coverage
VE	Vaccine effectiveness
VEBIS	Vaccine effectiveness, Burden and Impact Studies
WHO	World Health Organization

1 Background

1.1 Context

Influenza is a disease of public health importance due to the substantial seasonal morbidity and mortality and the high pandemic potential of the aetiologic agents, influenza viruses. The diagnosis is mainly based on laboratory testing (i.e. molecular testing) of nasopharyngeal samples. Although more acceptable for patients, saliva specimens are less used for diagnosis [1-3] due to a lower sensitivity, probably resulting from a low influenza viral load in such specimens. The influenza viruses are able to escape the human immune system by continuous evolution that can be caused by point mutations (antigenic drift) or recombination events (antigenic shift) [4]. As a consequence, the influenza vaccine components are re-evaluated each year and annual revaccination is recommended. Observed vaccine effectiveness (VE) varies from year to year among population subgroups (e.g. age- and risk-groups) and according to the measured outcome (laboratory confirmed influenza virus by (sub)type/clade or clinical outcome). VE may vary among vaccine types and products, by time since vaccination and depending on previous influenza infection and influenza vaccination history.

In many countries healthcare workers are included among the high-risk groups for influenza infection and priority groups for influenza vaccination due to occupational exposure, and the need to ensure work continuity during seasonal epidemics. Studies performed before the severe acute respiratory syndrome – coronavirus 2 (SARS-CoV-2) pandemic suggested that an increase in influenza vaccination coverage in health professionals results in an important decline in nosocomial influenza among patients [5-8]. EU/EEA countries have therefore been encouraged to improve vaccination coverage among healthcare workers [9,10]. During the SARS-CoV-2 pandemic, some studies show that the co-circulation of influenza and SARS-CoV-2 during winter increased awareness and acceptability of influenza vaccination among healthcare workers, mainly before the introduction of the COVID-19 vaccination [11-13].

1.2 ECDC vaccine effectiveness studies

In 2020, the European Commission stressed the importance of continuously monitoring the safety and effectiveness of vaccines in the EU/EEA during the post-authorisation phase, with particular emphasis on COVID-19 vaccines in the context of the ongoing pandemic [14]. Previously, the 2018 Council Recommendation on Strengthened Cooperation against Vaccine-preventable Diseases asked ECDC and the European Medicines Agency (EMA) to cooperate in ensuring the continued monitoring of vaccines and vaccination used in EU/EEA vaccination programmes [15]. Such a request was subsequently formalised as part of the extended EMA regulatory mandate [16] and ECDC's newly amended mandate [17], requiring the two Agencies to develop a structured and independent post-authorisation vaccine monitoring platform, initially prioritising COVID-19 vaccines. ECDC and EMA officially established and launched such a platform in May 2022, with the intention of bringing together public health and regulatory experts to discuss the studies needed to generate real-life evidence on the safety and effectiveness of vaccines used in EU/EEA immunisation programmes [18].

Since the end of 2020, ECDC has started building infrastructure to conduct COVID-19 VE studies in different settings, and to provide information on different outcomes (severe disease, moderate disease, infection, etc.). The studies have been embedded in a project called VEBIS (Vaccine Effectiveness, Burden and Impact Studies). The multi-country study related to a prospective cohort for this project is dedicated to studies of COVID-19 and influenza VE in healthcare workers from different countries, with a progressive inclusion of further countries planned over time.

The component related to COVID-19 VE against confirmed SARS-CoV-2 infection in hospital-based healthcare workers started in late 2021 and included a total of 19 hospitals during the implementation period (it is still ongoing). A generic protocol for this study is available at: https://www.ecdc.europa.eu/en/publications-data/generic-protocol-ecdc-studies-covid-19-vaccine-effectiveness.

This multi-country study constitutes an example of integrated VE studies for vaccine-preventable acute respiratory infections of public health importance, such as those caused by SARS-CoV-2 and influenza, contributing to further experience of such integration at national and international level.

1.3 Aim of the protocol

This document presents the first version of a pilot protocol for a prospective multi-country cohort study to measure the effectiveness of the influenza vaccines in hospital-based healthcare workers during a period of co-circulation of influenza and SARS-CoV-2. The protocol is embedded in the COVID-19 VE study, set up under the VEBIS multi-country cohort study investigating VE in healthcare workers. This document should be used by the pilot study sites to determine the feasibility of performing this study in hospital-based healthcare workers and to validate the use of saliva as an adequate sample for influenza testing in this population. This generic protocol can also be used in countries conducting similar studies that are not included in the ECDC VEBIS project.

