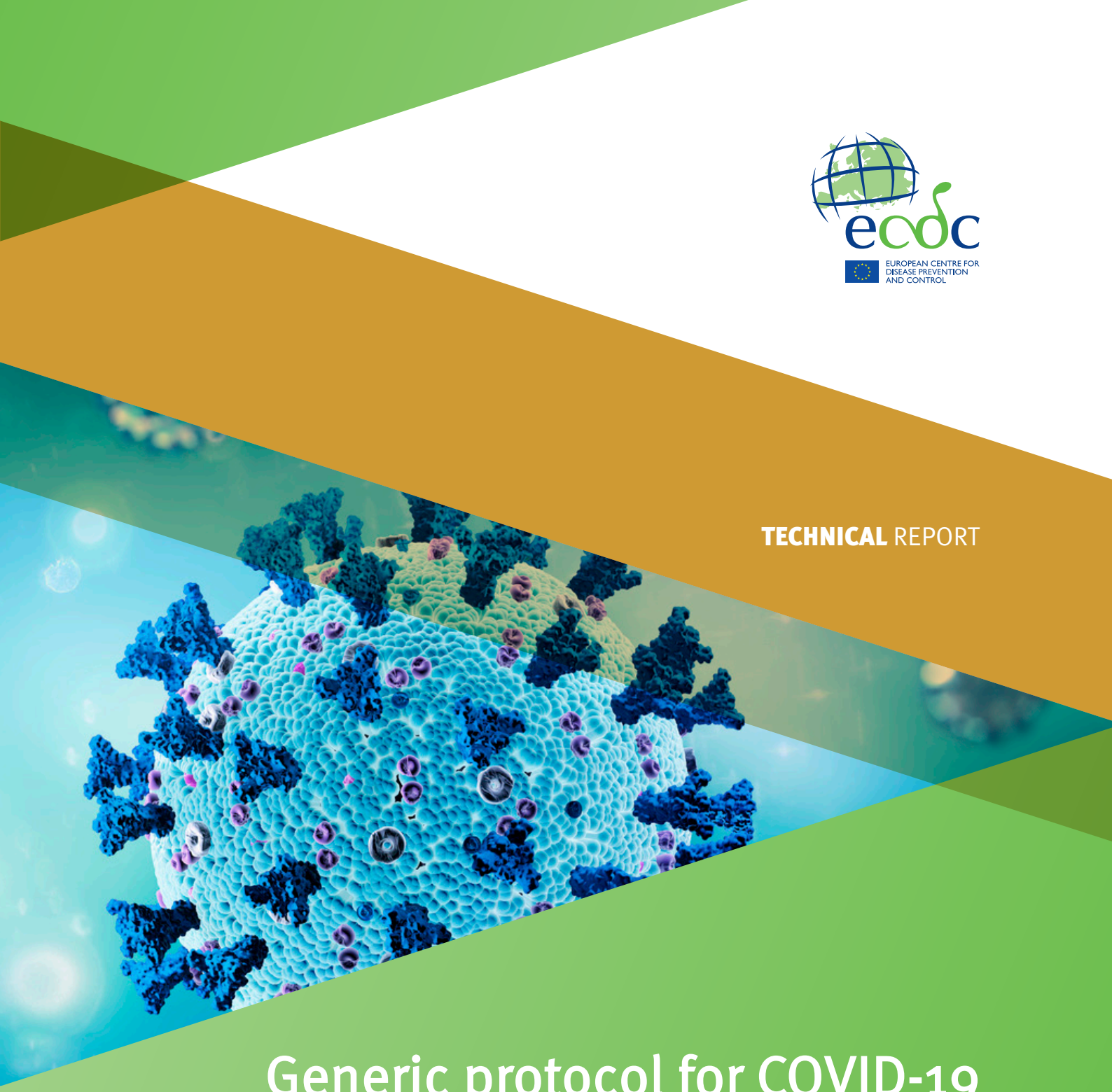

TECHNICAL REPORT

Generic protocol for COVID-19 vaccine effectiveness studies at long-term care facilities in the EU/EEA

