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TECHNICAL REPORT

Generic protocol for COVID-19 vaccine effectiveness in preventing transmission of infection in healthcare settings

July 2023

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Abbreviations

COVID-19	Coronavirus disease 2019
ECDC	European Centre for Disease Prevention and Control
EU	European Union
EEA	European Economic Area
GDPR	General Data Protection Regulations
IPC	Infection prevention and control
LTCF	Long-term care facility
OR	Odds ratio
RDT	Rapid Diagnostic Test
RT-PCR	Reverse transcriptase polymerase chain reaction
RR	Relative Risk
RVE	Relative Vaccine Effectiveness
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
VE	Vaccine effectiveness
WHO	World Health Organization

Executive summary

Since the emergence in late 2019 of the novel severe acute respiratory syndrome – coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), international collaboration has accelerated the development of COVID-19 vaccines. Within the EU/EEA, as of 16 June 2023, 12 vaccines, including four updated bivalent mRNA COVID-19 vaccines that contain both the original strain and either the Omicron BA.1 or BA.4-5 subvariants are authorised [1].

The aim of the study protocol is to measure product-specific COVID-19 vaccine effectiveness to prevent transmission of SARS-CoV-2 infection from healthcare workers to their contacts, which can be either other patients or healthcare workers, in healthcare settings. This document outlines a generic method to establish the study, collect data and undertake analysis as well as allowing for necessary local adaptions.

We propose a study design of a prospective cohort and the follow-up of contacts, both healthcare workers and patients, within a healthcare facility of a healthcare workers index case. The study setting is healthcare facilities participating in the VEBIS healthcare workers cohort study to estimate COVID-19 vaccine effectiveness, or other settings with similar attributes. The Vaccine Effectiveness, Burden and Impact Studies (VEBIS) healthcare workers study involves the regular screening of healthcare workers for possible SARS-CoV-2 infection so that both asymptomatic and symptomatic healthcare workers index cases can be identified using a consistent means of ascertainment.

The index case for the study will be healthcare workers with either an asymptomatic or symptomatic SARS-CoV-2 infection ascertained by regular screening. The contact of a healthcare workers index case will be defined as anyone who has had a contact with the healthcare workers in the three days prior to the index healthcare workers case confirmed SARS-CoV-2 infection status. The date of confirmed SARS-CoV-2 infection status of the healthcare workers index case (i.e. index date) will be the date which the saliva sample or swab (nasal, OP or NP) was taken from the healthcare workers, who subsequently was tested positive by PCR. This date will be counted as T0.

There are two classes of contact: Patient or healthcare workers. All patients and/or healthcare workers who conform to the definition of a contact should only be recruited if they satisfy all following criteria of: Eligible for COVID-19 vaccination; COVID-19 vaccination is not contra-indicated; report a negative PCR for SARS-CoV-2 at T0; and have provided informed consent.

All identified contacts who have agreed to participate in the study should be approached for molecular testing for SARS-CoV-2 infection at T0 (up to three days after date of confirmed infection in the index healthcare workers case) and at T5 of the last test in contacts. The sample taken can include saliva samples or nasal, oropharyngeal or nasopharyngeal swabs.

Outcomes will be classified as follows: healthcare workers Index Case; Co-primary index case among any patient or healthcare workers contact; Probable co-primary index case among any patient or healthcare workers contact; Secondary case of any patient or healthcare workers contact whose SARS-CoV-2 infection status is confirmed by PCR that conforms to the algorithm of a negative SARS-CoV-2 PCR test of sample or swab taken at T0 and a positive SARS-CoV-2 PCR test of sample or swab taken.

Introduction

Since the emergence, in late 2019, of the SARS-CoV-2 virus, which causes COVID-19, international collaboration has accelerated the development of COVID-19 vaccines. Within the EU/EEA, as of 16 June 2023, 12 vaccines, including four updated bivalent mRNA COVID-19 vaccines that contain both the original strain and either the Omicron BA.1 or BA.4-5 subvariants have been authorised [1].

Initially, countries prioritised COVID-19 vaccination in those at risk of severe outcomes (e.g. older adults, vulnerable individuals) as well as healthcare workers [2]. Healthcare workers have been identified as a priority group for COVID-19 vaccination in order to maintain essential healthcare services as they are considered at a higher risk of SARS-CoV-2 infection, and they can also transmit the infection to susceptible patients at high risk of severe COVID-19[3].

Measuring the real-world COVID-19 vaccine performance is critical for understanding the risks and benefits of vaccination programmes [4]. Since the rollout of COVID-19 vaccination, a large number of observational studies reported the direct effect (effectiveness) of these vaccines [5]. Fewer vaccine studies reported the effectiveness on transmission of infection [6].

Such studies require identifying an index case and estimating the secondary attack rate (SAR) in contacts by comparing SAR between vaccinated and unvaccinated index and secondary cases. To date, nearly all studies have

employed a cohort study design, both prospective and retrospective, and mostly reporting SAR in household contacts [5].

As part of the VEBIS 'Assessment of COVID-19 vaccine effectiveness among healthcare workers' project, the European Centre for Disease Prevention and Control (ECDC) initiated the development of a generic protocol to measure the effectiveness of the COVID-19 vaccine against transmission in healthcare facilities.

This document presents the core protocol of a cohort study and outlines a generic method to establish the study, collect data and undertake analysis and allow for necessary local adaptions. Sections of this generic protocol which require further local modification are highlighted as below.

Arrow marks with italicised text indicate the points that study sites should adapt and provide details in their study annexes.

Note that this protocol:

- Does not cover household transmission studies. If such a component is to be included as part of the study objectives, the WHO Unity protocol can be adapted: *https://www.who.int/publications/i/item/household-transmission-investigation-protocol-for-2019-novel-coronavirus-%282019-ncov%29-infection*.
- Aims specifically to measure vaccine effectiveness against SARS-CoV-2 transmission, although it can be easily adapted to other respiratory viruses such as influenza.

Rationale

Since December 2020, ECDC has supported the development and implementation of a multi-centre European study to evaluate the effectiveness of COVID-19 vaccines in hospital-based healthcare workers.

As part of the VEBIS 'Assessment of COVID-19 vaccine effectiveness among healthcare workers' project, it was agreed that a generic protocol to investigate the effectiveness of the COVID-19 vaccine against transmission in healthcare facilities would be developed.

Objectives

Overall objective

To measure product-specific COVID-19 vaccine effectiveness to prevent transmission of SARS-CoV-2 infection from healthcare workers to their contacts (either patients or other healthcare workers), in healthcare settings.

Secondary objectives

To measure COVID-19 vaccine effectiveness to prevent transmission of SARS-CoV-2 infection by:

- Vaccination history (e.g. different vaccine brands, number of doses, incomplete vaccination, time since last vaccination) in contacts;
- Previous SARS-CoV-2 infection in both index cases and contacts;
- Different high-risk comorbidities in contacts;
- Professional exposures of index cases;
- Outcomes (clinical severity: asymptomatic, symptomatic, or severe infection and variants) in index cases against various outcomes in contacts (clinical severity, variants).

Each study site to specify the secondary objectives of their study.

Methods

Study design

The study uses a prospective cohort with follow-up of contacts of a healthcare workers index case, both healthcare workers and patients, within a healthcare facility.

Each study site to specify if all contacts, both healthcare workers and patients, or if one group, either healthcare workers or patients, are to be recruited to the study.

Study setting

The study will be conducted in healthcare facilities participating in the VEBIS healthcare workers cohort study to estimate COVID-19 vaccine effectiveness, or a similar setting. The VEBIS healthcare workers study involves the regular screening of healthcare workers for possible SARS-CoV-2 infection so that both asymptomatic and symptomatic healthcare workers index cases can be identified using a consistent means of ascertainment.

Sites not participating in the VEBIS healthcare workers studies can participate in this study if there is regular screening of healthcare workers within the healthcare facility to ascertain index cases.