This document will be updated and revised after the pilot phase and on a regular basis afterwards.

Additional documentation is available upon request at vpd.vpd@ecdc.europa.eu and/or adminepidemio@epiconcept.fr.

Under each paragraph, arrow marks with italicised text indicate the points that countries/hospitals/study sites could further expand when creating a country-specific protocol based on the ECDC protocol.

2. Objectives

2.1 Primary objective

The primary objective of this study is two-fold:

- to measure influenza VE against laboratory-confirmed influenza infection among hospital healthcare workers eligible for influenza vaccination;
- to determine the reliability of RT-PCR testing using saliva specimens compared to specimens from nasopharyngeal swabs among symptomatic healthcare workers.

2.2 Secondary objectives

The secondary objectives are to measure the influenza VE by:

- type/subtype and/or clade/subclade of circulating influenza virus;
- vaccine type/brand;
- age group;
- underlying conditions.

➢ *Each study site/hospital/country should specify the objectives of their study.*

3. Methods

3.1 Study setting

The study will be embedded in the COVID-19 VEBIS VE cohort study among healthcare workers based in hospitals, or performed in similar settings (https://www.ecdc.europa.eu/en/publications-data/generic-protocol-ecdc-studies-covid-19-vaccine-effectiveness).

- *Each study should provide a brief description of the existing cohorts.*

3.2 Study design

This is a dynamic prospective cohort study.

3.3 Study population

The study population will be composed of healthcare workers eligible for influenza and COVID-19 vaccination, with no contraindication, who receive an influenza or COVID-19 vaccine.

3.4 Inclusion criteria

All categories of healthcare workers in hospitals may be included. Healthcare workers participating in COVID-19 VE studies will be prioritised.

3.5 Exclusion criteria

Healthcare workers who are not eligible for influenza or COVID-19 vaccination, for whom vaccination is contra-indicated or who have not signed an informed consent form will be excluded from the study.

3.6 Study period

The study should only be conducted after the study protocol is approved by the relevant ethical review committee. For this pilot study, the study period begins at the peak of influenza circulation in the hospital community, as established by the local influenza surveillance systems, and will continue for 6-8 weeks or until the end of peak circulation. Start and finish time of the study (study period) can be modified in subsequent seasons, depending on the results of the pilot project. Due to difficulties in identifying peak influenza season in real time, a set date could be considered for the beginning and end of data collection and analysis.

- *Each study site/hospital/country should define the study period.*

3.7 Exposure

Vaccination status documentation

Influenza vaccination status will be documented. Vaccination status ascertainment will depend on how the vaccination is delivered and registered in each setting. Self-reported vaccination status should be verified and confirmed through occupational health, vaccine registry, vaccination card or any other potential data source available at study site level. Participants should be informed in the consent form that these additional sources will be accessed, where relevant, to confirm their vaccination status.

Vaccine documentation should include:

- date of vaccination;
- vaccine brand;
- vaccine batch (where available);
- ascertainment (e.g. self-reported, documented, vaccine registry, etc.)

The following exposure definitions will apply:

Current seasonal influenza vaccine

- A healthcare worker is considered to be vaccinated against influenza if the vaccination occurred 14 or more days before disease onset.
- A healthcare worker is considered to be unvaccinated if he/she did not receive the influenza vaccine during the current season or received vaccination <14 days before disease onset, or the sample collection date of the laboratory test.

Brand-specific seasonal influenza vaccine

- A healthcare worker is considered to be vaccinated against influenza with a brand-specific vaccine if he/she has been immunised with an influenza vaccine (named brand) 14 or more days before disease onset.
- A healthcare worker is considered to be unvaccinated if he/she did not receive an influenza vaccine during the current season or received vaccination <14 days before disease onset, or the sample collection date of the laboratory test.

➢ *Each study site/hospital/country should describe how vaccination status will be ascertained. Ideally, study sites should ensure that vaccination status is documented.*

3.8 Definitions of outcomes

The **primary outcome** should be a confirmed influenza infection detected by laboratory RT-PCR in any participant, irrespective of symptoms or the type of specimen used for testing (nasopharyngeal swab or saliva sample).

