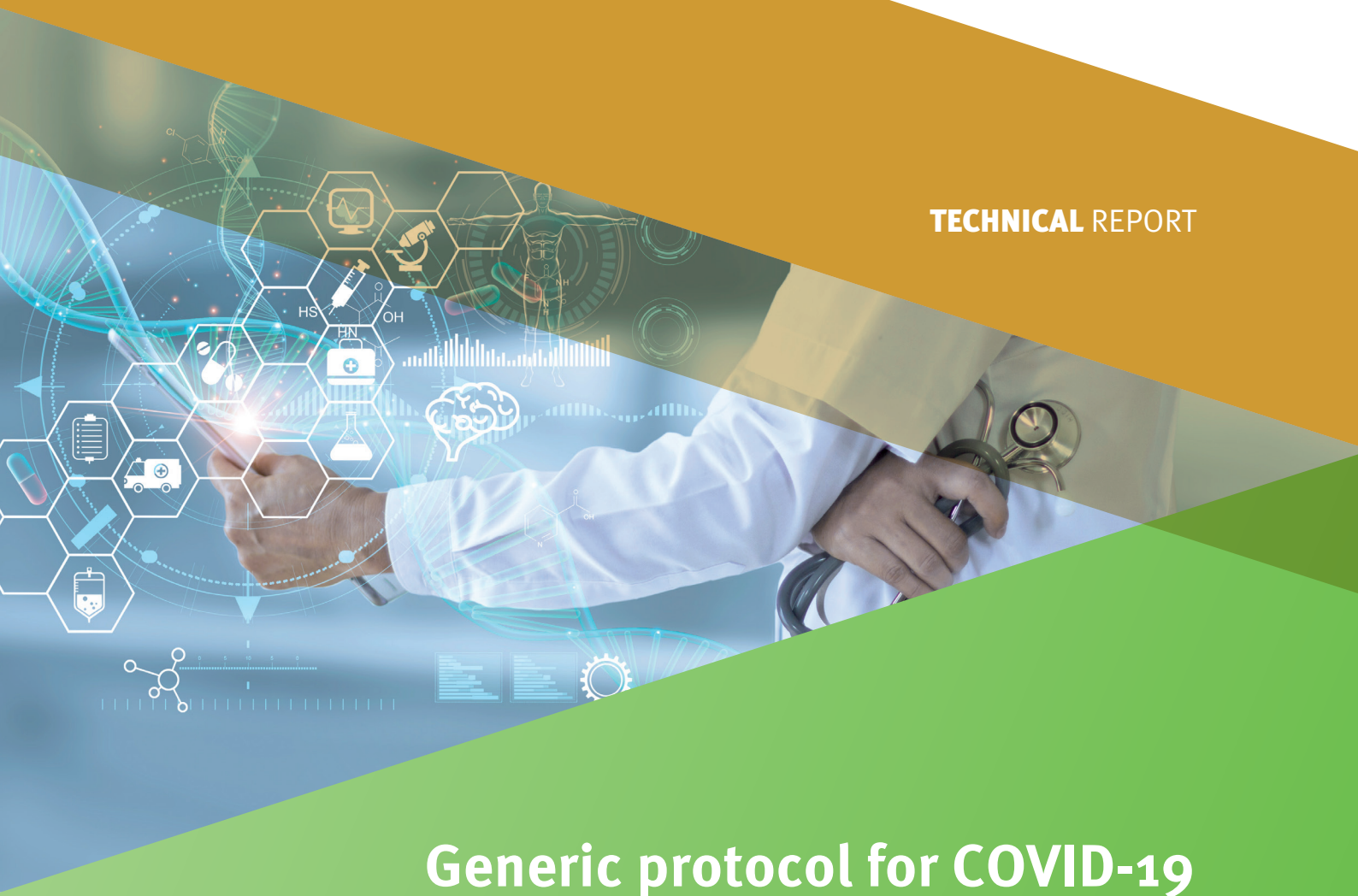
ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL



TECHNICAL REPORT

Generic protocol for COVID-19 vaccine effectiveness studies during outbreaks in semi-closed settings in the EU/EEA

Version 1.0

www.ecdc.europa.eu

ECDC TECHNICAL REPORT

Generic protocol for COVID-19 vaccine effectiveness studies during outbreaks in semi-closed settings in the EU/EEA

Version 1.0

This generic protocol was commissioned by the European Centre for Disease Prevention and Control (ECDC), as part of the activities referring to Direct Contract N. ECD.11486 'Developing an infrastructure and performing vaccine effectiveness studies for COVID-19 vaccines in the EU/EEA', coordinated by Sabrina Bacci and Christiana Carstairs.

Authors (alphabetical order)

Sandra Cohuet, Anthony Nardone, Marta Valenciano (Epiconcept, Paris, France)

Acknowledgements

The following ECDC staff provided substantial input during the production/revision of the document (alphabetical order): Sabrina Bacci, Agoritsa Baka, Orlando Cenciarelli, Marlena Kaczmarek, Nathalie Nicolay, Diamantis Plachouras, and Ettore Severi.

This core protocol is based on ECDC's Protocol for cluster investigations to measure influenza vaccine effectiveness in the EU/EEA, published in December 2009.

The current version 1.0 of this core protocol corresponds to version 1.2 used to implement the Direct Contract ECD.11486.

This protocol is intended as a template for outbreak investigations. If a study group/outbreak investigation team decides to follow this protocol, the wording and format of this document can be reproduced, with study-specific information added in relevant sections as indicated.

For questions or request of support in implementing the protocol, please email support@ecdc.europa.eu or vpd.vpd@ecdc.europa.eu

Suggested citation: European Centre for Disease Prevention and Control. Generic protocol for COVID-19 vaccine effectiveness studies during outbreaks in semi-closed settings in the EU/EEA – Version 1.0. Stockholm: ECDC; 2021.

Stockholm, December 2021

PDF
ISBN 978-92-9498-562-0
doi: 10.2900/099023
Catalogue number TQ-06-21-216-EN-N

Contents

Tables

Abbreviations

COVID-19	Coronavirus Disease 2019
EC	European Commission
EU	European Union
EEA	European Economic Area
GDPR	General Data Protection Regulations
NPIs	Non-pharmaceutical interventions
OR	Odds ratio
RT-PCR	Reverse transcriptase polymerase chain reaction
RR	Relative risk
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
WHO	World Health Organization

Executive summary

Late 2019 saw the emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19). As of 7 December 2021, over 46 million cases and more than 845 000 deaths have been reported in the European Union/European Economic Area (EU/EEA) [1].

During 2021, first the Alpha variant of concern (VOC) and then the Delta VOC have dominated virus circulation in the EU/EEA. In late 2021, the Omicron VOC was introduced into the EU/EEA and, although substantial uncertainty remains at the time of writing, it looks like it could become the dominant circulating variant in coming months.

As of week 48 2021, four vaccines (Comirnaty, Spikevax [previously COVID-19 vaccine Moderna], Vaxzevria, and Janssen) have been authorised by the European Commission (EC) based on the scientific opinion of the European Medicines Agency (EMA) for use in the EU, and several others are under rolling review [2].

Post-marketing authorisation monitoring of vaccine effectiveness is an essential tool to document how COVID-19 vaccines perform in real life. These studies are key to generating adequate evidence to support the continuous assessment of the benefits and risks of the vaccines and inform decision-making on their use in national or regional vaccination strategies for different populations.

While it is extremely important to monitor the vaccine effectiveness of COVID-19 vaccines using prospective study design, where adjustments with respect on most confounders can be made, it is also possible to assess vaccine effectiveness in outbreak settings [3]. Results from such studies may be rapidly collected and provide preliminary or additional evidence to other estimates. An advantage of outbreak investigations is that in some settings (e.g. schools) vaccination records might be easily obtainable. Investigation can take place at the same time as control measures are being carried out.

The collection of evidence available with rapid studies can be of particular interest in the context of new questions related to vaccine effectiveness, such as those associated with emerging VOCs.

This generic protocol is intended to be adapted to local/national contexts to guide the implementation of vaccine effectiveness studies against SARS-CoV-2 infection in the occurrence of an outbreak in semi-closed-settings. Semi-closed settings are defined as any setting in which the population can be easily identified from enrolment/employment registers (e.g. schools and other educational institutions, workplaces, etc.).

Two study designs and their respective methodologies are proposed: cohort and case control study. The format of the document allows the deletion of entire sections according to the study design and setting chosen, with the idea being to provide a ready-to-use tool in order to support the production of an outbreak investigation protocol at a local setting. The primary study objectives that are proposed are the estimation of vaccine effectiveness against SARS-CoV-2 infection for the cohort study and estimation against symptomatic SARS-CoV-2 for the case control study. Additional secondary objectives are proposed, which, according to the circumstances, can be included as a primary objective.

Background

Since the emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), etiological factor of coronavirus disease 2019 (COVID-19), and as of 7 December 2021, the COVID-19 pandemic has resulted in more than 46 million cases and more than 845 000 deaths in the EU/EEA [1].

During 2021, first the Alpha VOC and then the Delta VOC have dominated virus circulation in the EU/EEA. As of December 2021, cases of the Omicron VOC were being reported in the EU/EEA and, although substantial uncertainty remains, at the time of writing it looks like it could become the dominant circulating variant in coming months. Current evidence on transmissibility, severity, and immune escape is highly uncertain for the Omicron VOC, but the presence of multiple mutations in the spike protein raises serious concerns that it may be associated with significant reduction in vaccine effectiveness and increased risk for reinfections [4].

While control and mitigation strategies such as non-pharmaceutical interventions (NPIs) (physical distancing, appropriate use of face masks, testing, contact tracing, and isolation procedures) are important tools to limit SARS-CoV-2 circulation, having a critical level of immunised people in a population is the most important method of minimising transmission. Having effective and safe vaccines against SARS-CoV-2 helps reach this goal while reducing morbidity and mortality among the population. International collaborative efforts have accelerated the development of COVID-19 vaccines. As of week 48 2021, four vaccines (Comirnaty, Spikevax [previously COVID-19 vaccine Moderna], Vaxzevria, and Janssen) have been authorised by the European Commission (EC) based on the scientific opinion of the European Medicines Agency (EMA) for use in the EU, and several others are under rolling review [2].