Study population: index cases

Index cases for the study will be healthcare workers with either an asymptomatic or symptomatic SARS-CoV-2 infection ascertained by the regular screening in the healthcare workers vaccine effectiveness study. Healthcare workers are screened for possible SARS-CoV-2 infection by weekly saliva/NP or biweekly NP PCR testing.

The date of confirmed SARS-CoV-2 infection status of the healthcare workers index case will be the date which the saliva sample or swab (nasal, OP or NP) was taken from the healthcare workers, and was subsequently tested positive by PCR. This date will be counted as T0 for the index case.

Study population: contacts

A contact of an healthcare workers index case will be defined as anyone who has had the last contact with the healthcare workers in the three days prior to the date of specimen collection for the specimen testing SARS-CoV-2 positive in the healthcare workers index case, i.e. index date (Figure 1).

There are two classes of contacts:

- **Patient contacts:** Any in-patient in the participating healthcare facilities that has been in contact anytime in the three days prior to the index healthcare workers. The patient contacts will need to be defined by stricter (e.g. attendance of the patient by the healthcare workers index case) or looser (e.g. on the same ward as the healthcare workers index case) criteria. All possible contacts (patients) will be listed and need to be approached to participate in the study.
- **healthcare workers contacts:** Any healthcare workers who have been in contact with the index healthcare workers in the three days prior to the index healthcare workers case confirmed SARS-CoV-2 infection status. Contact will be defined according the ECDC case definition of a close contact: https://www.ecdc.europa.eu/en/covid-19/surveillance/surveillance-definitions.

Each participating site to describe if they will recruit contacts from both healthcare workers and patients or from one group only. If sites recruit from patient contacts, the local protocol should include a clear definition of a patient contact and how these are identified and recruited. The study team should keep records of the patient and healthcare workers contacts that were eligible to participate and refuse testing.

Inclusion and exclusion criteria

The inclusion and exclusion criteria should be applied to all individuals to be recruited to the study, and should be applied according to whether they are:

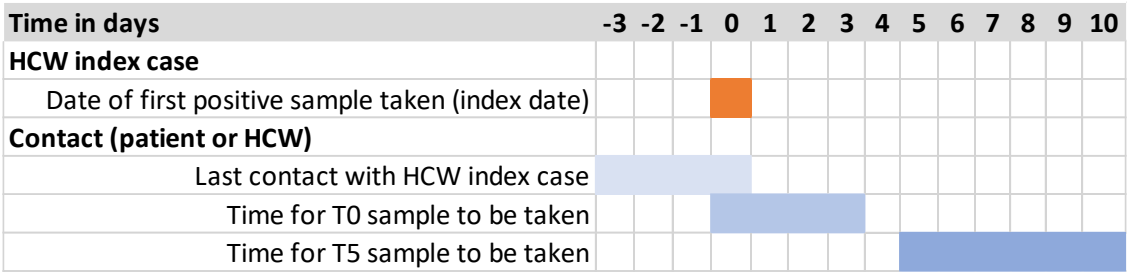
- **healthcare workers index cases:** All healthcare workers who conform to the definition of an index case (see section *Study population: Index case*) who satisfy the following criteria:
  - Have been at the healthcare facility at least one of the three days prior to the SARS-CoV-2 infection;
  - Have provided informed consent.
- **Contacts:** All patients and/or healthcare workers who conform to the definition of a contact (see section *Study population: Contacts*) should only be recruited in they satisfy all following criteria:
  - Are eligible for COVID-19 vaccination;
  - COVID-19 vaccination is not contra-indicated;
  - Report a negative PCR for SARS-CoV-2 at T0 (Figure 1);
  - Have provided informed consent.

Healthcare worker contacts participating in the VEBIS healthcare workers cohort study will have been regularly screened for SARS-CoV-2. Site investigators should use the VEBIS dataset to ascertain and record if the healthcare workers has reported a negative SARS-CoV-2 by PCR within the two weeks prior to the date of the confirmed SARS-CoV-2 infection in the index healthcare workers.

For healthcare workers contacts not participating in the VEBIS healthcare workers cohort study, if regular screening of all healthcare workers in the healthcare facility is being performed, site investigators should ascertain and record if the healthcare workers reported a negative SARS-CoV-2 test, either PCR or Rapid Diagnostic Tests (RDT), in the two weeks prior to the date of confirmed infection in the index case.

For those healthcare facilities that screen patients on admission for SARS-CoV-2, site investigators should ascertain and record if the patient reported a negative SARS-CoV-2 test, either PCR or Rapid Diagnostic Tests (RDT), in the two weeks prior to the date of confirmed infection in the index case.

Figure 1. Timeline used to sample contacts of the healthcare workers index case, VEBIS healthcare workers SARS-CoV-2 transmission study



Study period

The study should be conducted only after the study protocol is approved by the relevant ethical review committee. The study period should be for a minimum period of four months and a maximum of six months depending on local circumstances. Ideally, the study should be conducted during a period of intense community circulation of SARS-CoV-2 viruses to ensure adequate sample size.

Each study site to define the study period

Definitions and classification of outcomes among contacts

The **primary outcome in contacts** is a saliva sample or swab (nasal, OP or NP) taken from a patient or healthcare workers in which a SARS-CoV-2 virus infection is confirmed by laboratory RT-PCR. Outcomes will be classified as follows:

- **Co-primary index case:** a contact who provides sample or swab that tests positive for SARS-CoV-2 by PCR within three days of the confirmed SARS-CoV-2 infection status of the index case (T0 in Figure 1);
- **Probable co-primary index case:** a contact who provides sample or swab that tests positive for SARS-CoV-2 by PCR between three and five days of the confirmed SARS-CoV-2 infection status of the index case;
- **Secondary case:** A contact whose SARS-CoV-2 infection status is confirmed by PCR that conforms to the following algorithm:
  - Negative SARS-CoV-2 PCR test of saliva sample or swab taken at T0;
  - AND
  - Positive SARS-CoV-2 PCR test of sample or swab taken at between T5 (Figure 1).
- **Probable secondary case:** A contact who provides a sample or swab that tests negative by PCR between T0 and T5 (Figure 1) and provides a sample or swab that tests positive for SARS-CoV-2 by PCR at T5 or after (Figure 1).
- **Non-case**: A contact who provides a sample or swab that tests negative by PCR both at T0 and T5.

Index cases or contacts who report symptoms that conform with the ECDC possible case definition of COVID-19 will be defined as symptomatic if they report one or more of the following [9]:

- cough;
- fever;
- shortness of breath/dyspnoea;
- sudden onset of anosmia;
- sudden onset of ageusia/dysgeusia.

Categories of outcome severity are defined as participants who conform to the definition of a primary outcome measure with the following stages reported within two weeks of their first positive SARS-CoV-2 test:

- **Asymptomatic:** no reported symptoms consistent with the ECDC definition of COVID-19;
- **Mild disease:** reported symptoms consistent with the ECDC definition of COVID-19 requiring or not attendance at a medical service, but requiring no further assistance for activities of daily living;

- **Moderate disease:** reported symptoms consistent with the ECDC definition of COVID-19 requiring either hospitalisation but not requiring oxygen treatment or not hospitalised but requiring assistance for activities of daily living;
- **Severe disease:** reported symptoms consistent with the ECDC definition of COVID-19 requiring hospitalisation and oxygen treatment;
- **Very severe disease:** reported symptoms consistent with the ECDC definition of COVID-19 requiring hospitalisation and any of the following: admittance to an intensive care unit and/or intubation or mechanical ventilation and/or additional systems/organs support (vasopressors, dialysis, ECMO) or death.