Version 1.0

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ECDC TECHNICAL REPORT

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Abbreviations

COVID-19	Coronavirus disease 2019
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
EU	European Union
EEA	European Economic Area
EMA	European Medicines Agency
GDPR	General Data Protection Regulation
HDU	High dependency unit
HR	Hazard ratio
ICU	Intensive care unit
IPC	Infection prevention and control
LTCF	Long-term care facility
OR	Odds ratio
PPE	Personal protective equipment
RT-PCR	Reverse transcriptase polymerase chain reaction
RR	Rate ratio
RSV	Respiratory syncytial virus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOP	Standard operating procedure
VE	Vaccine effectiveness
VOC	Variant of concern
WHO	World Health Organization

Executive summary

The end of 2019 saw the emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19). By early August 2022, over 160 million cases and over one million deaths had been reported in the European Union/European Economic Area (EU/EEA)[1].

During 2021, first the variant of concern (VOC) Alpha and then the VOC Delta became the dominant viruses in circulation across the EU/EEA. At the beginning of December 2021, the Omicron VOC was introduced into the EU/EEA which then rapidly replaced SARS-CoV-2 Delta in most European Union/European Economic Area (EU/EEA) countries [2]. More recently, SARS-CoV-2 Omicron sub-lineages have also emerged [3].

As of 16 August 2022, six vaccines have been authorised by the European Medicines Agency (EMA) for use in the European Union (EU) [4], and many others are under development [5].

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

This protocol outlines the methods for a prospective cohort study in long-term care facilities (LTCFs) to evaluate the effectiveness of COVID-19 vaccines in preventing laboratory-confirmed SARS-CoV-2 symptomatic infection in LTCF residents. Given the priority assigned to older population groups for COVID-19 vaccination programmes, and the vulnerability seen for LTCF residents during the pandemic, ECDC encourages the active endorsement and implementation of this protocol to strengthen the evidence base for future policy decisions. The document is a ready-to-use tool to support establishment of studies with the primary objective of measuring product-specific COVID-19 vaccine effectiveness in residents of LTCFs. Additional secondary objectives are also proposed, which could be included as additional primary objectives depending on the circumstances. The document is broken down into several key sections including the outline of a protocol; definitions to use; a template for a protocol; laboratory methods; limitations and ethical considerations. In addition, the annexes provide templates of questionnaires for use at different points in time, an informed consent form and an outline for an analysis plan.

Background

Since the emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as the aetiological factor of coronavirus disease 2019 (COVID-19), and by early August 2022, the COVID-19 pandemic has resulted in over 160 million cases and over one million deaths in the EU/EEA [1].

During 2021, first the variant of concern (VOC) Alpha and then the VOC Delta were the dominant viruses in circulation across the EU/EEA. At the beginning of December 2021, the Omicron VOC was introduced into the EU/EEA and since then, it replaced SARS-CoV-2 Delta in most European Union/European Economic Area (EU/EEA) countries[2]. Omicron can to a degree evade the protective effects of antibodies elicited by vaccination or natural infection, depending on factors such as number of vaccinations or time since last vaccination, thus leaving large portions of the EU/EEA population susceptible to infection. This has resulted in sharp increases in the number of COVID-19 cases, reaching an unprecedented intensity of community transmission across the region [2]. More recently, SARS-CoV-2 Omicron sub-lineages have also emerged [3].

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 immunisation in a population is the most important method for minimising transmission. Having effective and safe vaccines against SARS-CoV-2 helps achieve this goal, while reducing morbidity and mortality among the population. International collaborative efforts have accelerated the development of COVID-19 vaccines. As of 16 August 2022, six vaccines had been authorised by the European Commission (EC) based on the scientific opinion of the European Medicines Agency (EMA) for use in the European Union (EU) [4], and many others are under development [5]. Vaccines currently authorised in the EU are: Comirnaty (Pfizer/BioNTech), COVID-19 Vaccine Valneva (Valneva), Jcovden (Janssen), Nuvaxovid (Novavax), Spikevax (Moderna), and Vaxzevria (AstraZeneca).

As the vaccines were first becoming available and in the context of limited supplies, target groups were identified for the prioritisation of COVID-19 vaccination. Most countries in the EU/EEA prioritised COVID-19 vaccination for both staff and residents of LTCF due to the high mortality rate among elderly residents [6, 7]. More recently, it has been recommended that individuals aged over 60 years and those with underlying comorbidities, irrespective of age, should receive an additional booster dose to prevent severe disease [8].