Evaluating the performance of COVID-19 vaccines post-licensure is critical, as several factors can impact real-world vaccine effectiveness, including transportation and storage conditions, vaccine administration, advanced age, presence of underlying medical conditions, and previous SARS-CoV-2 infection. In addition, post-licensure evaluation of COVID-19 vaccines allows public health authorities to estimate a) the duration of protection of vaccines and thus the need (and frequency) for re-vaccination; b) the level of protection against severe disease and death; c) the relative effectiveness of different vaccine types and of single doses; and d) vaccine effectiveness against new emerging virus variants.

In 2020, the European Commission emphasised the importance of continuously monitoring the safety and effectiveness of vaccines in the EU/EEA and called on ECDC and EMA to develop a structured post-authorisation monitoring platform for vaccines, prioritising COVID-19 vaccines. Therefore, at the end of 2020, utilising the lessons learned from other vaccine effectiveness studies, ECDC started building infrastructure to perform COVID-19 vaccine effectiveness studies. The infrastructure aims to build a system to regularly monitor vaccine effectiveness and perform studies in different settings, and depending on the setting, to provide information on different outcomes (severe disease, moderate disease, infection, transmission, etc) [5-7].

While it is extremely important to monitor the vaccine effectiveness of COVID-19 vaccines using prospective study design where results can be adjusted with respect to most confounders, it is also possible to assess vaccine effectiveness in outbreak settings [3]. Results from such studies may be rapidly collected and provide preliminary or additional evidence. An advantage of outbreak investigations is that in some settings (e.g. schools) vaccination records might be easily obtainable. Investigations can take place at the same time that control measures are being carried out.

The collection of evidence available with rapid studies can be of particular interest in the context of emerging variants of concern (VOCs) and questions related to vaccine effectiveness.

1 Scope of the document

Many critical questions remain about the effectiveness of COVID-19 vaccines in real-world settings. These questions can only be answered in post-marketing vaccine effectiveness studies. Vaccine effectiveness studies implemented as part of outbreak investigations may provide timely insights, contribute to hypothesis generating and provide and complement the evidence gathered through longitudinal studies.

This generic protocol is intended to be adapted to national/local contexts to guide the implementation of vaccine effectiveness studies against SARS-CoV-2 infection in the occurrence of an outbreak in a semi-closed setting. Semi-closed settings are defined as any setting where the population can be easily identified from enrolment/employment registers (e.g. schools and other educational institutions, workplaces, etc.).

Two study designs and their respective methodologies are proposed: cohort and case-control study design, where the study population at risk of infection is exposed or not exposed to COVID-19 vaccination in a semi-closed setting.

The format of the document allows the deletion of entire sections according to the study design and setting chosen, with the idea being to provide a ready-to-use tool in order to support the production of an outbreak investigation protocol adapted to the local/national setting. For a timely implementation of the study, the submission for approval by the national Ethical Review Committee of standard/generic study protocol before the occurrence of any COVID-19 outbreak in a semi-closed setting could be considered.

Ideally, the protocol should be implemented as part of the public health assessment and response to a COVID-19 outbreak.

Outbreak investigation steps conducted as part of the public health assessment and response are not described in this document, and neither are risk factors for SARS-CoV-2 infection during an outbreak in semi-closed settings measured in this study protocol.

ECDC encourages the use of this protocol as a basis for studies aiming at assessing vaccine effectiveness in semi-closed settings following the identification of a COVID-19 outbreak, as its use in the EU/EEA can facilitate results comparability from different outbreak investigations.

Below each paragraph, arrow marks with italicised text indicate the points that outbreak investigation teams could further expand/detail when creating an outbreak-specific adapted protocol for local/national use using this generic ECDC protocol.

2 Outline of a template for a generic protocol for vaccine effectiveness studies during an outbreak

The local/national protocol for vaccine effectiveness studies in the context of an outbreak should have different sections, including:

- background;
- aim and objectives of the study;
- study population, including inclusion criteria and definitions;
- study design;
- proposed data collection; and
- plan of statistical analysis.

Where the study population within an outbreak is well-defined and not too large, a retrospective cohort study could be the study design of choice; otherwise, a case-control (traditional, case-cohort or density case-control) study design could be considered.

The following sections of this generic protocol contain paragraphs that can be adapted for the respective two main study designs.

As the outbreak investigation team will adapt this generic protocol for the study, the structure of the document and paragraphs here below allow the deletion of sections that are not applicable and create a template for the local/national protocol to be developed.

The section on study population, inclusion criteria, and definitions is presented only once and before the respective sections related to the two study designs, and is referenced only briefly under the sections related to the two study designs.

3 Outline for a template to describe the study setting in a generic protocol

3.1 Semi-closed setting definition

For the purposes of this generic protocol, a semi-closed setting is defined as any environment where the local population can be easily distinguished from the general community, and where individuals spend a significant amount of time together in the same setting. Semi-closed settings allow a certain mobility of their members out and/or into the setting.

Examples of semi-closed settings may include (and are not limited to) schools/educational facilities, workplaces, locations in which individuals spend a significant period of time together (such as student dorms, open refugee/internally displaced camps, certain rural/urban communities, multi-day sports tournaments, school holiday 'camp' programs) [8].

Individuals within the semi-closed setting population may interact with the community, but their extended network of contacts (i.e. their family, friends, community contacts) should not be considered as part of this protocol.

In practice, the technical definition may vary due to social, political, and cultural practices.

3.2 Definition of a COVID-19 outbreak

An outbreak is defined as two or more cases of COVID-19 linked by time, place, or person. Within the population in the semi-closed settings, there may be a lower threshold of even only one symptomatic case signalling the likelihood of an outbreak.

Conducting a concurrent vaccine effectiveness study during the assessment (including any other epidemiological investigations e.g. into risk factors) and management of a COVID-19 outbreak requires substantial effort and resources. Studying the vaccine effectiveness of a new vaccine or vaccine schedule, or the vaccine effectiveness against an emerging SARS-CoV-2 VOC are situations in which such a study could be prioritised.

3.3 Definition of the study population

The study population is defined as the population at risk of SARS-CoV-2 infection within the semi-closed setting in which the outbreak occurs and who are eligible for COVID-19 vaccination. These may include depending on the setting:

- occupational setting: full-time workers, part-time workers;
- schools: students, staff;
- residential settings: staff, residents;
- open refugee/internally displaced camps: staff, residents.

3.4 Criteria for selecting outbreaks to be used for conducting COVID-19 vaccine effectiveness studies in semi-closed settings

For outbreaks occurring within a semi-closed setting the following criteria could be considered for performing a vaccine effectiveness study:

- absence of symptomatic COVID-19 cases during the last 14 days;
- adequate population size;
- high overall attack rate;
- availability of capacities for laboratory confirmation and, possibly, sequencing of samples;
- good vaccination records available to differentiate non-vaccinated from vaccinated;
- the outbreak has to be identified early enough to obtain samples within a short delay between symptom onset and swabbing (to reduce misclassification of outcome).

3.5 Preliminary steps for the vaccine effectiveness measurement in semi-closed settings

The current protocol and the data collection tools should be adapted to the setting and national/local conditions. Various activities are undertaken as part of every investigation. The order in which they are conducted will depend on the semi-closed setting, the local circumstances, and often multiple activities undertaken in parallel.

For all study designs, preliminary steps for the outbreak investigation in semi-closed settings aim to:

- Confirm the COVID-19 outbreak in the population of the semi-closed setting.
- Describe the semi-closed setting:
    - type of setting, activities performed at the setting;
    - number of individuals and roles (including pattern of contacts between individuals).
- Describe policies in place: COVID-19 contingency and plans, vaccination strategies, vaccination coverage, presence of a staff member responsible for COVID-19 infection prevention and control (IPC).
- Determine potential **risk factors** for increased transmission and potential **protective factors**: distance between individuals, physical barriers to separate individuals, policies and procedures for areas in which the individuals might congregate (e.g. break/dining areas, locker rooms, smoking areas, entrance/exits, parking lots), use of face masks, quality of ventilation of setting, accessibility to hand hygiene options (handwashing and/or hand sanitizer), procedures for cleaning and disinfecting surfaces in all areas, communication and training on COVID-19 to prevent infection including use of appropriate personal protective equipment if relevant, COVID-19 communication and information material: leaflets, posters, information sessions.
- Define **cases**: individuals testing positive for current SARS-CoV-2 infection. For information on case definitions and laboratory methods, see the respective study design chapters.
  In particular, see section on outcomes (see section 4.5) for a broader description of the characteristic of individuals testing positive using a cohort study design, and section 5.7 for a broader description of cases using the case control study design.
  In a well-defined outbreak within a setting with a population that is not too large, the entire population can be included in the vaccine effectiveness study, and swabs should be taken as soon as possible, and multiple times, for the entire population in the semi-closed setting.
  Active **case finding**: if appropriate and depending on the study design, individuals with fever and/or respiratory symptoms should be identified retrospectively (in the two weeks prior the symptom onset of the first outbreak case) and prospectively, and tested for SARS-CoV-2 infection. Active case finding might reveal symptomatic cases who were initially missed, increase the number of enrolled cases and, consequently, increase the power of the study analysis.
- Define **contacts**:
    - Close contact: any individual who was in the same semi-closed environment as, OR had direct physical contact with a confirmed case *in the same semi-closed setting* during their symptomatic period, as well as up to two days before disease symptom onset and the 14 days after the symptom onset in the primary/co-primary case; or a confirmed asymptomatic COVID-19 case, with the period of exposure being two days before the case was sampled, to 14 days after the date on which the sample that led to confirmation was taken. Examples of close contacts include:
        - classmates or working colleagues who shared at least one classroom/ staff room with the primary case;
        - members of the same study working group;
        - colleagues who had at least one class with the primary case;
        - individuals who shared material with a primary case;
        - individuals who performed indoor activities in the same group, such as music classes or indoor sports;
        - individuals who used the same transportation; etc.
    - Casual contact: any person present *in the same semi-closed setting* (and not outside the semi-closed setting) during the exposure period (two days before to 14 days after symptom onset in the primary case) of the primary case and not qualifying as a close contact. Examples of casual contacts include:
        - casual encounter with the primary case;
        - outdoor activities, such as a recess, but which took place at a different time than the recess the primary case attended, etc.
- Establish line listings for cases and contacts (close and casual) with basic set of variables (demographics, type of contact, etc) for the total population if the outbreak is small.
- Describe cases in terms of time, place, and person.
- Choose the appropriate study design for the vaccine effectiveness study (see next section).