Exposure

An individual will be considered as vaccinated against COVID-19 with a product-specific vaccine during the current pandemic under the following categories:

- **Fully vaccinated with a primary course plus booster(s) (two-dose vaccine):** Individuals will be considered fully vaccinated with booster(s) if they have received both doses followed by booster dose(s) at least seven days[i] before study participation.
- **Fully vaccinated with a primary course (two-dose vaccine):** Individuals will be considered fully vaccinated if they have received both doses at least 14 days* before study participation.
- **Fully vaccinated with a primary course (single-dose vaccine):** Individuals will be considered fully vaccinated if they have received one dose at least 14 days before study participation.
- **Partially vaccinated (two-dose vaccine only):** Individuals will be considered partially vaccinated if they have received one of two doses at least 14 days* before study participation.
- **Unvaccinated:** Individuals will be considered unvaccinated if they did not receive COVID-19 vaccine or if they were vaccinated within 14 days of study participation.

The precise vaccination status of both healthcare workers index cases and contacts is essential for this study. Vaccine ascertainment will depend on how the vaccination is delivered and registered in each setting but using documentation to ascertain vaccination status is recommended.

Self-reported vaccination status should be verified and confirmed through occupational health, vaccine registry, vaccination card or any potential data source. Participants should be informed in the informed consent form that these additional sources will be accessed, when relevant, to confirm their vaccination status.

Vaccine documentation should include for each dose:

- COVID-19 vaccination received and date of vaccination;
- Vaccine brand;
- Vaccine batch;
- Ascertainment (e.g. documented by vaccine card, vaccine registry, occupational health records etc).

Each study site to describe how vaccination status will be ascertained

Sample size

The sample size for cohort studies depends on the vaccination coverage in the population, the assumed vaccine effectiveness in preventing transmission, the transmissibility of the SARS-CoV-2 variant and the estimated incidence of SARS-CoV-2 infection over the follow-up time in the unvaccinated study population, and the desired precision.

In Table 1 below, we present the sample size to estimate the two proportions for each stratum, with a power of 80% and at a two-sided significance level of 5% for the scenarios of a vaccine effectiveness against transmission of 50, 40, 30, 20, 10% assuming an incidence in the control group of 20, 10 and 5% and a vaccination coverage of 70%[ii].

The sample size calculation does not account for any study dropouts, individuals who may choose to be vaccinated in the follow-up period or stratification of analyses.

[i] The exact number of days will depend on the vaccine employed and may change over time. The protocol should be updated according to manufacturers' recommendations. If any study participant was vaccinated earlier or later than recommended by manufacturers, sensitivity analyses will be performed for differing delays between first and second dose.

ii Harrell F, Power and Sample Size for Two-Sample Binomial Test, bpower function: https://search.r-project.org/CRAN/refmans/Hmisc/html/bpower.html using hmisc package in R v4.2.1: https://CRAN.R-project.org/package=Hmisc

Table 1. Number of subjects per stratum for vaccine effectiveness in a cohort study

Incidence in control group	Vaccine effectiveness against transmission				
	50%	40%	30%	20%	10%
20%	398	657	1 229	2894	12 078
10%	869	1 442	2 711	6426	26 990
5%	1 811	3 012	5 676	13 490	56 816

Each participating study site to define the expected sample size.

At each participating site, the sample size will be determined by length of study period, whether all or a group (i.e., patient or healthcare workers) contacts are recruited and the number of contacts per confirmed healthcare workers index case. Study investigators at each site should try to ensure that all contacts are recruited to the study to maximise the power of the study.

Laboratory methods

Specimen collection

Respiratory samples are to be taken by trained personnel (e.g. research staff or healthcare facility healthcare workers). All biological sampling for SARS-CoV-2 RNA should follow WHO COVID-19 technical guidance documents on the proper handling and processing of potentially infectious specimens ('Laboratory biosafety guidance related to coronavirus disease (COVID-19),' published 28 January 2021 and 'Laboratory testing for coronavirus disease (COVID-19) in suspected human cases,' published 19 March 2020), as well as WHO's general laboratory guidance ('General guidance of laboratory biosafety- 3rd edition,' updated 2004).

All collection tubes should be labelled with a coded identification number, which also should recorded on the interview questionnaire. Time of collection, location, and name of the person collecting will also be recorded.

Note: *Given the rapidly developing guidance related to SARS-CoV-2, it is recommended that investigators check for updates to these documents prior to study initiation to ensure that current recommendations are being followed.*

Specimen storage, shipment and transport

All those involved in collecting and transporting specimens should be trained in safe handling practices and spill decontamination procedures. For details regarding the transport of samples collected and infection control advice, please refer to the case management algorithm and laboratory guidance in the country, or to WHO laboratory guidance, available on the WHO website.

For each biological sample collected, the time of collection, the conditions for transportation and the time of arrival at the laboratory will be recorded. Specimens should reach the laboratory as soon as possible after collection.

If a respiratory specimen is not likely to reach the laboratory within 72 hours, it should be frozen, preferably at –80 C, and shipped on dry ice. It is recommended to aliquot samples prior to freezing, to minimise freeze thaw cycles. The storage of respiratory and serum specimens in domestic frost-free freezers should be avoided, owing to their wide temperature fluctuations.

The samples can be entered into a biobank for future research projects if participants consent.

Transport of specimens within national borders should comply with applicable national regulations. International transport of specimens should follow applicable international regulations as described in the WHO Guidance on regulations for the transport of infectious substances 2019–2020

Specimen testing

Each study site should describe all the laboratory procedures specific to their sites:

- Samples taken, storage, transport;
- Kits used and performance;
- Participation in quality assurance/quality control schemes;
- Selection of specimens for sequencing.

Molecular testing

Laboratory guidance for **molecular testing** for COVID-19 can be found on the WHO and ECDC websites as well as the VEBIS healthcare workers study protocol. Several assays that detect SARS-CoV-2 have been recently developed and the protocols or standard operating procedures (SOPs) can also be found on the WHO website. Quality assurance of assay performance at sites should be undertaken using international, national or research standards [13].

Index cases will be identified among healthcare workers regularly screened for SARS-CoV-2 infection either as part of their participation in VEBIS cohort studies or as part of normal hospital IPC practice. Healthcare workers can provide samples for screening using saliva (weekly only) or nasal (weekly only), nasopharyngeal (NP; weekly or biweekly), oropharyngeal (OP; weekly or biweekly) swabs.

Testing of contacts of the healthcare workers index case for SARS-CoV-2 with RT-PCR should be undertaken on the following specimens and time points:

- At enrolment (T0) of either a saliva sample or nasal, naso- or oropharyngeal swab;
- At follow-up (T5) of either a saliva sample or nasal, naso- or oropharyngeal swab.

Although naso- or oropharyngeal swabs are preferred in the study protocol, investigators may wish to consider the use of saliva samples or nasal swabs. Both saliva samples and nasal swabs have a lower sensitivity than NP swabs [15]. Both types of samples are considered to have similar performance to NP swabs [16], especially in the acute phases of infection [17]. Furthermore, all contacts will have reported a negative SARS-CoV-2 test within the previous two weeks.

Saliva samples are considered a much more acceptable and less intrusive sample than swabs which may facilitate recruitment to the study of contacts, especially those that are vulnerable or frail.

Genetic sequencing

All or a random sample of SARS-CoV-2 RT-PCR positive specimens with sufficiently low cycle threshold (Ct) values (usually Ct <30) collected among study participants should be further characterised using genetic sequencing [10,11]. Genetic sequencing is particularly important to undertake during the study to understand whether changes in vaccine effectiveness could be due in part to mutations in the circulating virus. Investigators should also ensure genetic sequences are uploaded into the appropriate GISAID platform and through the European portal: https://www.covid19dataportal.org/.

Data collection and data sources

Data should be collected using a standardised questionnaire. The questionnaire can be completed by the participant, a member of staff, a patient guardian or a study monitor. If available, medical records can be consulted to complete the questionnaire. A combination of approaches is permissible.

For VEBIS healthcare workers study participants, data regarding the healthcare workers index case should be collected from the VEBIS healthcare workers study enrolment and follow-up form. Similarly, for healthcare workers contacts who are actively participating in the VEBIS healthcare workers study, data should be collected using the enrolment and follow-up forms.