Evaluating the real-world COVID-19 vaccine performance informs understanding of the risks and benefits of vaccination programmes. Licensing of vaccines is based on clinical trial data, however people recruited to clinical trials for vaccines are often young and healthy, and therefore different from those who will receive vaccines in the real world [9]. Several factors can impact real-world vaccine effectiveness (VE), including transportation and storage conditions, vaccine administration, advanced age, presence of underlying medical conditions and previous SARS-CoV-2 infection. 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) VE against new emerging virus variants.

Real-world VE studies in LTCF can therefore answer questions about effectiveness in this vulnerable population. For example, the studies provide information on VE in the elderly and very elderly, those with one or more comorbidities, effectiveness of the vaccine against new strains of SARS-CoV-2 and the duration of vaccine protection, especially in older individuals [10] who will have been prioritised for vaccination earlier in the pandemic.

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, using the lessons learned from other VE studies, ECDC started building infrastructure to perform COVID-19 vaccine effectiveness studies. The infrastructure aims to build a system to regularly monitor VE and perform studies in different settings, and depending on the setting, to provide information on different outcomes (severe disease, moderate disease, infection, transmission, etc.) [11-13].

Given the priority assigned to older population groups for COVID-19 vaccination programmes, and the vulnerability that has been seen for LTCF residents during the pandemic, ECDC encourages the active endorsement and implementation of this protocol to strengthen the evidence base for future policy decisions.

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.

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 long-term care facility (LTCF) settings.

In this document, a cohort study design and methodology are proposed, where the study population at risk of infection is either exposed or not exposed to COVID-19 vaccination in the LTCF setting.

This document provides a ready-to-use tool to support EU/EEA Member States in developing a vaccine effectiveness study protocol adapted to their specific local/national setting. Under each paragraph, arrow marks with green-coloured text indicate the points that could be further expanded when creating an adapted protocol for local/national use.

Once adapted for the local/national setting, the protocol should be submitted for approval to the relevant national ethical review committee prior to implementation.

The protocol should be adapted and implemented taking into consideration all applicable local COVID-19 public health recommendations on vaccination, testing and non-pharmaceutical interventions.

In the event of a COVID-19 outbreak at a LTCF participating in the vaccine effectiveness study, outbreak investigation steps should be conducted in accordance with the local public health assessment and response. Such steps are not described in this document and risk factors for SARS-CoV-2 infection during an outbreak in a LTCF setting are not measured in this study protocol.

ECDC encourages the use of this protocol as a basis for studies to assess vaccine effectiveness in a LTCF setting, as its use in the EU/EEA can facilitate comparability of results from different LTCFs across EU/EEA Member States.

2. Outline of a protocol for vaccine effectiveness studies in a LTCF setting

The local/national protocol for vaccine effectiveness studies in LTCFs should have different sections, including the following:

- Background
- Aim and objectives of the study
- Study population, including inclusion criteria and definitions
- Study design
- Proposed data collection
- Plan of statistical analysis.

In a LTCF the study population is well-defined and generally not too large. As such, a prospective cohort study is the study design of choice.

This generic protocol should be adapted to suit the local/national LTCF settings and the local/national COVID-19 public health recommendations on vaccination, testing, and NPIs. The structure of this document allows for deletion of sections which are not applicable and therefore it can be used as a template for the local/national protocol to be developed.

2.1 Preliminary steps for designing a vaccine effectiveness study in a LTCF setting

The protocol template and the data collection tools should be adapted to the setting and national/local conditions. Various aspects of the setting and study design should be well defined when adapting the protocol template. Some of these aspects are set out below.

- Describe the LTCF setting (see Section 4.3.1):
  - type and size of LTCF setting;
  - number of residents, level of care, and 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. common areas, dining areas, recreational areas/rooms, entrances/exits/lifts); use of face masks; quality of ventilation in the 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 (PPE) if relevant, COVID-19 communication and information material (leaflets, posters, information sessions).
- Define cases: individuals testing positive for current SARS-CoV-2 infection. At a LTCF with a population that is not too large, the entire study population can be tested multiple times during the study period.
- Active case finding: if possible, individuals with fever and/or respiratory symptoms should be identified retrospectively (in the two weeks prior the symptom onset of the first case) as well as prospectively, and tested for SARS-CoV-2 infection. Active case finding might reveal symptomatic cases that were initially missed, increase the number of enrolled cases and, consequently, increase the power of the study analysis. Screening of the entire study population (for example with rapid antigen tests) may be considered to identify additional mild or asymptomatic cases.
- Describe cases in terms of time, place and person.