4 Template for a protocol for a cohort study (delete section if not applicable)

4.1 Background

- *Each outbreak investigation team/local or national protocol /local or national protocol to describe the epidemiological context and any other information relevant to the study*

4.2 Study objectives

4.2.1 Primary objective

To measure COVID-19 vaccine effectiveness against laboratory-confirmed SARS-CoV-2 infection in one or more outbreaks within semi-closed settings in EU/EEA countries.

4.2.2 Secondary objectives

Depending on sample size, to measure COVID-19 vaccine effectiveness:

- against symptomatic laboratory-confirmed SARS-CoV-2 infections;
- against severe laboratory-confirmed SARS-CoV-2 infections;
- against SARS-CoV-2 variants of interest (VOI)/concern (VOC);
- by vaccination status (e.g., partially or fully vaccinated);
- by vaccine product and by combination of different vaccine products;
- by time since vaccination and/or time between vaccine doses;
- by different age groups;
- by sex;
- by different high-risk comorbidities;
- by previous SARS-CoV-2 infection.

As vaccination coverage in some semi-closed settings could be high, investigators could consider as a secondary objective the estimation of a *comparative vaccine effectiveness* (vaccine effectiveness without an unvaccinated group as a comparison) by:

- vaccine schedules (e.g. schedules with different intervals);
- vaccine products;
- time since last vaccination (e.g. recent last dose (defined as within six months) versus vaccination more than six months ago) to assess the impact of waning immunity.

- *Each outbreak investigation team/local or national protocol /local or national protocol to specify the (additional) secondary objectives*

4.3 Study population and relative characteristics

- *Each outbreak investigation team/local or national protocol /local or national protocol to describe the study setting as per template (paragraph 4)*

4.3.1 Study population

The study population is defined as the population at risk of SARS-CoV-2 infection within the semi-closed setting in which the outbreak occurs and eligible for COVID-19 vaccination. These may include depending on the setting:

- occupational setting: full-time workers, part-time workers, service providers;
- educational setting: students, staff;
- residential settings: staff, residents;
- open migrant and refugee reception centres: staff and residents.

- *Each outbreak investigation team/ local or national protocol to describe the population at risk of SARS-CoV-2 infection, population eligible and not eligible for COVID-19 vaccination, and to exclude those not eligible for COVID-19 vaccination*

☑ **Note: in some countries it is possible that individuals previously infected are excluded as not eligible for COVID-19 vaccination at the time of the outbreak investigation.**

With the current uncertainty around the immunity conferred by past infections, it is recommended that sensitivity analyses are conducted including and excluding those individuals previously infected, e.g those with a history of an episode of COVID-19 or those IgG-positive.

4.3.2 Study participants

Depending on the population size of the semi-closed setting and the access public health authorities have to them, the whole study population can be included for the vaccine effectiveness study. If the population is very large, then a systematic or random sample of this population should be selected for the study.

- *Each outbreak investigation team/local or national protocol* to include a sample size calculation for the study.

Exclusion criteria: Study participants are excluded if they are not eligible for COVID-19 vaccination or if they refuse participation to the study. Reasons for exclusion should be clearly documented. Depending on national recommendation, it is possible that individuals with previous confirmed SARS-CoV-2 infection will result among those not eligible for COVID-19 vaccination at the time of the outbreak investigation.

4.3.3 Study period

The study period is the duration of the outbreak as defined by the study team. Data regarding vaccination status will be collected retrospectively.

The study should be conducted following the necessary research requirements such as approval by the relevant Ethical Review Committee at the institutional or national levels.

- *Each outbreak investigation team/local or national protocol to define the study period*

Under certain circumstances the study period could be restricted to part of the duration of the outbreak if the COVID-19 vaccination status changes substantially during this time period.

4.4 Exposure (vaccination)

4.4.1 Definition of vaccination status

Full and partial vaccination status should be defined according to the instructions of the manufacturer for each COVID-19 vaccine product. Specific delay other than 14 days may be applied or tested in the vaccine effectiveness analysis.

It is also important to take into account specific recommendation in place in the country and the eligibility criteria of a specific individual to get a dose of the vaccine.

The definition of full/partial vaccination might be evolving over time and in different context, is it therefore of pivotal importance to allow to collection of number of doses, product/s and date of administration for each dose.

- **Fully vaccinated status**
  - **with a two-dose**
  - **or two-dose plus one additional dose vaccine**
  - if the last dose was received at least 14 days before symptom onset (date of positive laboratory confirmation).

- **Fully vaccinated**
  - **with a** single-dose vaccine
  - **or a one-dose vaccine plus one additional dose**
  - if the last dose was received at least 14 days before symptom onset (date of positive laboratory confirmation).

- **Partially vaccinated**
  - incomplete series of vaccinations according to the above
  - if the last dose was most likely received <14 days before symptom onset (date of positive laboratory confirmation).

- **Unvaccinated** individual who had not received any dose of COVID-19 vaccine or who received a first dose after symptom onset.

4.4.2 COVID-19 vaccination status ascertainment

Vaccine 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 potential data source. Participants should be informed in the informed consent form that these additional sources will be accessed, when relevant, in order to confirm their vaccination status.

It is crucial that information on the vaccination status is collected with the utmost care to ensure data completeness and quality, and possibility of recoding the definitions of vaccination status as needed.

Vaccine documentation should include, if possible, for each dose:

- date(s) of each vaccination dose;
- vaccine product;
- vaccine batch;
- method of ascertainment (e.g., self-reported, documented, vaccination registry, etc.) and method of validation (if applicable).

➢ *Each outbreak investigation team/local or national protocol to describe vaccines and vaccination policy used in the country and adapt the definitions accordingly and the vaccination status ascertainment.*

4.5 Outcomes

The primary outcome should be a confirmed SARS-CoV-2 infection detected by laboratory RT-PCR in any study participant.

As an alternative, to improve acceptability and feasibility in this type of setting (schools, universities, work environment), and despite the existing limitations of detection, rapid antigen testing could be used to confirm SARS-CoV-2 infection following ECDC RADT updated guidance [9].

Depending on sample size, COVID-19 vaccine effectiveness could be measured:

- against symptomatic laboratory-confirmed SARS-CoV-2 infections;
- against severe laboratory-confirmed SARS-CoV-2 infections;
- against SARS-CoV-2 variants of interest (VOI)/concern (VOC);
- by vaccination status (e.g., partially or fully vaccinated);
- by vaccine product and by combination of different vaccine products;
- by time since vaccination and/or time between vaccine doses;
- by different age groups;
- by sex;
- by different high-risk comorbidities;
- by previous SARS-CoV-2 infection.

More specifically, symptomatic COVID-19 infection could be defined as:

A participant with confirmed SARS-CoV-2 infection detected by laboratory RT-PCR who reports one or more of the following clinical criteria to conform with the ECDC possible case definition of COVID-19 [10]:

- cough;
- fever;
- shortness of breath/dyspnoea;
- anosmia;
- ageusia/dysgeusia;
- gastrointestinal symptoms.

In order to define severity of disease (attendance to medical care: outpatient or hospitalisation) and death could be used for defining the severity of infection.

4.5.1 Case finding

In order to identify cases in a semi-closed setting outbreak, all persons at risk of infection inside the study population since the beginning of the outbreak should be swabbed.

➢ *Each outbreak investigation team/local or national protocol to collect o*ral or written informed consent according to country procedures are specified in the section 'Ethical considerations' below.

4.5.2 Laboratory methods

- *Each outbreak investigation team/local or national protocol to describe the relevant laboratory procedures, such as:*

  - sample collection, storage, transport;
  - kits used and their performance according to manufacturer;
  - quality assurance/quality control scheme; and
  - selection of specimens for whole genome sequencing, if included.

4.5.3 Specimen collection

Samples can be either nasal, naso- or oropharyngeal swabs which can be taken by a trained investigator or by the healthcare worker themselves after suitable training. As alternative to improve acceptability and feasibility in this type of setting, self-taken saliva samples have also been shown to perform well in comparison to naso- or oropharyngeal swabs, particularly in the early stages of infection [11-15]. The type of sample used for the study should be chosen carefully in collaboration with public health laboratory staff and used consistently for all study participants within the same outbreak investigation study. Evidence was found that RT-PCR tests with saliva as sample material show similar sensitivity to those using nasopharyngeal swabs for symptomatic patients, if the sample collection is performed within the first five days from symptom onset, and when the viral load is high. Saliva specimens can be collected by the individual themselves if they are properly instructed by the investigation team [15].

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 [16] and laboratory testing for coronavirus disease (COVID-19) in suspected human cases [17].

All collection tubes should be labelled with a coded identification number that should also be 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.

4.5.4 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. 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 [18].

4.5.5 Specimen testing

Molecular testing
COVID-19 laboratory confirmation will be done using RT-PCR, a high specificity test. Laboratory guidance for molecular testing for SARS-CoV-2 can be found on the WHO [19] and ECDC [20] websites.

Antigenic testing
As an alternative to improve acceptability and feasibility in this type of setting (schools, universities, work environment) and according to the last ECDC recommendations [9], antigenic testing could be used to confirm SARS-CoV-2 infection. Rapid antigen detection tests (RADTs) can help reduce further transmission through early detection of highly infectious cases, enabling a rapid start of isolation and contact tracing. RADTs are sensitive enough to detect cases with high viral load, early in the course of infection in pre-symptomatic and early symptomatic cases up to five days from symptom onset [9]. A common list of COVID-19 rapid antigen tests was agreed by the Health Security Committee (HSC) on 17 February 2021. The last update was agreed by the HSC on 20 October 2021 [21].

Serological testing
Assuming that previous infection provides immunity against future infections for a specific duration, individuals having had a SARS-CoV-2 infection before the start of the semi-closed setting outbreak and protected according to the duration of post-infection immunity, are not at risk of infection. Individuals previously infected (those having a history of an episode of COVID-19 or those IgG positive) should be identified to avoid underestimation of vaccine effectiveness. Rapid antibody tests based on host antibody detection could be used in the context of an outbreak in a semi-closed setting to improve feasibility in this type of settings. However, no commonly

accepted list of rapid antibody tests currently exists in the EU/EEA, therefore selection of the appropriate test should be done carefully taking into consideration its performance characteristics.

Genetic sequencing
All or a random sample of RT-PCR positive specimens collected among study participants should be further characterised using genetic sequencing. Genetic sequencing is particularly important to undertake during the study to understand whether potential changes in vaccine effectiveness are due in part to mutations in the circulating virus. Investigators should also ensure genetic sequences are uploaded into the appropriate GISAID platform as well as the COVID-19 Data Portal.