Secondary outcomes include symptomatic laboratory confirmed influenza, defined as confirmed influenza infection in a nasopharyngeal swab or saliva specimen detected by laboratory RT-PCR, in participants who report one or more of the following clinical criteria to conform with the acute respiratory infection (ARI) case definition [19]:

- sudden onset of symptoms

AND

- at least one of the following four respiratory symptoms:
  - cough;
  - sore throat;
  - shortness of breath;
  - coryza;

AND

- a clinician's judgement that the illness is due to an infection.

The ARI case definition is more sensitive than the influenza-like infection (ILI) which is usually used for influenza surveillance at primary-care level [19]. However, the high sensitivity of this case definition is necessary for the second primary objective of this study –to validate the saliva sample specimen taken in symptomatic patients.

3.9 Sample size and power calculation

The sample size for cohort studies depends on the vaccination coverage in the population, the assumed VE (based on estimates from the literature), the estimated incidence of influenza infection over the follow-up time in the unvaccinated study population (or other chosen denominator), and the desired precision.

In the current pilot study, the sample size is limited by the participation in the COVID-19 VEBIS VE study. Power calculation will be performed according to the influenza incidence in the community of participating hospitals.

3.10 Study procedures

3.10.1 Study preparation

This study will be embedded in the COVID-19 VEBIS VE cohort study among healthcare workers. The procedures are described in detail in the respective protocol: https://www.ecdc.europa.eu/en/publications-data/generic-protocol-ecdc-studies-covid-19-vaccine-effectiveness

To add the influenza component of this study, the participating healthcare workers should be asked to provide additional informed consent for the influenza testing of their sample (Annex 1).

➢ *Each study site/hospital/country should describe the procedure for the additional study.*

3.10.2 Enrolment: questionnaire, respiratory sample, and serology sample

Once informed consent has been obtained, healthcare workers should be enrolled, irrespective of their individual influenza or COVID-19 vaccination status. They should:

- provide a nasopharyngeal swab, and/or a saliva sample for RT-PCR testing;
- complete the enrolment questionnaire including demographic, clinical, and epidemiological information such as past infection, information on vaccination history, and occupation- and community-related behaviour.

➢ *The healthcare worker study site/hospital/country participating in the COVID-19 VEBIS VE study will use the same forms/data for this influenza study. Healthcare workers already enrolled into the COVID-19 VEBIS VE study only need to complete follow-up questionnaires (see Section 3.10.3 below). Healthcare workers enrolled for the first time in the VEBIS study will need to complete the enrolment questionnaire.*

3.10.3 Active follow-up

The objective of the follow-up is to identify new cases of influenza and changes in vaccination status (e.g. unvaccinated people who received the vaccine) among the cohort participants.

Study participants should be regularly and actively followed up.

Monitoring: participants are followed up using a weekly survey to report changes in health or vaccination status, along with probable professional and personal exposures. The questionnaire can be completed directly by the healthcare workers or by a study site monitor as part of regular weekly contacts.

➢ *The healthcare worker study site/hospital/country participating in the COVID-19 VE study will use the same forms/data.*

Molecular (RT-PCR and genomic sequencing) testing: samples are to be collected from participants on a weekly basis, irrespective of symptoms, and tested by RT-PCR for influenza. Samples can be either nasopharyngeal swabs or saliva specimens, either taken by a trained study monitor or by the healthcare workers themselves after suitable training. Saliva samples and nasopharyngeal swabs collected by the healthcare workers themselves will be provided solely with the objective of validating use of saliva specimens for influenza testing in symptomatic healthcare workers.

➢ *Each study site/hospital/country should describe the study procedures.*

3.11 Data collection and data sources

Data are to be collected using a standardised questionnaire/data collection form. At enrolment, data could be collected using an online platform and, if available, some data items may be extracted from electronic medical records, or through a combination of both approaches. The minimum data that should be collected at enrolment are:

- age;
- sex;
- smoking status, body mass index (BMI);
- presence of chronic disease(s): at least one chronic condition, specific conditions;
- vaccination status for influenza and COVID-19;
- molecular testing results.