For contacts (patients or healthcare workers) not participating in the VEBIS healthcare workers study, the following minimum data that should be collected at enrolment (T0):

- Age;
- Sex;
- Last SARS-CoV-2 infection (date of clinical or laboratory confirmation);
- Vaccination status for COVID-19 and other respiratory pathogens (influenza, pneumococcus);
- Contact or exposure to a possible or confirmed case(s) SARS-CoV-2 in the previous 14 days (in or outside of the healthcare facility);
- Symptoms in the previous 10 days;
- Molecular testing results; and
- Clinical history (chronic disease for all, frailty scores for patients).

At the follow-up (T5), the minimum data that should be collected are:

- Report of symptoms compatible with SARS-CoV-2 infection and the first symptom onset date;
- Contact with confirmed case(s) SARS-CoV-2 since T0; and
- Molecular test results.

The table below summarises the data to be collected and a more detailed list is provided in Annex 1.

Table 2. Data collection of common variables (key variables that should be collected, optional variables recommended) and questionnaires to be used

Categories	Variable	Key/optional variable	healthcare workers contact	Patient contact
Socio-demographic information	Age	Key	✓	✓
	Sex	Key	✓	✓
Admission	Ward admission	Key	X	✓
	Admission to healthcare facility and ward	Key	X	✓
Individual behaviours	Smoking (current/past/never)	Key	✓	✓
	BMI (height and weight)	Key	✓	✓
Clinical history	Frailty score	Key	✓	X
	Diagnosis chronic conditions (see Annex 1)	Key	✓	✓
	Medication for chronic condition (see Annex 1)	Key	✓	✓
COVID-19 vaccination	Vaccine offered	Key	✓	✓
	Vaccine dose (1st, 2nd, 3rd, 4th)	Key	✓	✓
	Vaccination date(s) (for each dose)	Key	✓	✓
	Vaccine product (for each dose)	Key	✓	✓
	Vaccine batch	Key	✓	✓
	Source used for vaccine ascertainment	Key	✓	✓
Other vaccinations	Influenza (date)	Key	✓	✓
SARS-CoV-2 infection	Laboratory/clinical/self-reported confirmed	Key	✓ (T0 and T5)	✓ (T0 and T5)
	List of symptoms	Key	✓ (T0 and T5)	✓ (T0 and T5)
	Date of onset	Key	✓ (T0 and T5)	✓ (T0 and T5)
	Severity	Key	✓ (T0 and T5)	✓ (T0 and T5)
Contact with SARS-CoV-2	Contact with confirmed SARS-CoV-2 infected individuals	Key	✓ (T0 and T5)	✓ (T0 and T5)
Laboratory results	PCR	Key	✓	✓
	Cycle threshold (Ct) value	Key	ü	ü
	Variant	Key	✓ (if reported)	✓ (if reported)

Each study site to list variables collected.

Data sources

Data can be collected through questionnaires completed by the study monitors, study participants, electronic medical records, vaccine registries or other relevant sources. Once collected, data should be inputted onto a centralised on-line platform which conforms to international standards (e.g. ISO027001), General Data Protection Regulations (GDPR) and to national legislation and regulations for the hosting of personal medical data.

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

Each study site to detail data sources to be used for each variable.

Data management and ensuring data confidentiality

All data management procedures must comply with the GDPR.

Each participant should be allocated a unique study ID number at enrolment that all documents will subsequently use as the identifier. The unique identifier will be randomly generated and will link each record.

The coordinating team will not have access to the dataset containing personal identifier information (i.e. names, email addresses and contact details). The study site principal investigator and study monitor will have access to the personal information but will not be able to export these data. Each record will be given a unique but anonymous identifier. The unique identifier will be used to link different records and so enable analyses to be conducted by the coordinating team when pooling data whilst maintaining the individual's anonymity. If there should be any further queries raised by the coordinating team during pooling of data, the unique identifier will be used by the site study teams to trace records back thereby ensuring that anonymity is maintained.

The records of the contacts will contain the unique identifier of the healthcare workers index case so ensuring that transmission dyads can be constructed.

Analysis plan

The analysis plan for the study is being continuously reviewed and updated by study coordinators, study sites and international experts. An outline analysis plan is presented in this section.

Participation

The study participants should be described in terms of:

- total number of healthcare workers index cases;
- total number of eligible contacts (total and by category of healthcare workers or patient);
- total number and proportion of index cases and contacts who refused to participate (total and by category of healthcare workers or patient);
- reason for refusal.

Separate flow charts for index cases and contacts will display the numbers of participants in the study and the numbers excluded that do not conform to each inclusion criterion.

Baseline characteristics

Baseline characteristics of study participants should be tabulated. Depending on variable type, the mean, median or proportion should be presented. The number of individuals with missing data for each variable should be presented.

Baseline characteristics for participants tabulated should include:

- age group;
- sex;
- comorbidities;
- obesity;
- smoking history;
- COVID-19 and other vaccination history (influenza, pneumococcal);
- Previous SARS-CoV-2 infection including diagnostic method;
- community-related exposures.

Vaccine effectiveness against transmission

The study design aims to report the secondary attack rate (SAR) in close contacts of the healthcare workers index case, whether the contacts are patients (i.e. healthcare workers-patient) or other healthcare workers (i.e. healthcare workers-healthcare workers). The SAR will be the proportion of contacts who acquire infection during the period during or following contact with the healthcare workers index case. It will be compared between vaccinated or unvaccinated contacts according to the vaccination status of the index case.

The healthcare workers cohorts recruited to date as part of the VEBIS healthcare workers activities have all reported coverage of >90% of healthcare workers with a primary vaccine course[iii]. In this cohort, recruiting sufficient numbers of unvaccinated index HEALTHCARE WORKERS cases and contacts will be difficult. Therefore, the objective of obtaining a vaccine effectiveness against transmission comparing SAR in vaccinated and

[iii] Interim analysis of COVID-19 vaccine effectiveness in healthcare workers - an ECDC multi-country study, May 2021-July 2022

unvaccinated contacts and stratifying according to vaccinated and unvaccinated HEALTHCARE WORKERS index case status is unachievable,.

Instead, a comparative vaccine effectiveness against transmission can be estimated in which an as-treated analysis will be performed so that the healthcare workers index case and contacts will be allocated as booster or primary course vaccinated rather than vaccinated or unvaccinated. We propose that these could be defined as:

- **Booster:** Having completed a primary vaccine course three or more months prior to receiving an additional vaccine booster dose seven or more days earlier;
- **Primary:** having completed 14 days or more earlier a primary course vaccination with two doses for a double dose vaccine or one dose of a single dose of vaccine.

For each category (booster and primary course) of healthcare workers index case and contacts, an overall SAR of secondary cases among all contacts will be reported and a relative risk (RR) calculated (Table 3). SAR will be reported for different categories of contacts by vaccination status of index cases and contacts (i.e. booster, primary course, unvaccinated) and RR calculated to estimate vaccine effectiveness against transmission for the different strata. An example of the outputs is presented in Table 3.