- *Each outbreak investigation team/local or national protocol to detail:*

  - ☑ to describe the tests and the kits used for COVID-19; and, if needed, respiratory virus detection.
  - ☑ to describe mode of selection of viruses for sequencing.
  - ☑ to specify sequencing methods.

Quality control tests should systematically be run using RT-PCR to test for presence of cells in the respiratory specimens. In addition, quality assurance of assay performance at sites should be undertaken using international, national or research standards.

- *Each outbreak investigation team/local or national protocol to describe quality controls for specimens.*

Guidance from ECDC and WHO details methods for the detection and identification of SARS-CoV-2 variants [22]. It is important to check on the existence of updated documents when conducting the outbreak investigation and to aim to perform genomic sequencing as part of the investigation.

4.5.5 Sample size

In a semi-closed setting that is of manageable size, all people in the study population should be included in the study.

In a semi-closed-setting situation where the study population is too large to survey everyone, the cohort study can be performed with individuals selected randomly or using a systematic sampling method. The sample size should allow the provision of robust estimates for the primary study objective. The sample size should be respected for each population subgroup in which a sub- (stratified) analysis (e.g., effect modification) is planned.

- *Each outbreak investigation team/local or national protocol* to include the sample size *calculation*.

The following table illustrates the various sample size needed in order to obtain a 20%, 30% and 40% confidence interval width around the vaccine effectiveness, assuming a ratio of vaccinated: unvaccinated of 1, an attack rate among the unvaccinated of 50% and varying vaccine effectiveness.

Table 1. Sample size calculations – Cohort study

Width of confidence interval	Ratio vaccinated: unvaccinated	Detectable RR	Attack rate among the unvaccinated	Number of vaccinated	Number of unvaccinated	VE	CI
0.4	1	0.1	0.5	27	27	90	57-97
0.4	1	0.2	0.5	43	43	80	52-92
0.4	1	0.3	0.5	60	60	70	44-84
0.4	1	0.4	0.5	79	79	60	35-75
0.4	1	0.5	0.5	98	98	50	26-56
0.4	1	0.6	0.5	117	117	40	17-57
0.4	1	0.7	0.5	137	137	30	7-47
0.5	1	0.1	0.5	19	19	90	48-98
0.5	1	0.2	0.5	29	29	80	43-93
0.5	1	0.3	0.5	39	39	70	36-86
0.5	1	0.4	0.5	51	51	60	28-78
0.5	1	0.5	0.5	64	64	50	19-69
0.5	1	0.6	0.5	76	76	40	10-60
0.5	1	0.7	0.5	88	88	30	1-51
0.3	1	0.1	0.5	44	44	90	67-97
0.3	1	0.2	0.5	73	73	80	60-90
0.3	1	0.3	0.5	105	105	70	51-81
0.3	1	0.4	0.5	138	138	60	42-72
0.3	1	0.5	0.5	173	173	50	33-63
0.3	1	0.6	0.5	207	207	40	23-53
0.3	1	0.7	0.5	241	241	30	13-43
0.2	1	0.1	0.5	88	88	90	75-95
0.2	1	0.2	0.5	158	158	80	67-87
0.2	1	0.3	0.5	233	233	70	58-78
0.2	1	0.4	0.5	309	309	60	48-68
0.2	1	0.5	0.5	386	386	50	39-59
0.2	1	0.6	0.5	463	463	40	29-49
0.2	1	0.7	0.5	540	540	30	19-39

4.6 Data

4.6.1 Data collection

Data will be collected from all study participants using a standardised questionnaire. The procedures to collect data will be defined by each study coordinator (e.g. face-to-face, by telephone, postal questionnaire, web-based, etc.).

The minimum data that should be collected are:

- age;
- sex;
- presence of chronic disease(s) (see Annex 1);
- previous SARS-CoV-2 infection (clinical or laboratory-confirmed) and date of symptom onset;
- vaccination status for COVID-19 including all vaccination details, including dose number(s), date(s), vaccine product (s), and batch number(s) of dose(s);
- molecular SARS-CoV-2 testing results.

➢ *Each outbreak investigation team/local or national protocol to describe data collection methods, data entry and data transmission*

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

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

Categories	Variable	Key/optional variable
Socio-demographic	Age	Key
	Sex	Key
	Ethnicity	Optional
	Blood group	Optional
	Socioeconomic status	Optional
Chronic conditions (includes pregnancy)	Diagnosed chronic condition (see Annex 1)	Key
	Medication for chronic condition (see Annex 1)	Optional
Individual behaviours/attitude	Smoking (current/past/never)	Key
	BMI (collect height and weight)	Key
	Alcohol use	Optional
COVID-19 vaccination	Vaccine dose received (for each dose) Yes/no	Key
	Vaccination date(s) (for each dose)	Key
	Vaccine product (for each dose)	Key
	Vaccine dose (first or second or third)	Key
	Vaccine batch (for each dose)	Key
	Source used for vaccine ascertainment	Key
Previous vaccinations	Influenza (month, year)	Key
SARS-CoV-2 infection (Last episode)	Laboratory/clinical/self-reported confirmed	Key
	List of symptoms	Key
	Date of onset	Key
	Severity	Key
Laboratory results	PCR	Key
	Sequencing	Optional
	Serology	Optional

4.6.2 Information collected regarding confounding factors and effect modifiers

To control for differences in vaccinated compared to non-vaccinated individuals, information on potential effect modifiers and confounding factors should be collected. The minimum confounding factors to be considered include age, time since the vaccine dose received, presence of a chronic disease, pregnancy, and indicators of the severity of chronic diseases.
Below is a list of potential confounding factors and effect modifiers. Not all information will be relevant or available given the nature of the outbreak and/or semi-closed setting.

- *Each outbreak investigation team/local or national protocol to ensure information collected in each study is specified in the study annexes.*

An individual will be classified as belonging to a group at increased risk of severe outcome if he/she reports having the following underlying conditions:

- chronic underlying conditions and severity indicators;
- pregnancy status (where applicable).

An individual may be classified as belonging to a group at increased risk of infection based on the specific qualities of the semi-closed setting(e.g. indoors versus outdoors, increased number of contacts, use of personal protection , etc).

Other confounding factors that should be considered if available or relevant include:

- level of social interaction (number of household members; children: nursery versus school-age children); indicators of socio-economic status (educational level; profession; and any other available and relevant for the study population (e.g. deprivation score by area of residence) (see detailed in Annex 1).

4.6.3 Data sources

A standardised questionnaire should be used. The procedures to collect data will be defined by each study coordinator (e.g. face-to-face, by telephone, postal questionnaire, web-based, etc.). Data can be also collected ,

from electronic medical records, vaccine registries, occupational health registries, or other relevant sources. For each variable, possible and optimal data sources should be identified.

Once collected, data should be input onto a centralised (on-line) platform that 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.

- *Each outbreak investigation team/local or national protocol to detail data sources to be used for each variable.*

4.6.4 Data validation

If data are collected using paper questionnaires, a sample of paper questionnaires will be cross-checked against the study database to validate data entry.

Where variables, such as those regarding vaccination, were self-reported, the details should be validated against an existing data source (e.g. immunisation registry).

- *Each outbreak investigation team/local or national protocol to specify the procedures for data validation.*

4.6.5 Data cleaning

Summary and frequency tables and graphic displays of appropriate variables will be used to find incorrect, implausible, or missing values within the dataset. Checks for inconsistencies will be carried out (e.g. date of swabbing before date of symptom onset). These values can be checked against the questionnaires or queried with the study participant. Any changes to the data will be documented and stored separately from the crude database. Any recoding of data (e.g. age from date of birth) will be documented.

4.6.6 Data management and ensuring data confidentiality

All data management procedures must comply with GDPR. Each participant should be allocated a unique study ID number that all documents will subsequently use as the identifier. The unique identifier will be randomly generated and will link each record. The coordinating team would 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 would not be able to export these data.

4.6.7 Data analysis

Analyses should be carried separately for different vaccine products, if possible.

Separate analyses will be carried out for the different primary and secondary outcomes.

Analyses will be carried out including and excluding people with recent respiratory symptoms (prior to outbreak) that were not laboratory-confirmed, where information is available.

An analysis will be carried out including only people 'fully vaccinated' in the vaccinated group. A second analysis will include people 'fully' and 'partially vaccinated' in the vaccinated group.

Sensitivity analysis is further detailed in paragraph 4.6.12.

4.6.8 Descriptive and univariable analyses

Participation variables include:

- total number not eligible;
- total number eligible;
- total number included: vaccinated and unvaccinated; and
- total number of subjects that refused participation.

The baseline characteristics of the individuals included into the study include the following, which should be described by vaccination status:

- age;
- sex;
- socio-economic status indicators;
- comorbidities;
- pregnancy status;
- occupation or main activities (depending on the setting).

Baseline characteristics of vaccinated and unvaccinated participants will be described using proportions and mean/medians (depending on variable type). Missing data for each characteristic will be described, along with approaches on how the missing data were dealt with.

Calculating attack rates (AR; i.e. the proportion of cases among all individuals at risk of infection in the group under observation) provides an estimation of the risk of infection during a specified period. The calculation of ARs in vaccinated and unvaccinated is an essential feature of the description of the outbreak and a necessary step to calculate vaccine effectiveness. ARs can also be calculated for other groups (e.g. in vaccinated since ≤6 months or >6 months; or in vaccinated ≥80 years or <80 years) and are helpful to formulate hypothesis on risk factors.

In order to test for differences between vaccinated and unvaccinated characteristics, students' t-test for continuous variables and chi square tests (or Fisher's exact test for small samples) for categorical variables will be used.

Table 3. Study population baseline characteristics by COVID-19 vaccination status

(to complete/modify according to the variables collected)

Characteristics	Unvaccinated		Vaccinated		Total
	n	%	N	%	
Demographic - Age - Sex - Socio-economic status					
Comorbidities					
Pregnancy status					
Etc					

4.6.9 Unadjusted (Crude) vaccine effectiveness estimates

The (unadjusted) vaccine effectiveness (VE) will be computed as

VE = (1-RR) X 100

Or

VE = ((AR in unvaccinated – AR in vaccinated) / (AR in unvaccinated)) X 100

exact 95% CI are computed around the estimate for each outcome.