The weekly monitoring form can be completed by the participant, either online or using a mobile-enabled platform. Where participants receive a confirmed diagnosis of influenza, the participants or study site investigators should complete the online questionnaire. The minimum data that should be collected during follow-up are:

- absence or presence of symptoms with date of symptom onset;
- date of RT-PCR testing and RT-PCR results;
- clinical course of infection (including out-patient and in-patient visits);
- additional vaccinations (COVID-19, influenza or pneumococcal).

Data can be collected through questionnaires completed by healthcare workers for the study, electronic medical records, vaccine registries, occupational health registries, or other relevant sources. Data are to be collected using a standardised questionnaire/data collection form.

For each variable, possible and optimal data sources should be identified.

➢ *Each study site/hospital/country should detail data sources to be used for each variable.*

3.12 Data analysis

Data validation, cleaning and verification will be performed at study site level.

The pooled analysis will be carried out in a similar manner to the study site-specific analysis. The study participants will be described according to the baseline characteristics. Confounding and effect modifications will be assessed in stratified analyses.

Participants will be followed from baseline to censoring from the study, either due to detection of infection/disease (i.e. detection of outcome) or study exit for any other reason. VE will be measured by comparing outcomes against a person's time at risk among vaccinated and unvaccinated groups. VE will be calculated using Cox regression (VE = 1 – hazard ratio [HR]). Country or study site will be included potentially as a fixed effect or as a random effect in a multilevel model. Statistical heterogeneity between study sites will be determined using the Q-test and the I^2 index.

Sensitivity analyses will be conducted by excluding those vaccinated 0−13 days before symptom onset/date of the sample collection and excluding the saliva sample of the healthcare worker tested.

For the saliva reliability study (validation study), we will estimate the degree of agreement between the results of the PCR tests for saliva samples and nasopharyngeal swabs using the Cohen's kappa coefficient [20] (15) If sample size allows, the VE will be measured by type of specimen collected. If both specimens are collected at the same time from the same person, we will use the nasopharyngeal swab results.

4. Laboratory methods

The following two specimen types can be collected as part of this study:

- **Nasopharyngeal swabs:** to be taken by a dedicated member of the medical staff (i.e. research nurse) or by study participants if they undergo brief training;
- **Saliva samples:** to be taken by study participants after undergoing brief training.

Specimens are collected at enrolment and on a weekly basis during the study period. Influenza laboratory confirmation is provided by RT-PCR. Samples will be subtyped for circulating influenza A viruses (subtypes H3 and H1) and lineages of influenza B.

For the validation study, pairs of saliva specimen and nasopharyngeal swabs from the same symptomatic healthcare workers, collected at the same time and transported under the same conditions, will be tested using RT-PCR. The results will be compared using the kappa coefficient (Section 3.12).

All or a random sample of viruses undergo gene sequencing of at least the influenza virus hemagglutinin segment. The sampling procedure can include sequencing of all viruses, where technically possible, or a random sample. See downloadable file 'Worksheet for genetic data collection' for this report[i].

Where possible, samples will also be tested for other respiratory pathogens. This could include SARS-CoV-2, and other coronaviruses, respiratory syncytial virus (RSV), enteroviruses, human metapneumovirus, bocavirus and adenoviruses.

➢ *Each study site should describe all the laboratory procedures:*

- Samples taken, storage, transport
- Laboratory platforms/assays used and performance
- Participation in quality assurance/quality control schemes, accreditation (ISO/national standards)
- Genetic and antigenic testing performed, including the selection of specimens for sequencing.

[i] 'Worksheet for genetic data collection' available at: https://www.ecdc.europa.eu/en/publications-data/influenza-vaccine-effectiveness-pilot-protocol-healthcare-worker-cohorts

5. Limitations

The following are some of the possible limitations of the pilot protocol involving healthcare workers.