Table 3. Presentation of study outputs to estimate vaccine effectiveness against transmission[iv]

Healthcare workers Index case	Contact*			Relative Risk**(RR)	Vaccine effectiveness
Relative vaccine effectiveness for infectiousness/transmission (*I*)					
	Contact overall				
	Secondary case	**Non-case**			
healthcare workers booster	a	b	$SAR_{B.}$ =a/a+b	$SAR_{B.}/SAR_{P.}$	rVE_{I}=1- $SAR_{B.}/SAR_{P.}$
healthcare workers primary	c	d	$SAR_{P.}$=c/c+d		
vaccine effectiveness for infectiousness/transmission stratified by the vaccine status of index and contacts					
	Contact				
	Secondary case	**Non-case**			
healthcare workers booster	Contact unvaccinated	Contact unvaccinated	SAR_{BU}	SAR_{BU}/SAR_{UU}	$VE_{I\,BU/UU}$=1- SAR_{BU}/SAR_{UU}
healthcare workers unvaccinated	Contact unvaccinated	Contact unvaccinated	SAR_{UU}		
	Secondary case	**Non-case**			
healthcare workers booster	Contact booster	Contact booster	SAR_{BB}	SAR_{BB}/SAR_{UB}	$VE_{I\,BB/UB}$=1- SAR_{BB}/SAR_{UB}
healthcare workers unvaccinated	Contact booster	Contact booster	SAR_{UB}		
Relative vaccine effectiveness for infectiousness/transmission stratified by the vaccine status of index and contacts					
	Secondary case	**Non-case**			
healthcare workers booster	Contact primary	Contact primary	SAR_{BP}	SAR_{BP}/SAR_{PP}	$rVE_{I\,BP/PP}$=1- SAR_{BP}/SAR_{PP}
healthcare workers primary	Contact primary	Contact primary	SAR_{PP}		
	Secondary case	**Non-case**			
healthcare workers booster	Contact booster	Contact booster	SAR_{BB}	SAR_{BB}/SAR_{PB}	$rVE_{I\,BB/PB}$=1- SAR_{BB}/SAR_{PB}
healthcare workers primary	Contact booster	Contact booster	SAR_{PB}		

**Patients or healthcare workerss*
***Calculated without taken the clustering by index case into account*

The vaccine effectiveness will be calculated using a mixed model (with the index case as a separate level) to account for transmission chains (vaccine effectiveness = 1 - RR). RR can be estimated using binomial regression, or Poisson regression with robust variance, or using logistic regression to obtain standardised risk ratios.

[iv] Based on Halloran, M.E., Longini, I.M., Struchiner, C.J. (2010). Overview of Vaccine Effects and Study Designs. In: Design and Analysis of Vaccine Studies. Statistics for Biology and Health. Springer, New York, NY. https://doi.org/10.1007/978-0-387-68636-3_2

Effect modification should be explored. Analysis will be stratified depending on the sample size, by factors associated with infectiousness (index cases) or factors associated with susceptibility (contacts), such as:

- vaccine dose as illustrated in Table 3;
- age groups;
- sex;
- underlying conditions;
- categories of exposure;
- specimen collection method;
- any other effect modifier identified.

Confounding factors will be assessed by comparing crude and adjusted estimates for each baseline characteristic in stratified analyses.

Both unadjusted and adjusted estimates of vaccine effectiveness should be presented. Adjustment should be made in the multivariable regression model for all potential confounders which should include age, sex, site and calendar time and other confounders identified in the stratified analysis.

Missing data

Missing data should be categorised and an appropriate approach to handle missing data chosen. Depending on assumptions regarding the variables, we will account for missing data by either undertaking analyses on a complete case series (i.e. only including those records without missing data) or multiple imputation approach (e.g., multiple imputation using chained equations).

Sensitivity analyses

- The primary analysis will exclude co-primary index cases and a sensitivity analysis will be performed with co-primary cases included as secondary cases.
- Another sensitivity analysis will be performed by excluding patients-contacts admitted less than four days prior to the date of confirmed SARS-CoV-2 infection in the index healthcare workers case.

Study procedures

Study preparation

Healthcare workers in the site will be key as from this group both the index cases and contacts, if appropriate, will be recruited. The study preparation will focus on the recruitment of healthcare workers prepared to be index cases.

After the study has been approved by the relevant ethical review committee, investigators should make themselves available to healthcare workers at the site to describe the study, answer all questions with potential participants either individually or in groups.

All healthcare workers should provide informed consent prior to their enrolment into the study (see section on *Ethical Considerations* for more details) as index cases. Study staff should review the informed consent form with the potential participant in a private area designated for study use. If feasible, to assess non-response/non-participation bias study staff will administer a short set of anonymous questions to individuals that refused to participate. The minimum information collected should include age, sex, healthcare workers role and reasons for declining for all those refusing.

An added benefit of the promotion of the study among healthcare workers is that there will be a level of knowledge already of the study aims, objectives and procedures, so facilitating recruitment of healthcare workers as contacts in the study.

T0: Study initiation

The study starts from the date when the index healthcare workers case provides a sample (saliva) or swab (nasal, OP or NP) that has tested positive for SARS-CoV-2 infection by RT-PCR, either as part of the VEBIS healthcare workers study or another study in the site. At this point site, although the healthcare workers index case will have already provided informed consent with the study, site investigators should confirm the intention of the healthcare workers to participate in the study.

The study team will start compiling the list of contacts either by interview with the index case or by reviewing his/her activity in the prior three days before the sample collection of the positive test. Contacts, as defined in sections above, of the healthcare workers index case may be either patients and/or other healthcare workers:

- **Patient contact:** Either all or a random selection of those patients that conform to the local definition of a contact should be invited to participate in the study. If a random selection of patient contacts is to be

invited to the study, the sample should be selected using the sampling frame of all possible patient contacts. All participants should provide informed consent prior to their enrolment into the study. Study staff should describe the study in detail, answer all questions, and review the informed consent form with the potential participant (and/or their guardian) in a private area designated for study use. Patients refusing to be involved in the study will be replaced by the next individual in the list. If feasible, to assess non-response/non-participation bias study staff will administer a short set of anonymous questions to individuals that refused to participate. The minimum information collected should include: age, sex and reasons for declining for all those refusing; and whether a guardian declined for residents.

- Once informed consent has been obtained, participants should be enrolled regardless of their individual vaccination status and should:
  - Provide a sample (saliva) or swab (nasal, OP or NP) for RT-PCR within three days of the date of the specimen taken that was SARS-CoV-2 positive of the healthcare workers index case;
  - Complete an enrolment questionnaire that includes demographic, previous history of SARS-CoV-2 infection, comorbidities including frailty scores, vaccination status for COVID-19, and possible recent exposure to the index healthcare workers case.
- **healthcare workers contact:** A similar approach should be undertaken for the recruitment of healthcare workers contacts as described above for patient contacts. The healthcare workers contacts who are invited to participate in the study should have the study aim and methodology explained to them and they should provide informed consent, although informed consent may be obtained at their enrolment into the VEBIS healthcare workers study. For those healthcare workers that are actively participating in the VEBIS healthcare workers study, the sample taken could be taken as part of the VEBIS healthcare workers study and the enrolment data can be downloaded from the VEBIS healthcare workers study. For those healthcare workers contacts not participating in the VBEIS healthcare workers study, after informed consent has been obtained, the healthcare workers should:
  - Provide a sample (saliva) or swab (nasal, OP or NP) for RT-PCR in the up to two days after the index date; and
  - Complete an enrolment questionnaire that includes for all participants demographic, previous history of SARS-CoV-2 infection, comorbidities, vaccination status for COVID-19 and other infections (e.g. influenza), and possible recent exposure to the confirmed index healthcare workers case.

Each study site to define selection procedure employed to establish contacts.

T5: Active follow-up of contacts

All identified contacts who have agreed to participate in the study should be approached for a further molecular testing for SARS-CoV-2 infection from between five and seven days) after T0 (date of confirmed infection in the index healthcare workers case, i.e. index date). The sample taken can include saliva sample or nasal, oropharyngeal or nasopharyngeal swabs.

Each study site to describe precisely all the study procedures.