Table 4. Calculation of unadjusted vaccine effectiveness estimate in the cohort study

Exposure	Outcome [Infected] *(n)*	Outcome [not infected] *(n)*	Total	Attack rate
Unvaccinated (n)	A	B	a+b	a/a+b
Vaccinated (n)	C	d	c+d	c/c+d

RR = (a/a+b)/(c/c+d)
VE = 1-RR

4.6.10 Stratified analysis

The analysis will be stratified (where possible) according to the comparison groups/options listed above under '4.2.2 Secondary Objectives':

- against symptomatic laboratory-confirmed SARS-CoV-2 infection;
- against severe laboratory-confirmed SARS-CoV-2 infection;
- against SARS-CoV-2 VOI/VOC;
- by vaccination status (e.g., partially or fully vaccinated);
- by vaccine product and by combination of different products;
- by time since vaccination and/or time between vaccine doses;
- by different age groups;
- by sex;
- by different high-risk comorbidities;
- by previous SARS-CoV-2 infection.

Effect modifiers are assessed one by one comparing the RR across the strata of the baseline characteristic. Confounding is assessed by comparing crude and adjusted RR for each baseline characteristic.

4.6.11 Multivariable analysis

A multivariable analysis is conducted to control for negative and positive confounding factors and to calculate adjusted vaccine effectiveness estimates. Variables will be tested for multicollinearity. The type of multivariable analysis depends on the nature (high or low incidence) of the outbreak and the type of denominator used (persons or person-time). Regression methods could include Cox, Poisson, or negative binomial regression.

- *Each outbreak investigation team/local or national protocol to describe the multivariable analysis type and model building strategy.*

Results from the multivariable analysis should be presented in a table or tables, possibly presenting vaccine effectiveness by key/all variables of interest, and with both the unadjusted vaccine effectiveness and the adjusted (for those variables included in the multivariable model) vaccine effectiveness. See an example below.

Table 5. Frequency of SARS-CoV-2 infection in unvaccinated and vaccinated individuals, vaccine effectiveness against infection (or other outcome with SARS-CoV-2) by selected key variables of interest, place, time (n = xx)

Variables	Unvaccinated events/total people	Vaccinated events/total people	*Rate ratio (95% C.I)*	*Vaccine effectiveness (unadjusted)*	*Vaccine effectiveness (adjusted)*
Overall	Xxx/xxx	Xx/xxx			
Vaccine product					
Product 1					
Product 2					
Sex					
male					
female					
Age group Age group 1 Age group 2					
Socio-economic status					
Comorbidities					

(to complete/modify according to the variables collected)

4.6.12 Sensitivity analysis

In order to assess the effect of potential confounding factors not included in the analysis on vaccine effectiveness estimates, a sensitivity analysis could be conducted:

- by previous infection, using different definitions of previous infection (for instance previous infections defined by self-reported symptoms versus by a confirmatory laboratory result; or different timelines of previous infections depending on how long before the outbreak these occurred);
- using different delays between symptom onset and specimen collection;
- using different time periods for defining vaccination status, for instance a seven-day cut-off after a dose versus 14 days for a certain dose; and
- calculating E-values to quantify the potential for bias due to unmeasured confounding.

- *Each outbreak investigation team/local or national protocol to specify the sensitivity analysis carried out.*

5 Template for a protocol for a case control study (delete section if not applicable)

If within an outbreak in a semi-closed setting, the study population is too large to survey the whole population, a case-control study could be undertaken. As an example, during an outbreak in a large factory with more than one thousand full-time and part-time workers it could be difficult to identify, interview and test all the people at risk of infection during the outbreak period. A case control study can be implemented instead. Depending on the disease incidence in the outbreak, a specific case-control design could be chosen between: traditional case-control design; density case-control design; and case-cohort design [23].

5.1 Background

- *Each outbreak investigation team/local or national protocol /local or national protocol to describe the epidemiological context and any other information relevant to the study*

5.2 Study objectives

5.2.1 Primary objective

In the context of a case-control study, the primary objective will be to measure COVID-19 vaccine effectiveness against symptomatic laboratory-confirmed SARS-CoV-2 infection.

5.2.2 Secondary objectives

Depending on sample size, to measure COVID-19 vaccine effectiveness:

- against severe laboratory-confirmed SARS-CoV-2 infections;
- against SARS-CoV-2 variants of interest (VOI)/concern (VOC);
- by vaccination status (e.g. partially or fully vaccinated);
- by vaccine product and by combination of different vaccine products;
- by time since vaccination and/or time between vaccine doses;
- by different age groups;
- by sex;
- by different high-risk comorbidities; and
- by previous SARS-CoV-2 infection.

As vaccination coverage in some semi-closed settings could be high, investigators could consider as a secondary objective the estimation of a *comparative vaccine effectiveness* (vaccine effectiveness without an unvaccinated group as a comparison) by:

- vaccine schedules (e.g. schedules with different intervals);
- vaccine products; and
- time since last vaccination (e.g. recent last dose (defined as within six months) versus vaccination more than six months ago) to assess the impact of waning immunity.

In order to define severity of disease (attendance to medical care: outpatient or hospitalisation) and death could be used for defining the severity of infection.

- *Each outbreak investigation team/local or national protocol /local or national protocol to specify the (additional) secondary objectives*

5.3 Study population

The study population is defined as the population at risk of SARS-CoV-2 infection within the semi-closed setting in which the outbreak occurs and eligible for COVID-19 vaccination. These may include depending on the setting:

- occupational setting: full-time workers, part-time workers;
- schools: students, staff;
- residential settings: staff, residents; and
- open refugee/internally displaced camps: staff, residents.

- *Each outbreak investigation team/local or national protocol/local or national protocol to describe the population at risk as per generic template (Section 4.3.1).*

☑ **Note: in some countries it is possible that that individuals previously infected are excluded as not eligible for COVID-19 vaccination at the time of the outbreak investigation.**

With the current uncertainty around the immunity conferred by past infections, it is recommended that sensitivity analyses are conducted including and excluding those individuals previously infected, e.g those with a history of an episode of COVID-19 or those IgG-positive.

5.4 Study period

The study period is the duration of the outbreak as defined by the study team. Data regarding vaccination status will be collected retrospectively.

The study should be conducted following the necessary research requirements such as approval by the relevant Ethical Review Committee at the institutional or national levels.

➢ *Each outbreak investigation team/local or national protocol to define the study period*

Under certain circumstances the study period could be restricted to part of the duration of the outbreak if the COVID-19 vaccination status changes substantially during this time period.

5.5 Outcomes

The primary outcome should be a confirmed SARS-CoV-2 infection detected by laboratory RT-PCR in any participant reporting the following symptoms that conform with the ECDC possible case definition of COVID-19 [10]:

- cough;
- fever;
- shortness of breath/dyspnoea;
- sudden onset of anosmia;
- sudden onset of ageusia/dysgeusia;
- other non-respiratory symptoms of headache, chills, muscle pain, fatigue, vomiting and/or diarrhoea.

Depending on sample size, to measure COVID-19 vaccine effectiveness:

- against symptomatic laboratory-confirmed SARS-CoV-2 infections;
- against severe laboratory-confirmed SARS-CoV-2 infections;
- against SARS-CoV-2 variants of interest (VOIs)/variants of concern (VOCs);
- by vaccination status (e.g. partially or fully vaccinated);
- by vaccine product and by combination of different vaccine products;
- by time since vaccination and/or time between vaccine doses;
- by different age groups;
- by sex;
- by different high-risk comorbidities;
- by previous SARS-CoV-2 infection.

5.6 Laboratory methods

➢ *Each outbreak investigation team/local or national protocol to describe the relevant laboratory procedures, such as:*

- sample collection, storage, transport;
- kits used and their performance according to manufacturer;
- quality assurance/quality control scheme;
- selection of specimens for whole genome sequencing, if included.

See section 4.5.2 for details.

5.7 Cases

5.7.1 Case finding

All suspect cases (individuals with symptoms described above) and their selected contacts eligible for vaccination inside the study population since the beginning of the outbreak should be swabbed, and they should then be classified as cases or controls based on the result of the laboratory test.

5.7.2 Case inclusion criteria

Cases will be included in the study if they meet the above case definition, if they are eligible for COVID-19 vaccination and agree to participate.

☑ Oral or written informed consent according to country procedures are specified in the section 'Ethical considerations' below.

5.7.3 Case exclusion criteria

Cases are excluded if they are not eligible for COVID-19 vaccination or if they refuse participation. Reasons for exclusion will be documented. Depending on national recommendations, it is possible that individuals with previous confirmed SARS-CoV-2 infection will be among those not eligible for COVID-19 vaccination at the time of the outbreak investigation.

5.8 Controls

5.8.1 Control identification

The selection of controls varies by the nature of the outbreak (high frequency or low frequency of infections). Controls must be representative of the population source from which the cases arise in respect to COVID-19 vaccination coverage and are part of the study population, which includes having had risk of exposure to the virus.

- Control selection excluding people with symptoms and a positive laboratory result forms a traditional case-control study design (if incidence in the outbreak is not too high).

In such circumstance, the control can be defined as:

- Individuals without symptoms and without a positive laboratory result and as part of the study population.

  Controls can be unmatched or matched to cases by age, by role in the workplace, by classroom. Matched to case onset, control selection among people still free of symptoms and laboratory confirmation when a case arises forms a density case-control study design.

- Control selection including people with symptoms and a positive laboratory result (proportional to incidence if incidence is high inside the outbreak) forms a case-cohort study design.

☑ *Each outbreak investigation team/local or national protocol to describe the selection of controls*.

5.8.2 Control inclusion criteria

Controls are selected if they meet the above control definitions and accept to participate.

☑ *Each outbreak investigation team/local or national protocol to describe informed consent procedures*

5.8.3 Control exclusion criteria

Controls are excluded if they don't meet the above control definitions or if they refuse participation. Reasons for exclusion will be documented.

5.8.4 Matching

Matching controls to cases on one or more variables increases the precision of the results obtained from the analysis of the case-control study. Matching also help control for confounders. To avoid over-matching, and the consequent loss of statistical power, variables used for matching should be those both associated both with vaccination and with disease (e.g. age). It should be noted that matching also increases the challenges in recruiting controls. Individual level matching is usually preferred in vaccine effectiveness studies; however, frequency matching is also a possibility, particularly in case of reduced availability of controls [24]. A matching design requires a matching analysis plan (e.g. using conditional logistic regressions) [25].