- **Selection bias**
  - Previous infections: healthcare workers are a population at high risk of exposure to influenza and other respiratory infections. The role of a previous influenza infection is difficult to determine. Although post-infection immunity is considered broader and longer-lived than the antibody response induced by influenza vaccines for influenza A for example [21], it does not sterilise and only immuno-attenuates [22].
  - Indication bias: Professional exposure (activities) to the virus and underlying conditions among the participants may affect the likelihood of being vaccinated. This potential bias will be adjusted in the analysis using information collected on potential exposure and underlying conditions.
  - Healthy vaccinee effect: individuals in better health are more likely to get vaccinated and less likely to be infected, which could potentially lead to an underestimation of VE. In addition, vaccinated healthcare workers may be more (or less) likely to use PPE and less (or more) likely to be exposed to the virus.
- **Misclassification of the outcome** can occur due to the different types of samples used. Although indicated for influenza testing on some PCR platforms, saliva samples have to be validated by each laboratory in the hospitals where they are used for screening. VE will be stratified by the type of sample used, if the sample size allows.
- **Reporting bias:** vaccinated cases may be more likely or less likely to report symptoms and VE may be overestimated or underestimated accordingly.
- **Sample size/power:** inadequate sample size may limit the power of some stratified analyses.
- **Unmeasured or residual confounding** between those vaccinated and those unvaccinated may occur – e.g. risky behaviour, beliefs affecting exposure and vaccine acceptancy. In addition, pre- or post-exposure prophylaxis less used in EU/EEA [23], can influence the VE results if those who are unvaccinated are more likely to use this type of chemoprophylaxis.
- **The quality of self-reporting information** may differ between those vaccinated and those unvaccinated.
- **Differences of incidence and vaccination policy and coverage over time or between hospitals:** the risk of exposure to the influenza virus and vaccination coverage will differ between hospitals, regions/countries and over time. Multi-level analysis and adjustment by time will be necessary to minimise the effect of these differences in exposure.

6. Ethical considerations

The influenza component of the healthcare worker VEBIS VE studies should be approved by the relevant local ethics review committee.

All healthcare workers approached for enrolment should be informed that participation is voluntary and that they will be able to withdraw, without justification, at any time during the study without consequences. It should be clearly stated that participation in this study will not impact the offer of vaccination.

The informed consent form should include a description of the methods and frequency of respiratory samples and clinical and epidemiological data to be collected for the purpose of this investigation. Informed consent should also mention that samples may be shipped outside of the country for additional testing (if applicable) and/or used for future research purposes (if applicable).

6.1 Personal data protection

Each study site/country conducting the study shall comply with any requirement stemming from data protection legislation, and with national ethics committee requirements. This includes obtaining informed consent where necessary. The study site/country shall put in place technical and organisational measures (including those covering the security of their IT systems) that are adequate for the protection of the personal data they are processing.

ECDC acts as data controller for the purpose of conducting the studies covered by this protocol where they are carried out on behalf of ECDC. Each study site/country shall ensure that data subjects have received information about any processing operation that is carried out on behalf of ECDC. The privacy statement on vaccine effectiveness studies, available on ECDC's website, can be used for this purpose.

In the event that a study site/country carries out additional processing operations on its own initiative, the study site/country shall be the controller for that specific processing operation and shall take all the necessary measures accordingly.

7. Data governance

Biological materials and related data should only be collected and stored in collaboration with local health authorities and in compliance with any applicable law. The governance structure of any such collection should conform with all relevant regulations applicable to the study site. All governance systems should follow the principle of accountability and maintain good stewardship of stored biological materials and related data. None of the regulations concerning the storage, use and final fate of biological samples should contradict or overrule conditions originally stated in (broad) informed consent documents, signed by research participants.

Site-specific protocols, along with informed consent forms, should address the governance issues surrounding biological materials and data. Data governance statements should address the duration of data storage, date on which data will be destroyed, access to data during and after the study, and the procedure for participants wishing to withdraw permission for use of their data.

All points relating to governance of biological samples and data should be addressed in the informed consent form. For more information, please see International Ethical Guidelines for Health-related Research Involving Humans: https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf.

8. Risks and benefits for subjects

This study poses minimal risk to participants since it only involves the collection of respiratory specimens. Results of RT-PCR tests will be shared with participants as soon as they are available. The direct benefit to the participant will be the potential detection of respiratory infections, which would then allow for appropriate monitoring and treatment. The primary benefit of the study is indirect in that the data collected will help to measure the effectiveness of the influenza vaccines and guide vaccination policies.

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Annex 1

1. Informed consent (outline)

Cohort study to measure COVID-19 and influenza vaccine effectiveness among health workers

[Name of Principle Investigator]
[Name of Organisation]
[Name of Sponsor]
[Name of Project and Version]

This informed consent form consists of two parts:

I. Information sheet (to share information about the study with you)
II. Certificate of consent (for signatures if you agree to participate)

You will be given a copy of the full informed consent form.