Limitations

- **Ascertainment of infection bias:** Misclassification of the outcome can occur due to type of PCR platform used, timing of testing and specimen collected. In the analysis, sensitivity and specificity of the tests can be accounted for. As a minimum, laboratories testing samples should be appropriately ISO accredited and participate in a national Quality assurance Scheme for PCR testing. Nonetheless, sites will employ different tests and thus investigators should seek to use common international, national or research standards to address possible variation in test performance at sites. Currently the National Institute of Biological Standards and Control offers international standards for molecular and serological testing [12].
- **Transmission chains:** A further source of ascertainment bias is the assumption that contacts will have become infected only by the healthcare workers index case. Patient and healthcare workers contacts may have acquired SARS-CoV-2 infection from other healthcare workers, patients or visitors. This limitation is mitigated by the exclusion of transmission chains with co-primary cases or by using WGS to identify the same virus in the index and contact cases. Healthcare workers contacts may have acquired infections in the community or at home. However, information on these possible sources will be collected regularly if the healthcare workers participates in the VEBIS healthcare workers cohort study. Similar information is also collected from patients at T0 (enrolment) and at follow-up (T5). Patients may have acquired infections in the community prior to admission into the healthcare facility, this source of bias is mitigated by excluding those patients admitted less than four days prior to the date of confirmed SARS-CoV-2 infection in the index healthcare workers case in a sensitivity analysis.

- Selection bias:
  - **Previous infections:** The study population may have been highly exposed to SARS-CoV-2 infection and, with the current knowledge, it is difficult to determine the immunity conferred by natural infection. Individuals previously infected may be less likely to accept vaccination and may have some immunity. This will result in an underestimation of the vaccine effectiveness.
  - In the absence of serology, previous infection status of patients will need to be ascertained by self-reporting or documented evidence. Previous SARS-CoV-2 infection among healthcare workers participating in the VEBIS cohort will be assessed by self-report and by PCR and serological testing at enrolment and regularly during their participation in the cohort. Until recently, all vaccines deployed in the EU/EEA use a spike protein to induce immunity and so testing for anti-nucleocapsid (anti-N) antibodies may indicate previous infection either at enrolment or follow-up.
  - **Negative confounding:** Conversely, individuals who have a high-risk of developing severe disease (i.e. those with chronic conditions) may be more likely to be vaccinated and thus vaccine effectiveness will be underestimated unless estimates are adjusted.
- **Reporting bias:** Reporting of patient vaccination status may be dependent on self-reports. Other patient data (e.g. co-morbidities) can be extracted from medical records and should be of high quality. Vaccinated cases may be more likely or less likely to report symptoms and vaccine effectiveness against symptomatic SARS-CoV-2 may be overestimated or underestimated accordingly. It is anticipated that good quality vaccination data (both self-reported and registers) will be available for healthcare workers. Healthcare worker professional and non-professional activities will be self-reported and open to a social desirability bias (i.e. reporting high adherence to IPC measures). Professional activities may be assessed by also collecting ward/hospital level data.
- **High vaccine coverage:** Sites that have very high vaccine coverage in residents may find:
  - Reduced study power with insufficient number of outcomes in the study population who are unvaccinated. If vaccine coverage is very high this may require relative vaccine effectiveness to be estimated. This is likely to be the case amongst healthcare workers.
  - Selection bias as those study participants who remain unvaccinated may have very different exposures and/or precedents to those who have been vaccinated.
- **Sample size/power:** Inadequate sample sizes may limit the power of some stratified or secondary analyses. An assessment of vaccine effectiveness by severity of infection may be difficult to obtain if only a small number of severe cases is anticipated. Furthermore, if vaccine coverage is very high in the study population, the study may lack power (see above).
- **Study design:** The study design may be more accurately described as a case-ascertained cluster [7], the proposed design is stated as a prospective cohort. The study design is very closely linked in both design and setting to nosocomial outbreak investigations, although these are more often retrospective in design [8].
- **Unmeasured or residual confounding** between vaccinated and unvaccinated may be present like risky behaviours, beliefs affecting exposure and vaccine acceptancy.

Ethical considerations

Studies of COVID-19 vaccine effectiveness against SARS-CoV-2 transmission in healthcare facilities should be approved by the relevant local Ethics Review Committee.

All individuals (healthcare workers and patients) approached to participate in the study must give their informed consent. The informed consent form should include a description of the methods and frequency of collecting respiratory samples, clinical and epidemiological data for the intended purpose of this investigation. Informed consent should also mention that data will be shared with study coordinator and ECDC (if part of the VEBIS healthcare workers study) and that samples may be shipped outside of the country for additional testing (if applicable) and may be used for future research purposes (if applicable). All individuals (healthcare workers and patients) invited to join the study should be informed that participation is voluntary and that they can withdraw from the study, without providing any justification, at any time during the study without consequences. Investigators should take particular care to ensure that the anonymity of the healthcare workers index case is maintained and avoid accidental or deductive disclosure.

For those patients with limited capacity, investigators should ensure that national regulations for obtaining consent are followed. This may include an appropriate guardian (e.g. next of kin or friend) being contacted and provided with all necessary materials and opportunities to discuss the study before giving informed consent on behalf of the resident. If an appropriate guardian cannot be identified, the investigators can appoint a proxy (e.g. staff member or an external clinical or lay member) to act on behalf of the patient.

Each study site to provide a copy of the Ethic review committee approval and of the informed consent.

Data governance

Biological materials and related data should only be collected and stored in collaboration with local health authorities. The governance structure of such collection should have representation of the original setting. All governance systems should follow the principle of accountability and should 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 and agreed to by research participants.

Site-specific protocols, along with informed consent forms, should address governance issue surrounding biologic materials and data. Data governance statements should address how long data will be stored, when data will be destroyed, access to data during and after the study, and how participants can withdraw permission for use of their data.

All points relative 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

Prevention of SARS-CoV-2 infection in investigation personnel

Study staff should be trained in IPC procedures (standard contact, droplet, contact and airborne precautions, as determined by national or local guidelines). These procedures should include proper hand hygiene and the correct use of medical or respiratory face masks, if necessary. Investigators should review ECDC guidance for IPC in healthcare settings [13]. Furthermore, investigators can complete WHO's online training course 'Infection Prevention and Control (IPC) for Novel Coronavirus (COVID-19)' https://openwho.org/courses/COVID-19-IPC-EN

Risks and benefits for subjects

This study poses minimal risk to participants. Respiratory specimens should be collected from patients in response to contact with a confirmed case of SARS-CoV-2 infection. In many healthcare facilities this would be part of normal health care and standard IPC procedures. Healthcare workers will provide both respiratory and serological samples regularly as part of the VEBIS healthcare workers cohort study. Investigators should take particular care to ensure that the anonymity of the healthcare workers index case is maintained and avoid accidental or deductive disclosure.

Results of PCR tests should be shared with participants as soon as they are available. The direct benefit to the participant will be the potential timely detection of SARS-CoV2 infection, 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 COVID-19 vaccines and guide vaccination and IPC policies.

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Annex 1: Questionnaires

Example of variables, definitions and coding of study data

List of questionnaires:

1. Pre-enrolment questionnaire (to be completed by study team)
2. Questionnaire T0 (to be completed by contact or, for patient, by staff or study team)
    a. Identifier and contact details
    b. Admission date (patient only)
    c. Socio-demographic information
    d. Individual behaviours
    e. Clinical history: Chronic health conditions
    f. Clinical history: General health (patients only)
    g. Vaccination history: COVID-19 vaccine
    h. Vaccination history: Other vaccines
    i. Previous history of COVID-19
3. Laboratory questionnaire (to be completed by study team)
4. Follow up (T5) questionnaire (to be completed by contact or, for patient, by staff or study team)
    a. Administration
    b. Vaccination history
    c. Confirmed/possible SARS-CoV-2 infection
    d. Contact with confirmed SARS-CoV-2 infection

Note: personal information should be kept confidential according to local data security

Part 1. Pre-enrolment questionnaire (to be completed by study monitor)			
Form completion date	dd/mm/yyyy		Date Date should be that when participant was approached.
Country			Text
Name/code of long-term health care facility			Text
Participant unique ID			Alphanumeric. Generated by study tool.
Does the participant report any contraindication for the COVID-19 vaccine?	o Yes o No o Unknown		Categorical If yes, contact can participate in study
Informed consent given by contact	Patient o Yes, by participant o Yes, by guardian o No, by participant o No, by guardian	healthcare workers o Yes o No	Categorical Contact (or appropriate guardian for patients) must give consent to participate in the study.
Nature of relationship of guardian Only to be asked of patients			Text
If invitee does not agree to participate:			
What are your reason(s) for not participating?			Text
What sex are you?	o Male o Female		Categorical
How old (in years) are you?			Integer Allowable range 18-110