3. Definitions to use in the study protocol

3.1 Long-term care facility setting definition

For the purposes of this generic protocol, a LTCF setting should conform with the ECDC definition [14] and typically includes residents who:

- need constant (24 hours a day) supervision;
- need basic or high-skilled nursing care on a daily basis;
- are medically stable and do not need constant 'specialised medical care' (i.e. care administered by specialist physicians);
- do not need invasive medical procedures (e.g. ventilation).

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

In practice, the technical definition may vary depending on social, administrative and cultural circumstances.

3.2 Definition of a COVID-19 outbreak

An outbreak can be defined as one or more possible or confirmed COVID-19 case in the LTCF within a seven-day period, however the national/local definitions should be used as applicable [14]. The study protocol should define the outbreak definition used and all outbreak management procedures to be implemented in the event of an outbreak (as required under national/local guidelines).

Given the low threshold for defining an outbreak at a LTCF, outbreaks will occur during the course of vaccine effectiveness studies in LTCFs. Conducting a concurrent vaccine effectiveness study during the assessment (including any other epidemiological investigations – for example 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 where such a study could be prioritised.

3.3 Definition of the study population

The study population is defined as the resident population at risk of SARS-CoV-2 infection within the LTCF where the study is being conducted and who are eligible for COVID-19 vaccination.

4. Template for a protocol for a cohort study

4.1 Background

➢ Add information here about local or national protocols for COVID-19 (particularly those applying to LTCFs), describe the epidemiological context and any other information relevant to the study and study sites.

4.2 Study objectives

4.2.1 Primary objective

When measuring product-specific COVID-19 vaccine effectiveness (VE) in LTCF residents eligible for vaccination against all symptomatic laboratory-confirmed SARS-CoV-2 infection:

➢ Investigators should note that achieving an objective of VE for all laboratory-confirmed SARS-CoV-2 infections (i.e. both asymptomatic and symptomatic) will require regular swabbing of the resident population which may be logistically difficult, not conform with local screening guidelines, prove costly and raise ethical concerns in vulnerable and frail populations. If an objective of VE for all laboratory-confirmed SARS-CoV-2 infections is pursued, the protocol should be adapted accordingly, especially with regard to testing frequency and methods (saliva samples could be considered for asymptomatic screening).

This objective can be achieved using data from individual participating sites where sample size allows, or by analysing data pooled from several participating sites.

4.2.2 Secondary objectives

Depending on sample size, to measure COVID-19 VE by:

- disease severity: mild and severe symptomatic laboratory-confirmed COVID-19 infection;
- SARS-CoV-2 variants of interest/concern;
- vaccination status: partially or fully vaccinated, including possible booster or additional doses, vaccine product and by combination of different products and time since vaccination and between vaccine doses;
- history of previous infection, either confirmed or possible;
- age groups, especially in the elderly and very elderly;
- different high-risk comorbidities, including resident frailty;
- other sociodemographic characteristics (e.g. gender, ethnicity).

As vaccination coverage at LTCFs is reported to be very high, investigators could consider as a secondary objective the estimation of comparative VE (i.e. comparing VE between different groups) by:

- number of doses (e.g. VE for two doses compared to VE for three doses, or VE for three doses versus four doses);
- VE by different vaccine brands (or combinations of brands), especially if there is diversity in vaccines or if novel vaccines are used at the LTCF (e.g. VE for one brand versus VE for another brand);
- time since last vaccination (e.g. last dose within six months versus those last vaccinated over six months ago);
- time between doses, particularly for booster doses (e.g. booster given within six months of previous vaccination versus booster given >6 months after previous vaccination).

➢ Each study site should specify the secondary objectives of their study.

4.3 Methods

4.3.1 Study setting

The study is to be conducted among residents of LTCFs because of the high mortality and morbidity in the population of older and vulnerable adults. The LTCF recruited for this study should conform with ECDC's definition [14] and typically include residents who:

- need constant (24-hour) supervision;
- need basic or high-skilled nursing care on a daily basis;
- are medically stable and do not need constant 'specialised medical care' (i.e. care administered by specialist physicians);
- do not need invasive medical procedures (e.g. ventilation).