5.9 Exposure (vaccination)

5.9.1 Definition of vaccination status

Full and partial vaccination status should be defined according to the instructions of the manufacturer for each COVID-19 vaccine product. Specific delays other than 14 days may be applied or tested in the vaccine effectiveness analysis.

It is also important to take into account the specific recommendations in the country and the eligibility criteria of a specific individual to receive a dose of the vaccine.

The definition of full/partial vaccination might be evolving over time and in different contexts, so it is of pivotal importance to allow the collection of the number of doses, product/s, and date of administration for each dose.

- **Fully vaccinated status**
  - **with a two-dose vaccine**
  - **or two-dose plus one additional dose vaccine**
  - with the last dose most likely received at least 14 days before symptom onset (date of positive laboratory confirmation).
- **Fully vaccinated**
  - **With a** single-dose vaccine
  - **Or a one-dose vaccine plus one additional dose**
  - with the last dose most likely received at least 14 days before symptom onset (date of positive laboratory confirmation).
- **Partially vaccinated**
  - Incomplete series of the above
  - with the last dose most likely received at least 14 days before symptom onset (date of positive laboratory confirmation).

- **Unvaccinated**
  - individual who did not receive any dose of COVID-19 vaccine or who received their first dose after symptom onset.

5.9.2 COVID-19 vaccination status ascertainment

Precise vaccination status documentation is essential for this study. Vaccine 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 potential data source. Participants should be informed in the inform consent form that these additional sources will be accessed, when relevant, in order to confirm their vaccination status.

Vaccine documentation should include for each dose:

- COVID-19 vaccination received and date of vaccination;
- Vaccine product;
- Vaccine batch; and
- Method of ascertainment (e.g. self-reported, documented, vaccination registry, etc.) and method of validation (if applicable).

☑ *Each outbreak investigation team/local or national protocol to describe vaccines and vaccination policy used in the country and adapt the definitions accordingly and the vaccination status ascertainment.*

5.9.3 Sample size

In a semi-closed setting, the number of cases available is often fixed, which limits the power of the study. Prior to the study beginning, calculations to determine its power to detect a given measure of effect with a set number of cases can be useful. This can also help determine if the control to case ratio needs to be increased to give more power.

Table 4 illustrates the various sample sizes that would ensure a detectable odds ratio ranging from 0.1 to 0.4 and a vaccination coverage among the source population (or among controls) ranging from 60 to 70 %.

The sample size should be respected for each population sub-group in which a sub (stratified) analysis (e.g. effect modification) is planned.

Table 6. Sample size calculations – Case-control study

Precision of lower CI boundary	Control/ Case	Detectable OR	Vaccine coverage in source population/ controls	Number of cases	Number of controls	CVE	CI
0.3	1	0.1	0.6	26	26	90	60-98
0.3	1	0.2	0.6	45	45	80	50-92
0.3	1	0.3	0.6	71	71	70	40-85
0.3	1	0.4	0.6	103	103	60	30-77
0.2	1	0.1	0.6	41	41	90	70-97
0.2	1	0.2	0.6	78	78	80	60-90
0.2	1	0.3	0.6	130	130	70	50-82
0.2	1	0.4	0.6	197	197	60	40-73
0.1	1	0.1	0.6	104	104	90	80-95
0.1	1	0.2	0.6	229	229	80	70-87
0.1	1	0.3	0.6	410	410	70	60-78
0.1	1	0.4	0.6	651	651	60	50-68
0.3	1	0.1	0.7	23	23	90	60-98
0.3	1	0.2	0.7	43	43	80	50-92
0.3	1	0.3	0.7	71	71	70	40-85
0.3	1	0.4	0.7	108	108	60	30-77
0.2	1	0.1	0.7	36	36	90	70-97
0.2	1	0.2	0.7	75	75	80	60-90
0.2	1	0.3	0.7	131	131	70	50-82
0.2	1	0.4	0.7	205	205	60	40-73
0.1	1	0.1	0.7	90	90	90	80-95
0.1	1	0.2	0.7	219	219	80	70-87
0.1	1	0.3	0.7	413	413	70	60-78
0.1	1	0.4	0.7	676	676	60	50-68

5.10 Data

5.10.1 Data collection

Data will be collected from all study participants using a standardised questionnaire. The procedures to collect data will be defined by each study coordinator (e.g. face-to-face, by telephone, postal questionnaire, web-based, etc.).

The minimum data that should be collected are:

- age;
- sex;
- presence of chronic disease(s);
- previous SARS-CoV-2 infection (clinical or laboratory-confirmed);
- vaccination status for COVID-19, including all vaccination details (number, date/s, product/s, and batch number/s of dose/s); and
- molecular SARS-CoV-2 testing results.

➢ *Each outbreak investigation team/local or national protocol to describe data collection methods, data entry and data transmission*

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

Table 7. Data collection of variables (key variables that should be collected, optional variables recommended) and questionnaires to be used

Categories	Variable	Key/optional variable
Socio-demographic	Age	Key
	Sex	Key
	Ethnicity	Optional
	Blood group	Optional
	Socioeconomic status	Optional
Chronic conditions (includes pregnancy)	Diagnosed chronic condition (see Annex 1)	Key
	Medication for chronic condition (see Annex 1)	Optional
Individual behaviours/attitude	Smoking (current/past/never)	Key
	BMI (collect height and weight)	Key
	Alcohol use	Optional
COVID-19 vaccination	Vaccine dose received (for each dose) Yes/no	Key
	Vaccination date(s) (for each dose)	Key
	Vaccine product (for each dose)	Key
	Vaccine dose (first or second or third)	Key
	Vaccine batch (for each dose)	Key
	Source used for vaccine ascertainment	Key
Previous vaccinations	Influenza (month, year)	Key
SARS-CoV-2 infection (Last episode)	Laboratory/clinical/self-reported confirmed	Key
	List of symptoms	Key
	Date of onset	Key
	Severity	Key
Laboratory results	PCR	Key
	Sequencing	Optional
	Serology	Optional

5.10.2 Information collected regarding confounding factors and effect modifiers

To control for differences in cases and controls, information on potential effect modifiers and confounding factors will be collected. The minimum confounding factors to be considered include age, time since the vaccine dose received, presence of a chronic disease, pregnancy, and indicators of the severity of chronic diseases.
Below is a list of potential confounding factors and effect modifiers. Not all information will be relevant or available given the nature of the outbreak and/or semi-closed setting.

☑ *Each outbreak investigation team/local or national protocol to ensure information collected in each study is specified in the study annexes.*

An individual will be classified as belonging to a high-risk group if he/she reports having the following underlying conditions: Chronic underlying conditions and severity, Pregnancy status (where applicable): Information on pregnancy status will be collected if applicable. Semi-closed setting specific: variables related to exposure to the virus (occupation, location, activities, etc). Other confounding factors that should be considered if available or relevant include: Level of social interaction (Number of household members, Children: nursery versus school-age children).

Indicators of socio-economic status (education level, profession, others (e.g. deprivation score by area of residence) and any other available and relevant for the study population (see details in Annex 1).

5.10.3 Data sources

Data can be collected through questionnaires completed by the study monitors, study participants, electronic medical records, vaccine registries, occupational health 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 outbreak investigation team/local or national protocol to detail data sources to be used for each variable.*

5.10.4 Data validation

If data are collected using paper questionnaires, a sample of paper questionnaires will be checked against the study database to validate data entry.

Where variables, such as those regarding vaccination, were self-reported, the details should be validated against an existing data source (e.g. immunisation registry).

☑ *Each outbreak investigation team/local or national protocol to specify the procedures for data validation.*

5.10.5 Data cleaning

Summary and frequency tables and graphic displays of appropriate variables will be used to find incorrect, implausible or missing values within the dataset. Checks for inconsistencies will be carried out (e.g. date of swabbing before date of symptom onset). These values will be checked against the questionnaires or queried with the study participant. Any changes to the data will be documented and stored separately from the crude database. Any recoding of data (e.g. age from date of birth) will be documented.

5.10.6 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 that all documents will subsequently use as the identifier. The unique identifier will be randomly generated and will link each record. The coordinating team would 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 would have access to the personal information but will not be able to export these data.

5.11 Data analysis

Analyses should be carried separately for different vaccine products, if possible.

Separate analyses will be carried out for the primary and secondary outcomes. Analyses will be carried out including and excluding people with recent respiratory symptoms (prior to outbreak) that were not laboratory-confirmed, where information is available.

An analysis will be carried out including only people 'fully vaccinated' in the vaccinated group. A second analysis will include people 'fully' and 'partially vaccinated' in the vaccinated group.

5.11.1 Descriptive and univariable analyses

The proportion of eligible cases and controls accepting to participate in the study will be calculated (response rate).

Study participants will be described by baseline characteristics. Baseline characteristics of cases and controls in unmatched studies are compared using the chi-square test, Fisher's exact test, or the Mann-Whitney test (depending on the nature of the variable and the sample size). In matched case-control studies, characteristics of cases and controls are compared using McNamara's chi-square test or the Kruskal-Wallis test.

The association between vaccination status and baseline characteristics is assessed for both case and control groups.

Table 8. Study population baseline characteristics by COVID-19 vaccination status

Characteristics	Cases		Controls		P values
	n	%	n	%	
Demographic - Age - Sex - Socio-economic status					
Comorbidities					
Pregnancy status					
Etc					

5.11.2 Measure of effect

The (unadjusted) vaccine effectiveness will be computed as

VE = (1-OR) X 100

Where OR (odds ratio) represents the odds of COVID-19 in vaccinated / odds of COVID-19 in unvaccinated individuals.

Exact 95% CI are computed around the estimate for each outcome.

Table 9. Calculation of unadjusted vaccine effectiveness estimate in a case control study

Exposure	Cases	Controls	Odds
Vaccinated	A	b	a/b
Unvaccinated	C	d	c/d

OR = (a/b)/(c/d)
VE = 1-OR

5.11.3 Stratified analysis

Analysis will be stratified (where possible) according to the comparison groups/options listed below.

- against severe laboratory-confirmed SARS-CoV-2 infection;
- against SARS-CoV-2 variants of interest/concern;
- by vaccination status (i.e. partially or fully vaccinated);
- by vaccine product and by combination of different products;
- by time since vaccination and/or time between vaccine doses;
- by different age groups;
- by sex;
- by different high-risk comorbidities;
- by previous SARS-CoV-2 infection.