Part I: Information sheet

Introduction
Briefly state who you are and explain that you are inviting the potential study participant to participate in the investigation being conducted. Inform them that they may talk to anyone that they feel comfortable talking with about the research and that they can take time to reflect on whether they want to participate or not. Assure the potential participant that if they do not understand some of the words or concepts, you will explain to them as you go along and that they may ask questions now or later.

Purpose
Explain in lay terms why the research is being done and what is expected from the results.

Type of research
Briefly state the methods involved in the study, including the length of the study, the frequency of blood draws, respiratory swabs and questionnaires. This will be expanded upon in the Procedure section.

Selection of participants
State clearly why they have been selected to participate in this study.

Voluntary participation
Indicate clearly that they can choose whether or not to participate and reassure there will be no work or health impact, should they choose not to participate. This can be repeated and expanded upon later in the form as well. It is important to state clearly at the beginning of the form that participation is voluntary so that the other information can be heard in this context.

Procedure
Explain the type of questions that the participants are likely to be asked and the kinds of samples that will be collected during the course of the study.

Duration
Include a statement about the time commitments of the study, including the duration of the study and follow-up, if relevant.

Risks and discomforts
Explain any risks or discomforts including the collection of blood samples, respiratory samples and any limits on confidentiality.

Benefits
Describe any benefits to the participant in the future, such as getting frequent information about potential SARS-CoV-2 and influenza infections, as a result of the research.

Reimbursements
State clearly what reimbursements will be provided to the participant. We do not encourage incentives beyond reimbursements for expenses incurred as a result of participation in the investigation. For example, the expenses may include travel costs and reimbursement for time lost. The amount should be determined in accordance with national regulations.

Confidentiality
Explain how the investigation team will maintain the confidentiality of data, particularly as regards information about the participant. Outline any limits on confidentiality.

Sharing of research findings
Include a statement indicating that the individual findings will be shared with the participant and the overall findings will be shared in a timely fashion with the hospital. Assure the participant that in the latter, all confidential information will remain confidential. If you have a plan and timeline for the sharing of information, include the details. In addition, inform the participant that the overall findings of the investigation will be shared more broadly, for example, through publications and conferences, again on the condition that personal identifiable information will remain confidential.

Storage of tissue samples:
Explain that you are seeking permission to store their unused respiratory samples for possible future use, either in your own research or someone else's research. State that they need to make some decisions about storage and future use of their respiratory and blood samples because they will only be giving you permission to use it for the current research.

Inform participants that their sample will not be sold for profit and that any research which uses their sample will have been approved.

Right to refuse or withdraw
Explain again the voluntary nature of consent – a participant can refuse to participate or withdraw from the investigation, without justification, at any time by informing one of the members of the investigation team.
If a participant decides to drop out, he/she will need to inform the investigation team as soon as possible. Any remaining samples from those previously collected along with data will be discarded, unless the participant informs the investigation team that they can be kept for the purpose of this specific investigation.

PART II: Certificate of consent

Certificate of consent

This section can be written in the first person. It should include a few brief statements about the research and be followed by a statement similar to the one in bold below. A researcher or the person explaining the informed consent must sign each consent. Since the certificate is an integral part of the information sheet and not a stand-alone document, the layout or design of the form should reflect this.

- **I confirm that I have read the information sheet dated dd/mm/yyyy (version XX) for the study of influenza vaccine effectiveness and validation of the saliva sample for influenza testing. I have had the opportunity to consider the information and ask questions, and these have been answered satisfactorily.**
- **I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.**
- **I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the Sponsor, the regulatory authorities and [site relevant], where this is relevant to my taking part in this research. I give permission for these individuals to have access to my records.**
- **I agree for my anonymised samples to be used in future research, here or abroad, which has ethics approval and will not be undertaken for profit.**

Printed name of participant _____

Signature of participant _____

Date _____ **Day/month/year.**

Statement by the researcher/person obtaining consent

I confirm that the participant was given an opportunity to ask questions about the study and all the questions asked have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and that consent has been given freely and voluntarily.

A copy of this informed consent form has been provided to the participant: _____

Printed name of researcher/person obtaining the consent _____
Signature of researcher/person obtaining the consent _____

Date _____ **Day/month/year.**

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