Furthermore, LTCFs should be selected that preferably:

- have existing continuous surveillance or registers of infections;
- have residents with a median stay of at least the duration of a six-month study period (see Section 4.3.6);
- are recruited in the following order of preference: general nursing homes > residential homes > mixed type facilities (see Table 1 for descriptions).
- do not include facilities such as hospital long-term care wards, hostel care, sheltered care houses, day centres, home-based centres or sheltered housing.

Table 1. Description of LTCF types

LTCF Type	Description
General nursing homes	In these facilities, residents need medical or skilled nursing and supervision 24 hours a day. These facilities principally provide care to older people with severe illnesses or injuries.
Residential homes	In these facilities residents are unable to live independently. They require supervision and assistance for day-to-day living. These facilities usually include personal care, housekeeping and three meals a day.
Mixed LTCFs	These facilities provide different types of care at the same facility.

**This classification does not imply that the characteristics of residents in each facility type are strictly homogenous.*

➢ Each local/national protocol should describe the participating LTCF against criteria such as type and size (e.g. number beds, types of residents), number of COVID-19 cases reported since the beginning of the pandemic (until the start of the study), along with IPC measures and their coverage. Furthermore, data on the local and national incidence of COVID-19, implementation of public health and social measures should be collected [15].

4.3.2 Study design

This is a prospective longitudinal cohort study of residents at LTCFs eligible for vaccination.

4.3.3. Study population

The study population will be composed of residents in participating LTCFs, eligible for vaccination, with no contra-indication for receiving the COVID-19 vaccine.

➢ Although they are a key group LTCF staff have not been included in this protocol due to major differences in the study design, particularly in objectives and, consequently, sampling and survey procedures. If investigators wish to investigate VE in LTCF staff, they should adapt the current protocol for healthcare workers available through ECDC and WHO[1].

4.3.4 Inclusion criteria

All residents present at the site on Day 1 of the study will be included and all those admitted during the period of the study.

Residents enrolled into the study should have an anticipated stay of longer than two months. Residents admitted for short-term care (e.g. transition from hospital to home or for respite care) should be excluded. The proposal to exclude short-stay residents is partly pragmatic, as data will only be collected for a short time before they will be lost to follow-up, and partly technical, as short-term residents will have different exposures (e.g. in hospital settings) which may confound results.

Residents who have already been vaccinated against COVID-19 as part of the routine COVID-19 vaccine roll-out can be included, as long as information can be collected on vaccination status (i.e. vaccine brand(s), number of doses and dates of vaccination, see Section 4.4.1) and previous history of infection (i.e. date of previous infection, case status, diagnostic tests).

[1] World Health Organization. Cohort study to measure COVID-19 vaccine effectiveness among health workers in WHO European Region: Guidance Document. Copenhagen: WHO Regional Office for Europe; 2021.

4.3.5 Exclusion criteria

Residents of the LTCF who satisfy any one of the following five exclusion criteria should not be recruited to the study:

- not eligible for COVID-19 vaccination;
- vaccination is contra-indicated;
- residents who are scheduled to stay <2 months (i.e. for transition or respite care);
- informed consent has not been given by the resident or their nominated guardian;
- residents who have already been vaccinated against COVID-19 vaccine in clinical trials.

4.3.6 Study period

The study should be conducted only after the study protocol is approved by the relevant ethical review committee. The study period should be for a minimum of four months and a maximum of six months, depending on local circumstances.

➢ Each individual study site should define the study period.

4.4 Exposure

4.4.1 Vaccination status documentation

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 medical records, vaccine registry, vaccination card or any potential data source. Participants should be notified through the informed consent form that these additional sources will be accessed, where relevant, in order to confirm their vaccination status.

For each dose of COVID-19 vaccine received vaccine documentation should include:

- dose number (e.g. first, second, third, fourth)
- date of vaccination
- vaccine brand
- vaccine batch
- ascertainment (e.g. documented in medical records, vaccine registry, vaccination card, etc.)

➢ Each individual study site should describe how vaccination status will be ascertained.