A sufficient sample size should be planned in order to ensure sufficient individuals in each stratum. Studies should aim to have at least 80 individuals in each of the strata. Effect modification is assessed comparing the OR across the strata of the baseline characteristics. Confounding is assessed by comparing crude and adjusted OR for each baseline characteristic.

In order to define severity of disease (attendance to medical care: outpatient or hospitalisation) and death could be used for defining the severity of infection.

5.11.4 Multivariable analysis

A multivariable (conditional, if using a matched design) logistic regression analysis will be conducted to control for negative and positive confounding and to computer the adjusted vaccine effectiveness estimates. Odds ratios and standard errors will be obtained. Preferably, the model will include: vaccination, underlying chronic conditions, age, sex and smoking and functional status. Variables will be tested for multicollinearity. Interactions will be tested using the Likelihood Ratio test (or Wald test) and included in the model if significant at 5% level.

Table 10. Frequency of SARS-CoV-2 infection in unvaccinated and vaccinated individuals, vaccine effectiveness against infection (or other outcome with SARS-CoV-2) by selected key variables of interest, place, time (n = xx)

Variables	Cases/ Vaccinated cases	Controls / Vaccinated controls	*Odds ratio (95% C.I)*	*Vaccine effectiveness (unadjusted)*	*Vaccine effectiveness (adjusted)*
Overall	Xxx/xxx	Xx/xxx			
Vaccine product					
Product 1					
Product 2					
Sex					
male					
female					
Age group Age group 1 Age group 2					
Socio-economic status					
Comorbidities					
Etc					

6 Limitations of the vaccine effectiveness studies in semi-closed settings

6.1 Sample size

An investigation in a semi-closed setting often has a fixed sample size that can be low. It is possible that the study will not have enough power to give a precise estimate of vaccine effectiveness in overall or stratified analysis.

6.2 Negative confounding factors

These are biases reflecting that high-risk groups are more likely to be vaccinated, therefore reducing vaccine effectiveness. Negative confounding factors will be minimised by taking into account the presence of chronic diseases in the adjustment and by stratifying by risk group if sample size allows.

6.3 Positive confounding factors

These are biases reflecting a healthy vaccine effect. People with a healthy behaviour and a good functional status are more likely to accept / request vaccination, therefore increasing the measured vaccine effectiveness.

Positive and negative confounding factors will be minimised through stratification and multivariable analysis, including presence of chronic diseases, and variables collected to measure positive and negative confounding. We cannot rule out the presence of characteristics in the study population leading to positive or negative confounding for which information is not collected in the study questionnaire. Therefore, residual positive or negative confounding may be present. A sensitivity analysis will be conducted to assess the effect of a potential unmeasured confounding factor.

6.4 Misclassification bias

Notification of an outbreak within a semi-closed setting is often not prompt. This can lead to a delay between symptom onset and laboratory confirmation which can result in misclassification of cases. If this misclassification is irrespective of vaccination status it can lead to an underestimation of vaccine effectiveness.

6.5 Inclusion of people with SARS-CoV-2 infection prior to the outbreak

While information on history of prior COVID-19 is recommended to be collected, reliable information of illness prior to the outbreak might not be available. Depending on the nature of the vaccine, including people with previous infection could result in overestimating or underestimating the vaccine effectiveness estimates.

6.6 Overestimation of vaccine effectiveness

If the incidence of SARS-CoV-2 infections is high in the outbreak and a traditional case-control study design is used – or a cohort design using logistic regression to obtain ORs – then the vaccine effectiveness may be overestimated.

7 Ethical considerations

Studies of COVID-19 vaccine effectiveness in semi-closed settings should be approved by the relevant Ethical Review Committee.

According to country-specific regulations, informed (oral or written) consent will be required from each participant enrolled into the study.

All residents and staff approached for inclusion in the study should be informed that participation is voluntary and that they will be able to withdraw from the study, without justification, at any time during the study without consequences. It should be clearly stated that participation to this study will not have any adverse impact on participants including offer for vaccination.

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 could be shared with the study coordinator and ECDC 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).

☑ *Each outbreak investigation team/local or national protocol to include a copy of the Ethical Review Committee approval and a copy of the informed consent in the study annexes.*

7.1 Risks and benefits for subjects

This study poses minimal risk to participants involving the collection of respiratory specimens. Results of 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 SARS-CoV-2 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 measure the effectiveness of the COVID-19 vaccines and guide vaccination policies.

8 Dissemination of results

Study sites coordinators are responsible for the publication and communication of their results.

The list of authors will respect the recommendations of authorship stated by the International Committee of Medical Journal Editors: http://www.icmje.org/ethical_1author.html

☑ *Each outbreak investigation team/local or national protocol to specify how results will be disseminated.*

References

1. European Centre for Disease Prevention and Control (ECDC). COVID-19 Situation update week 46, updated 26 November 2021. Stockholm: ECDC; 2021. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/communicable-disease-threats-report-week%2047-2021.pdf
2. European Medicines Agency (EMA). COVID-19 vaccines: authorised. Amsterdam: EMA; 2021. Available at: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-diseasecovid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-authorised
3. World Health Organization (WHO). Evaluation of COVID-19 vaccine effectiveness. Geneva: WHO; 2021. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccine_effectiveness-measurement-2021.1
4. European Centre for Disease Prevention and Control (ECDC). Implications of the further emergence and spread of the SARS CoV 2 B.1.1.529 variant of concern (Omicron) for the EU/EEA first update. Stockholm: ECDC; 2021. Available at: https://www.ecdc.europa.eu/en/publications-data/covid-19-threat-assessment-spread-omicron-first-update
5. European Centre for Disease Prevention and Control (ECDC). Core protocol for ECDC studies of COVID-19 vaccine effectiveness against hospitalisation with Severe Acute Respiratory Infection laboratory-confirmed with SARS-CoV-2, version 1.0. Stockholm: ECDC; 2021. Available at: https://www.ecdc.europa.eu/en/publications-data/core-protocol-ecdc-studies-covid-19-vaccine-effectiveness-against-hospitalisation
6. European Centre for Disease Prevention and Control (ECDC) and European Medicines Agency (EMA). EMA and ECDC join forces for enhanced post-marketing monitoring of COVID-19 vaccines in Europe. Stockholm and Amsterdam: ECDC and EMA; 2021. Available at: https://www.ecdc.europa.eu/en/news-events/ema-and-ecdc-join-forces-enhanced-post-marketing-monitoring-covid-19-vaccines-europe
7. European Centre for Disease Prevention and Control (ECDC). Interim analysis of COVID-19 vaccine effectiveness against Severe Acute Respiratory Infection due to laboratoryconfirmed SARS-CoV-2 among individuals aged 65 years and older, ECDC multi-country study. Stockholm: ECDC; 2021. Available at: https://www.ecdc.europa.eu/en/publications-data/interim-analysis-covid-19-vaccine-effectiveness-against-severe-acute-respiratory
8. Kotsiou OS, Papagiannis D, Fradelos EC, Perlepe G, Miziou A, Siachpazidou DS, et al. Understanding COVID-19 Epidemiology and Implications for Control: The Experience from a Greek Semi-Closed Community. Journal of clinical medicine. 2021;10(13):2765. Available at: https://www.mdpi.com/2077-0383/10/13/2765
9. European Centre for Disease Prevention and Control (ECDC). Options for the use of rapid antigen tests for COVID-19 in the EU/EEA - first update. Stockholm: ECDC; 2021. Available at: https://www.ecdc.europa.eu/en/publications-data/options-use-rapid-antigen-tests-covid-19-eueea-first-update
10. European Centre for Disease Prevention and Control (ECDC). Case definition for coronavirus disease 2019 (COVID-19). Stockholm: ECDC; 2020. Available at: https://www.ecdc.europa.eu/en/covid-19/surveillance/case-definition
11. To KK-W, Tsang OT-Y, Leung W-S, Tam AR, Wu T-C, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. The Lancet Infectious Diseases. 2020;20(5):565-74. Available at: https://www.sciencedirect.com/science/article/pii/S1473309920301961
12. Williams E, Bond K, Zhang B, Putland M, Williamson DA. Saliva as a noninvasive specimen for detection of SARS-CoV-2. Journal of Clinical Microbiology. 2020;58(8):e00776-20. Available at: https://journals.asm.org/doi/full/10.1128/JCM.00776-20
13. Brotons P, Perez-Argüello A, Launes C, Torrents F, Subirats MP, Saucedo J, et al. Validation and implementation of a direct RT-qPCR method for rapid screening of SARS-CoV-2 infection by using non-invasive saliva samples. International Journal of Infectious Diseases. 2021;110:363-70. Available at: https://www.sciencedirect.com/science/article/pii/S120197122100607X
14. Infectious Disease Society of America (IDSA). Nucleic Acid Amplification Testing (e.g. RT-PCR). Arlington: IDSA; 2021. Available at: https://www.idsociety.org/covid-19-real-time-learning-network/diagnostics/RT-pcr-testing/
15. European Centre for Disease Prevention and Control (ECDC). Considerations for the use of saliva as sample material for COVID-19 testing. Stockholm: ECDC; 2021. Available at: https://www.ecdc.europa.eu/en/publications-data/considerations-use-saliva-sample-material-covid-19-testing