Part 1. Pre-enrolment questionnaire (to be completed by study monitor)		
What is your occupation in the healthcare facility? Only to be asked of healthcare workers	[0] Medical doctor (MD) [1] Registered nurse/midwife or equivalent [2] Nursing assistant/nurse technician [3] Radiology/x-ray [4] Phlebotomist [5] Physical therapist [6] Nutritionist/dietician [7] Laboratory personnel [8] Admission/reception [9] Patient transporter [10] Catering staff [11] Cleaner [12] Administration [13] Paramedic [14] Student/trainee [88] Other	Categorical
Part 2. Enrolment (T0) questionnaire		
2.a. Identifier and contact details		
1. First name		Text
2. Surname		Text
3. Type of contact	o Patient o healthcare workers	Categorical
4. Participant ID of contact		Alphanumeric
5. Participant ID of healthcare workers index case		Alphanumeric
2.b. Admission date (Patients only)		
6. Ward identifier		Alphanumeric
7. What was the admission date of the patient to the healthcare facility?	dd/mm/yyyy	Date Enter the first date of admission to the healthcare facility regardless of which ward.
8. What was the admission date of the patient to the ward?	dd/mm/yyyy	Date Enter the first date of admission to the ward which index healthcare workers case worked.
2.c. Contact and socio-demographic information		
9. What sex are you?	o Male o Female o Other o Unknown	Categorical
10. How old are you? (years)		Integer (continuous)
2.d. Individual behaviours		
11. What is your height?		Numeric with limits
12. What is your weight?		Numeric with limits
13. Do you smoke or have you ever smoked (any smoking: cigarettes, cigars, vaping)?	o I've never smoked o I stopped smoking more than one year ago o I stopped smoking within the last year o Yes, I currently smoke o I don't know	Categorical
2.e. Clinical history: Chronic health conditions		
14. Do you have a chronic health condition?	o Yes o No o Unknown	Categorical If responds: No or Unknown, go to next section
If yes, please specify:		
a) Diabetes	o Yes o No o Unknown	Categorical

Part 1. Pre-enrolment questionnaire (to be completed by study monitor)		
b) Cardiovascular disease (excluding hypertension)	o Yes o No o Unknown	Categorical
c) Hypertension	o Yes o No o Unknown	Categorical
d) Immunodeficiency/organ transplant	o Yes o No o Unknown	Categorical
e) Lung disease	o Yes o No o Unknown	Categorical
f) Asthma	o Yes o No o Unknown	Categorical
g) Cancer	o Yes o No o Unknown	Categorical
h) If height and weight are not collected: BMI		Numeric
i) Renal disease	o Yes o No o Unknown	Categorical
j) Liver disease	o Yes o No o Unknown	Categorical
k) Rheumatological disease	o Yes o No o Unknown	Categorical
l) How many times have you been hospitalised for the chronic condition(s) in the last 6 months		Numeric Hospitalisation if the resident has been admitted to hospital for 1 or more nights. Combine hospitalisations for all chronic conditions.
2.f. Clinical history: General health (patients only)		
15. Do you (or does the patient) need help with daily living (e.g. eating or bathing)?	o Yes o No o Unknown	Categorical
16. Have you (or the patient) been assessed for any type of clinical frailty score?	o Yes o No o Unknown	Categorical If responds: • Yes, go to Qu 17 • No or Unknown, go to next section
If yes:		
17. Which scale has been used to assess your (or the patient's) frailty?	o Barthel Index o Clinical Frailty Score o ADL Score o Other scale or index o Unknown	Categorical • No or Unknown, go to next section
a. If Barthel Index, please specify the score		Numeric • Maximum 100
b. If Clinical Frailty Score, please specify the score		Numeric • Maximum 9
c. If ADL Score, please specify the score		Numeric • Maximum 16
d. If other scale:		
i. Please specify the scale		Text
ii. Please specify the score		Numeric
iii. Please specify the maximum score for the scale		Numeric

2.g. Vaccination history: COVID vaccine		
18. Have you been offered the COVID-19 vaccine?	o Yes o No o Unknown	Categorical If responds: • No or Unknown, go to next section
19. Have you received the first dose of any COVID-19 vaccine?	o Yes o No o Unknown	Categorical If responds: • Yes, go to question 20 • No, go to question 21 and then next section • Unknown, go to next section
20. If yes, for each dose, specify:		
a) Which dose did you receive	o 1st dose o 2nd dose o 3rd dose o 4th dose	Categorical
b) What date you received that dose?	dd/mm/yyyy	Date
c) Which vaccine did you receive for that dose?	o Astra Zeneca (Vaxzevria) o Janssen (Johnson&Johnson) o Moderna o Pfizer/Biotech (Comirnaty) o Other, please specify _____ o Don't know	Categorical Product names to be updated
d) What was the batch number of the vaccine received?		Text Batch number to be taken from documents or state Unknown
21. If No, what were your reason(s)? (Please tick all that apply)	o I haven't had time o I don't believe in vaccination o I am concerned by possible side-effects o Declined by resident's guardian o Other, please specify _____	Categorical
2.h. Vaccination history: Other vaccines		
22. Have you received an influenza vaccine in the current (as of October 2022) influenza season?	o Yes o No o Unknown	Categorical If responds: • No or Unknown, go to next section
23. If yes, when did you receive the influenza vaccine?	dd/mm/yyyy	Date
2.i. Previous history of COVID-19		
24. Have you (or the patient) had a SARS-CoV-2 test in the previous 14 days?	o Yes o No o Unknown	Include only for healthcare workers contacts in VEBIS study or for sites where regular screening of patients and/or healthcare workers performed
If yes:		
a. What date was the test taken	dd/mm/yyyy	Date
b. What was the result?	o Negative (PCR) o Negative (RDT) o Positive (PCR) o Positive (RDT) o Unknown	If answers positive, go to question 33.
25. Since the beginning of the pandemic, have you ever been diagnosed (or self-diagnosed) as having COVID-19?	o Yes o No o Unknown	Categorical If responds: • No or Unknown, go to next section
26. Please specify the date of onset of the last episode COVID-19	dd/mm/yyyy	Date
27. Which, if any, test was used for confirmation of the COVID-19 at that last episode?	o No test was done o Rapid Antigen Test o PCR o Serology o I don't remember what kind of test was done	Categorical

28. Please specify the date of test:	dd/mm/yyyy	Date
29. At the last episode, did you have any COVID-like symptoms?	o Yes o No o Unknown	Categorical If responds: • No or Unknown, go to question 28
a) Fever (≥ 38 °C) or history of fever	o Yes o No o Unknown	Categorical
b) If yes to fever, please specify maximum temperature		Numeric
c) Cough	o Yes o No o Unknown	Categorical
d) General weakness/fatigue	o Yes o No o Unknown	Categorical
e) Dyspnoea/Shortness of breath	o Yes o No o Unknown	Categorical
f) Loss of smell (anosmia)	o Yes o No o Unknown	Categorical
g) Loss of taste (ageusia)	o Yes o No o Unknown	Categorical
h) Other (please specify)		Text
i) On what date did the first symptom start?	dd/mm/yyyy	Date
2.j. Contact with a confirmed SARS-CoV-2 case in the previous 14 days		
30. In the last 14 days, have you been in contact with a confirmed case of SARS-CoV-2?	o Yes o No o Unknown	Categorical If responds: • No or Unknown, go to question 42
If yes:		
a. How many confirmed cases have you been in contact with?		Number
b. What date was the last contact	dd/mm/yyyy	Date
c. Were the person(s) with confirmed SARS-CoV-2 (please tick all that apply):	o Another patient o Staff member o Household member o External visitor o Other, please specify ___	Categorical
d. Were you in close contact (<2 metres for >15 minutes) with any of the persons with confirmed SARS-CoV-2?	o Yes o No o Unknown	Categorical If responds: No or Unknown, go to next section
31. In the last 5 days, have you made any external (i.e. not patients or healthcare workers) visitors?	o Yes o No o Unknown	Categorical • Only to be asked of patients
a. How many visitors have you had?		Number
Part 3. Laboratory questionnaire		
Laboratory identification number		Alphanumeric
Participant ID number		Alphanumeric
Timing of virology test	o Enrolment (T0) o Follow-up (T5) o Unknown	Categorical
Date sample collected	dd/mm/yyyy	Date
Date sample received	dd/mm/yyyy	Date
Type of sample (virology)	o Nasal swab o Throat swab o Nasopharyngeal swab o Saliva o Oropharyngeal o Other	Categorical
Virology test brand		Text
Virology test result	o Positive o Negative o Inconclusive/Equivocal o Unknown	Categorical