4.5 Definition of outcomes

The primary outcome should be a confirmed SARS-CoV-2 infection, detected by laboratory RT-PCR in any symptomatic participant that meets ECDC's case definition of COVID-19 [17].

ECDC's case definition of COVID-19 [16] refers to those reporting one or more of the following clinical criteria:

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

COVID-19 disease severity, among participants who show symptoms consistent with ECDC's COVID-19 case definition and have SARS-CoV-2 infection detected by laboratory RT-PCR, can be categorised in the following stages:

- **mild disease:** reported symptoms consistent with ECDC's definition of COVID-19 requiring attendance at a medical facility, but no further assistance
- **moderate disease:** reported symptoms consistent with ECDC's definition of COVID-19, requiring hospitalisation but not oxygen treatment, or assistance but not hospitalisation.
- **severe disease:** reported symptoms consistent with ECDC's definition of COVID-19, requiring hospitalisation and oxygen treatment
- **very severe disease:** reported symptoms consistent with ECDC's definition of COVID-19, requiring either admittance to an intensive care unit, and/or intubation or mechanical ventilation.

➢ Investigators should note that to achieve an objective of VE for all laboratory-confirmed SARS-CoV-2 infections (i.e. both asymptomatic and symptomatic), the primary outcome should be amended to confirmed SARS-CoV-2 infection detected by laboratory RT-PCR in any participant, and an additional disease severity stage (Asymptomatic: no reported symptoms consistent with the ECDC definition of COVID-19) should be added.

4.6 Sample size

The sample size should allow the provision of robust estimates for the primary study objective.

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

Table 2 presents the sample size required to obtain a detectable VE (based on a hazard ratio) between 50% and 90%, with COVID-19 vaccine coverage among study participants ranging from 60–90% (5% significance level and 80% power level), at different levels of incidence of SARS-CoV-2 infection among unvaccinated participants during a six-month study.

The sample size calculation does not account for any study drop-outs, or unvaccinated individuals who choose to be vaccinated during the study period, or for stratification of analyses.

The estimates presented in Table 2 were calculated using the following command in STATA (version 16) statistical software:

```
power exponential (0.025 0.05 0.1), power(0.8) hratio(0.1(0.1)0.5)
fperiod(0.5) p1(0.1(0.1)0.4) table(N N1 Ea1 N2 Ea2 p1 hratio h1
```

Table 2. Sample size estimation (for one stratum), assuming six months follow up

Yearly hazard rate in unvaccinated	Vaccine effectiveness (%)	Vaccine coverage (%)	Total sample size	Unvaccinated		Vaccinated	
				Number	Number events	Number	Number events
0.1	90	90	765	77	4	688	3
		80	508	102	5	406	2
		70	437	131	6	306	2
		60	420	168	8	252	1
	80	90	1 199	120	6	1 079	11
		80	753	151	7	602	6
		70	626	188	9	438	4
		60	589	236	12	353	4
	70	90	1 850	185	9	1 665	25
		80	1 123	225	11	898	13
		70	912	274	13	638	9
		60	843	337	16	506	8
	60	90	2 888	289	14	2 599	51
		80	1 714	343	17	1 371	27
		70	1 369	411	20	958	19
		60	1 250	500	24	750	15
	50	90	4 678	468	23	4 210	104
		80	2 733	547	27	2 186	54
		70	2 155	647	32	1 508	37
		60	1 945	778	38	1 167	29
0.05	90	90	1 518	152	4	1 366	3
		80	1 008	202	5	806	2
		70	866	260	6	606	2
		60	832	333	8	499	1
	80	90	2 380	238	6	2 142	11
		80	1 493	299	7	1 194	6
		70	1 242	373	9	869	4
		60	1 167	467	12	700	3
	70	90	3 672	368	9	3 304	25
		80	2 227	446	11	1 781	13
		70	1 809	543	13	1 266	9
		60	1 672	669	17	1 003	7
	60	90	5 729	573	14	5 156	51
		80	3 399	680	17	2 719	27
		70	2 714	814	20	1 900	19
		60	2 475	990	24	1 485	15