16. World Health Organization (WHO). Laboratory biosafety guidance related to coronavirus disease (COVID-19): Interim guidance, 28 January 2021. Geneva: WHO; 2021. Available at: https://www.who.int/publications/i/item/WHO-WPE-GIH-2021.1
17. World Health Organization (WHO). Laboratory testing for coronavirus disease (COVID-19) in suspected human cases: interim guidance. Geneva: WHO; 2021. Available at: https://apps.who.int/iris/handle/10665/331501
18. World Health Organization (WHO). Guidance on regulations for the transport of infectious substances 2019 – 2020: applicable from 1 January 2019. Geneva: WHO; 2019. Available at: https://apps.who.int/iris/handle/10665/325884
19. World Health Organization (WHO). Country & Technical Guidance - Coronavirus disease (COVID-19). Geneva: WHO; 2021. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance-publications
20. European Centre for Disease Prevention and Control (ECDC). Diagnostic testing and screening for SARS-CoV-2. Stockholm: ECDC; 2021. Available at: https://www.ecdc.europa.eu/en/covid-19/latest-evidence/diagnostic-testing; https://www.ecdc.europa.eu/en/publications-data/sequencing-sars-cov-2
21. European Commission (EC). EU health preparedness: A common list of COVID-19 rapid antigen tests and a common standardised set of data to be included in COVID-19 test result certificates. Sixth update. Brussels: EC; 2021. Available at: https://ec.europa.eu/health/sites/default/files/preparedness_response/docs/covid-19_rat_common-list_en.pdf
22. European Centre for Disease Prevention and Control (ECDC) and World Health Organization - Regional Office for Europe (WHO/Europe). Methods for the detection and identification of SARS-CoV-2 variants. Stockholm and Copenhagen: ECDC and WHO/Europe; 2021. Available at: https://www.ecdc.europa.eu/en/publications-data/methods-detection-and-identification-sars-cov-2-variants
23. European Centre for Disease Prevention and Control (ECDC). Field Epidemiology Manual Wiki - Case-control studies Stockholm: ECDC; 2016. Available at: https://wiki.ecdc.europa.eu/fem/Pages/Case-control%20studies.aspx
24. Verani JR, Baqui AH, Broome CV, Cherian T, Cohen C, Farrar JL, et al. Case-control vaccine effectiveness studies: Preparation, design, and enrollment of cases and controls. Vaccine. 2017;35(25):3295-302. Available at: https://www.sciencedirect.com/science/article/pii/S0264410X17305157
25. Verani JR, Baqui AH, Broome CV, Cherian T, Cohen C, Farrar JL, et al. Case-control vaccine effectiveness studies: data collection, analysis and reporting results. Vaccine. 2017;35(25):3303-8. Available at: https://www.sciencedirect.com/science/article/pii/S0264410X17305133

Annex 1. List of variables, definitions, and coding

This table represents a selection of confounders. Variables can be included or excluded as necessary.

Variable name	Type	Values and coding	Definition
participate	Numeric (binary)	0 = No 1 = Yes	Agrees to participate
refuse	Text		Reasons refused to participate
contra	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Exclusion criteria: contraindication for COVID vaccination
id	Numeric (continuous)	Unique integer	Unique number for each record
dob	Date	dd/mm/yyyy	Date of birth of study participant
age	Numeric (continuous)	Integer	Age of each participant in years
sex	Numeric (binary)	0 = female 1 = male	Sex of study participant
occup	Numeric (categorical)	1 = [Occupation 1] 2 = [Occupation 2] 3 = [Occupation 3] 4 = [Occupation n] 5 = Other, specify:	Patient occupation (specify location/facility) should reflect the semi-closed setting being investigated (e.g. students, staff etc).
loc	Numeric (categorical)	1 = [Location 1] 2 = [Location 2] 3 = [Location 3] 4 = [Location n] 5 = Other, specify:	Patient location within semi-closed setting should reflect the semi-closed setting being investigated (e.g. office, factory floor, room).
smoke	Numeric (categorical)	0 = I've never smoked 1 = I stopped smoking more than one year ago 2 = I stopped smoking within the last year 3 = Yes, I currently smoke 8 = don't know	Smoking behaviour
weight	Numeric (continuous)	Integer	Weight of the study participant
height	Integer	Integer	Height of the study participant
onsetdate	Date	dd/mm/yyyy	Date of onset of symptoms
swabdate	Date	dd/mm/yyyy	Date swabbing
fever	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Fever
sore throat	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	sore throat
cough	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Cough
sudden onset of anosmia	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Anosmia
sudden onset of ageusia/dysgeusia	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Ageusia
shortness of breath/dyspnoea	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Dyspnoea
Variable name	Type	Values and coding	Definition
hosp	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Was hospitalized for respiratory infection during current outbreak
ICU (intensive care unit) admission	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Was hospitalized in ICU for respiratory infection during current outbreak

Variable name	Type	Values and coding	Definition
Mechanical ventilation	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Was under mechanical ventilation for respiratory infection during current outbreak
lab_res	Numeric (categorical)	0 = Negative 1 = Positive 2 = Not done 8 = Don't know	Laboratory result (positive/negative/not done)
lab_virus	Text		Laboratory result: virus type
lab_subtype	Text		Laboratory result: virus subtype
covidvacc	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Received COVID-19 vaccination
Covidvaccdate first	Date	dd/mm/yyyy	COVID-19 vaccination date first dose
Covidvaccdate second	Date	dd/mm/yyyy	COVID-19 vaccination date second dose
Covidvaccdate third	Date	dd/mm/yyyy	COVID-19 vaccination date third dose
Covidvacctype first	Numeric (categorical)	1 = Astra Zeneca 2 = Janssen 3 = Moderna 4 = Pfizer/Biotech 5 = Other, please specify	Type of vaccine (product name)
Covidvacctype second	Numeric (categorical)	1 = Astra Zeneca 2 = Janssen 3 = Moderna 4 = Pfizer/Biotech 5 = Other, please specify	Type of vaccine (product name)
Covidvacctype third	Numeric (categorical)	1 = Astra Zeneca 2 = Janssen 3 = Moderna 4 = Pfizer/Biotech 5 = Other, please specify	Type of vaccine (product name)
vaccinascert	Numeric (categorical)	1 = Vaccination card 2 = Vaccination registry 3 = Self-report 4 = Other, please specify 5 = Not documented	Vaccination ascertainment
vaccininfl	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	influenza vaccine in the current influenza season? (as of October 2021)
Vaccininfl_date	Date	dd/mm/yyyy	influenza vaccine Date
diabetes	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Diabetes and endocrine
heart_dis	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Heart disease
immuno	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Immunodeficiency and organ transplant
lungdis	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Lung disease
severitychron	Numeric (count)	Integer	Nb of hospitalizations previous year for the chronic disease
pregnant	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Pregnancy status
COVID symptoms prior	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	COVID-19 symptoms since beginning of pandemic, but prior to cluster
COVID symptoms prior_date	Date	dd/mm/yyyy	Date of onset COVID-19 symptoms prior to cluster
COVID-19_prior_lab	Numeric (categorical)	0 = Negative 1 = Positive 2 = Not done 8 = Don't know	Laboratory result of episode prior to cluster (positive/negative)
COVID-19_prior_lab_date	Date	dd/mm/yyyy	Date of lab results prior to cluster

Variable name	Type	Values and coding	Definition
COVID-19_prior_virus	Text		Laboratory result: virus type and subtype
COVID-19_prior_sero	Numeric (categorical)	0 = Negative 1 = Positive 2 = Not done 8 = Inconclusive	Rapid test detection antibodies to determine prior infection
COVID-19_prior_sero_date	Date	dd/mm/yyyy	Date of serological test
COVID-19_prior_sero_pos	Numeric (categorical)	0 = Total 1 = IgM 2 = IgA 3 = IgG	If positive, specify type of antibody detected (Total, IgM, IgA, IgG)

Annex 2. Closed setting investigation form

Information in this form should be completed every time a new cluster is identified in the semi-closed setting at the investigation team visit. The questionnaire will need to be adapted to the relevant context for each semi-closed setting. Policies and procedures available in the semi-closed setting should be consulted and compared with what is observed during the investigation.

1. Unique [Closed Setting] ID/Cluster number (if applicable)

2. Current status of the semi-closed setting
□ First identification of a case □ Recurrent □ Unknown

3. Semi-closed setting type (e.g. factory, office, school, open camp)

4. Data collector information	
Name of data collector	
Data collector institution	
Data collector telephone number	
Data collector email	
Form completion date (dd/mm/yyyy)	___/___/___

5. Interview respondent information	
First name	
Family name	
Occupation/Function	
Address	
Country	
Telephone (mobile) number	
Email	

6. Semi-closed setting description	
Number of individuals in semi-closed setting	___ Total Number individuals by different roles: ___ Operational ___ Administrative ___ Ancillary ___ Other (please specify)
Number of individuals in different areas of semi-closed setting:	___ Factory floor/classroom ___ Offices ___ Canteen ___ Area n ___ Other
Measures to restrict movement in the semi-closed setting	1 = Yes 0 = No 8 = Unknown • If Yes, specify:
Measures to limit mixing individuals in place	1 = Yes 0 = No 8 = Unknown • If Yes, specify how and for each area:
Physical distancing measures in place	1 = Yes 0 = No 8 = Unknown • If Yes, specify how and for each area:
Enforcement of hand hygiene in place	1 = Yes 0 = No 8 = Unknown

6. Semi-closed setting description	
	• If Yes, specify: When it was started/(or stopped), Training, Visual aids, Availability (water/soap, alcohol-based disinfectants)
Use of masks/other barrier measures in place	1 = Yes 2 = No 3 = Unknown • If Yes, specify how and for each area and when they started and stopped
Respiratory hygiene (cough etiquette, etc.) in place	1 = Yes 2 = No 3 = Unknown • If Yes, specify: Training pupils/staff, Visual aids, etc.
Temperature and humidity of the semi-closed setting monitored	1 = Yes 2 = No 3 = Unknown • If Yes, specify how and average/acceptable values for each area:
Ventilation of semi-closed setting assured	1 = Yes 0 = No 8 = Unknown • If Yes, specify how and for each area:
Cleaning and disinfection (surfaces, toilets, frequently touched objects, tablets, etc.), environmental sampling results, if possible	1 = Yes 0 = No 8 = Unknown • If Yes, specify how and for each area:
Water, sanitation and waste management	Give details:
Measures for sick individuals 1. General measures (stay home when symptomatic) 2. Measures when an individual develops or presents symptoms at the semi-closed setting	
Measures for individuals with underlying health conditions xxxxxx	

European Centre for Disease Prevention and Control (ECDC)

Gustav III:s Boulevard 40
169 73 Solna, Sweden

Tel. +46 858 60 1000
Fax +46 858 60 1001
www.ecdc.europa.eu

An agency of the European Union
www.europa.eu

Subscribe to our publications
www.ecdc.europa.eu/en/publications

Contact us
publications@ecdc.europa.eu

Follow us on Twitter
@ECDC_EU

Like our Facebook page
www.facebook.com/ECDC.EU

ECDC is committed to ensuring the transparency and independence of its work

In accordance with the Staff Regulations for Officials and Conditions of Employment of Other Servants of the European Union and the ECDC Independence Policy, ECDC staff members shall not, in the performance of their duties, deal with a matter in which, directly or indirectly, they have any personal interest such as to impair their independence. Declarations of interest must be received from any prospective contractor(s) before any contract can be awarded.
www.ecdc.europa.eu/en/about-us/transparency