CT value		Numeric
Date virology result	dd/mm/yyyy	Date
Was sequencing performed?	o Yes o No o Unknown	Categorical
If yes: Result of sequencing Please use the Pango dynamic nomenclature for lineages	Variant	Text
Methodology to sequence	o RT-PCR o Next-generation sequencing o Unknown	Categorical
Specimens shipped to other laboratory for confirmation/sequencing?	o Yes o No o Unknown	Categorical
If yes, specify date of shipment	dd/mm/yyyy	Date
Name of laboratory		Text
Part 4. Follow-up (T5) questionnaire		
4.a. Administration		
1. Participant ID number		Alphanumeric
2. Date of completion	dd/mm/yyyy	Date Date is that which questionnaire administered
4.b. Vaccination: COVID vaccine		
3. In the last 5 days (i.e. since T0) have you received any vaccinations?	o Yes o No o Unknown	Categorical If responds: • No or Unknown, go to next section
If yes:		
a. Which vaccination did you receive? (please tick all that apply)	o COVID-19 o Influenza o Other (please specify) o Unknown	Categorical
4.c. Possible COVID-19 infection		
4. In the last 5 days (i.e. T0) have you had any test for confirmation of COVID-19?	o No test was done o Yes, Rapid Antigen Test o Yes, PCR o Yes, unknown test	Categorical This does not include tests undertaken as part of the study
a. If yes, what was the test result?	o Positive o Negative o Inconclusive/Equivocal o Unknown	Categorical
5. In the last 5 days (i.e. T0), have you developed any COVID-like symptoms?	o Yes o No o Unknown	Categorical If responds: • No or Unknown, go to next section
a. Fever (≥ 38 °C) or history of fever	o Yes o No o Unknown	Categorical
b. If yes to fever, please specify maximum temperature		Numeric
c. Cough	o Yes o No o Unknown	Categorical
d. General weakness/fatigue	o Yes o No o Unknown	Categorical
e. Dyspnoea/Shortness of breath	o Yes o No o Unknown	Categorical
f. Loss of smell (anosmia)	o Yes o No o Unknown	Categorical

g. Loss/distortion of taste (ageusia/dysgeusia)	o Yes o No o Unknown	Categorical
h. Other (please specify)		Text
i. On what date did the first symptom start?	dd/mm/yyyy	Date
j. Radiological evidence of lesions compatible to COVID-19 (e.g. by chest X-ray or computed tomography scan)?	o Yes o No o Unknown	Categorical
k. Did you seek or receive any medical attention for that episode?	o Yes o No o Unknown	Categorical If responds: • Yes, clinical monitor to complete hospitalisation questionnaire
4.e Contact with confirmed SARS-CoV-2 infection		
6. In the past 5 days (i.e. since T0), have you been in contact with a person with confirmed SARS-CoV-2 infection?	o Yes o No o Unknown	Categorical If responds: • No or Unknown, go to next section
a. How many persons with confirmed SARS-CoV-2 infection have you been in contact with in the last 5 days?		Numeric
b. What was the date of your last contact with a possible/confirmed case?	dd/mm/yyyy	Date
c. Were the person(s) with confirmed SARS-CoV-2 infection (please tick all that apply):	o Another resident o Staff member o Household member o External visitor o Other, please specify _____	Categorical
d. Were you in close contact (<2 metres for >15 minutes) with any of the persons confirmed SARS-CoV-2 infection?	o Yes o No o Unknown	Categorical If responds: No or Unknown, go to next section
7. In the last 5 days (i.e. since T0), have you had any external (i.e. not patients or healthcare workers) visitors?	o Yes o No o Unknown	Categorical If responds: • No or unknown, go to question 72
a. How many visitors have you had?		Number

Annex 2. Templates for the informed consent form

Informed consent

COMMENT: This template is given as an example for country adaptation, if relevant and aligned with national ethical requirements.

Notes to implementers:

- Please note that this is a template developed to assist the investigators in the design of their informed consent forms (ICFs). It is important that investigators adapt their own ICFs to the requirements of their particular investigation and those of their national and institutional regulations. **The logo of the institution must be used on the ICF.**
- The informed consent form consists of two parts: the information sheet and the consent certificate.
- Do not be concerned by the length of this template. It is long only because it contains guidance and explanations that are for you and that you will not include in the informed consent forms that you develop and provide to participants in your investigation.
- This template includes examples of key questions that may be asked at the end of each section, which could ensure understanding of the information being provided, especially if the investigation is complex. These are just examples and suggestions, and the investigators will have to modify the questions depending upon their study.
- In this template:
  - square brackets indicate where specific information is to be inserted;
  - bold lettering indicates sections or wording that should be included; and
  - standard lettering is used for explanations to researchers only and must not be included in your consent forms.

TEMPLATE ON FOLLOWING PAGE

[YOUR INSTITUTIONAL LETTER HEAD]

Template for Informed Consent Form

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

[Name of Principle Investigator]

[Name of Organization]

[Name of Sponsor]

[Name of Project and Version]

This Informed Consent Form has two parts:

Information Sheet (to share information about the study with you)

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 take time to 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 and respiratory swabs and questionnaires. This will be expanded upon in the procedures section.

Selection of Participants

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

Voluntary Participation

Indicate clearly that they can choose to participate or not 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 over 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 during the study, if relevant.

Risks and Discomforts

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

Benefits

Describe any benefits to the participant in the future, such as receiving timely information about potential SARS-CoV-2 infections, as a result of the research.

Reimbursements

State clearly what reimbursements you will provide the participants with as a result of their participation. We do not encourage incentives beyond reimbursements for expenses incurred as a result of participation in the investigation. The expenses may include, for example, travel expenses 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, especially with respect to the information about the participant. Outline any limits there are to confidentiality.

Sharing of Research Findings

Include a statement indicating that the individual findings will be shared with the participant and the overall findings of the investigation will be shared in a timely fashion with the hospital. In the latter, all confidential information will remain confidential. If you have a plan and timeline for the sharing of information, include the details. Also 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 and blood samples for possible future use in either 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 gave you permission only 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, participants need to inform the investigation team as soon as possible. Any of the previously collected remaining samples and data will be discarded except if 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. If the participant is illiterate but gives oral consent a witness must sign. A researcher or the person going over the informed consent must sign each consent. Because 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 this study. I have had the opportunity to consider the information, ask questions and have had these 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, from regulatory authorities and [site relevant], where it 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.

Print Name of Participant _____

Signature of Participant _____

Date (day/month/year) _____

Or if signed by legal guardian

Print Name of Guardian _____

Signature of Guardian _____

Specify nature of guardianship _____

Date (day/month/year) _____

Statement by the researcher/person taking consent

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

A copy of this Informed Consent Form has been provided to the participant/guardian:
_____

Print Name of Researcher/person taking the consent _____

Signature of Researcher/person taking the consent _____

Date (day/month/year) _____

PDF TQ-08-23-075-EN-N

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