Yearly hazard rate in unvaccinated	Vaccine effectiveness (%)	Vaccine coverage (%)	Total sample size	Unvaccinated		Vaccinated	
				Number	Number events	Number	Number events
	50	90	9 274	928	23	8 346	104
		80	5 417	1 084	27	4 333	54
		70	4 270	1 281	32	2 989	37
		60	3 853	1 541	38	2 312	29
0.025	90	90	3 026	303	4	2 723	3
		80	2 007	402	5	1 605	2
		70	1 726	518	6	1 208	2
		60	1 658	663	8	995	1
	80	90	4 743	475	6	4 268	11
		80	2 974	595	7	2 379	6
		70	2 473	742	9	1 731	4
		60	2 323	929	12	1 394	3
	70	90	7 313	732	9	6 581	25
		80	4 435	887	11	3 548	13
		70	3 602	1 081	13	2 521	9
		60	3 328	1 331	17	1 997	7
	60	90	11 412	1 142	14	10 270	51
		80	6 769	1 354	17	5 415	27
		70	5 404	1 621	20	3 783	19
		60	4 928	1 971	24	2 957	15
	50	90	18 466	1 847	23	16 619	104
		80	10 783	2 157	27	8 626	54
		70	8 499	2 550	32	5 949	37
		60	7 670	3 068	38	4 602	29

Each participating country should aim to recruit a minimum of 600 participants from national study sites.

- Each participating country and study site should define the expected sample size.
- The sample sizes presented in Table 2 will need to be reviewed if investigators wish to calculate comparative VE. It is probable that larger sample sizes may be required as the expected comparative VE will be much lower and yearly hazard rates may be much lower in a highly vaccinated population.

If multiple countries conduct studies using comparable study protocols, the results could be pooled. With an anticipated five countries conducting comparable studies, each with a minimum of 600 participants, the total pooled sample size would be approximately 3 000 participants.

4.7 Study procedures

4.7.1 Study preparation and identification of potential participants

After the study has been approved by the relevant ethical review committee, investigators should make themselves available to residents and their proxies and guardians to describe the study to answer all questions for potential participants, either individually or in groups.

Either all or a random selection of residents should be invited to participate in the study. Separate lists of all residents eligible for vaccination at the LTCF should be obtained at the beginning of the study and these will constitute the sampling frame (T_0) from which participants will be invited into the study, irrespective of their intention of being vaccinated or their vaccination status. If a sample of LTCF residents are to be recruited, the sampling frame (T_0) will be used to select a random sample proportionally representative of either the physical structure (e.g. wards, departments or buildings) or types of residents (e.g. age, frailty) at the facility. Participants not wishing to be involved in the study will be replaced by the next individual on the list.

- Each individual study site should define the selection procedure employed to establish the LTCF cohort.

4.7.2 Participant enrolment: questionnaire, respiratory sample and serology sample

All participants should provide informed consent prior to their enrolment into the study (see Section 7 for more details). Study staff should describe the study in detail, answer all questions and review the informed consent form with the potential participant (and/or their guardian) in a private area designated for study use. If feasible, to assess non-response/non-participation bias, study staff should provide a short set of anonymous questions to individuals that did not wish to participate. For this group, the minimum information collected should include age, sex and reasons for declining, and whether a guardian declined on behalf of a resident.

Once informed consent has been obtained, participants should be enrolled, irrespective of their individual vaccination status. Participants should also:

- have a nasal, naso- or oropharyngeal swab for RT-PCR, collected by an appropriately trained staff member;
- complete an enrolment questionnaire that includes details of demographics, previous history of SARS-CoV-2 infection, comorbidities including frailty scores, vaccination status for COVID-19 and other infections (e.g. influenza), and any recent exposure to confirmed or possible COVID-19 cases.

4.8 Active follow-up

The objective of the follow up is to identify new cases of SARS-CoV-2 infection, changes in vaccination status (e.g. unvaccinated who received the vaccine, those vaccinated with one dose who received the second dose, etc.) and changes in potential exposure (e.g. contact with COVID-19 cases) among the cohort of participants.

Study participants will be actively followed up as detailed below (see also Table 3).

- **Testing using Rapid Antigen Tests (RATs) or RT-PCR (followed by genomic sequencing where possible) -** swabs (nasal/naso- or oropharyngeal swabs as recommended by local testing guidelines) are to be collected from participants who report symptoms compatible with a SARS-CoV-2 infection and tested by RT-PCR. An appropriately trained staff member should collect the swab.
  Participants diagnosed with SARS-CoV-2 infection should be followed-up for outcomes, including disease severity. Site investigators should select all or a proportion of SARS-CoV-2 viruses from participants with a confirmed infection for genetic sequencing.
  If screening or testing asymptomatic residents at the LTCF, investigators should consider the study objectives outlined below. Investigators could consider using RATs for regular screening of asymptomatic residents (individuals with positive RAT results could be subsequently tested using RT-PCR for confirmation and genetic sequencing). Appropriately-trained staff members should collect the RAT specimen or observe (and assist/advise as needed) for self-collected specimens.
- **Monitoring -** participants are followed up by means of a weekly survey to report changes in health (i.e. symptoms compatible with SARS-CoV-2 infection) or vaccination status, as well as possible exposure. The questionnaire can be completed directly by the participant, by a study site monitor or a guardian as part of the regular weekly contact.

Table 3. Timing of questionnaires and specimen collection

Timing in the study	Questionnaire	Laboratory testing
Enrolment	Enrolment questionnaire	Nasal/naso- or oropharyngeal swab or saliva specimen
Follow-up		
Weekly†	Follow-up questionnaire	Nasal/naso- or oral-pharyngeal swab or saliva specimen†
Onset of symptoms*	Follow-up questionnaire	Nasal/naso- or oral-pharyngeal swab or saliva specimen
Confirmed SARS-CoV-2 infection*	Medical attention questionnaire	Genetic sequencing of all or a sample of confirmed cases

** Compatible with ECDC COVID-19 case definition [14]*
† Includes testing or screening of asymptomatic residents if screening measures deployed.

➢ Each study site to describe precisely all the study procedures, including testing methods and frequency.

Note: Irrespective of the sampling regimen proposed in the vaccine effectiveness study, the appropriate screening should be deployed (Table 4) according to national testing policy or, if one or more possible/confirmed COVID-19 cases have been identified at the LTCF [14]. If residents are screened as part of national policy or if asymptomatic residents are tested in response to one or more possible or confirmed cases, investigators should consider the feasibility of including the estimation of VE against infection acquisition as a study objective.

LTCFs should ensure that necessary IPC measures are implemented, surveillance for COVID-19 is undertaken and timely screening for SARS-CoV-2 infection is conducted. Staff should report any respiratory symptoms, self-isolate and be tested for COVID-19 according to local recommendations or procedures (See also ECDC guidance 'Infection prevention and control and preparedness for COVID-19 in healthcare settings – sixth update' [17]).

Table 4. Testing recommendations for LTCF based on different epidemiological scenarios

Measure/scenario	Laboratory testing of residents
No cases	Affected area: random samples, dependent on testing capacities* Unaffected area: dependent on national testing policy for LTCFs.
≥1 possible case	As soon as possible, test at least all possible case(s)*.
≥1 confirmed case	Comprehensive testing of all residents, including those who have died, dependent on testing capacity*. Post-mortem testing (as per local protocols) should be considered for any residents who die during a time period close in proximity.

Affected area: ongoing or presumed ongoing community transmission; according to definition in The European Surveillance System (TESSy).
Testing schemes should be in line with national recommendations for LTCFs and dependent on the epidemiological situation in the country and region and should include testing of asymptomatic residents and staff.
**If testing capacity is limited, consider random testing or a pooling of samples*
https://jamanetwork.com/journals/jama/fullarticle/2764364

4.9 Data collection and data sources

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

The minimum data that should be collected at enrolment are:

- age;
- sex;
- previous SARS-CoV-2 infection (clinical or laboratory confirmed);
- vaccination status for COVID-19 and other respiratory pathogens (influenza, pneumococcus);
- contact or exposure to a possible or confirmed case(s) SARS-CoV-2 at LTCF in the previous 14 days;
- molecular testing results;
- clinical history including chronic diseases (see Annex 1 for proposed list) and frailty scores;
- personal exposure (number of external visitors, visits outside LTCF) in the previous 14 days.

During weekly follow-up, the minimum data that should be collected are:

- report of symptoms compatible with SARS-CoV-2 infection;
- molecular test results if resident reports symptoms compatible with a SARS-CoV-2 infection;
- change in vaccination status for COVID-19, influenza and pneumococcus;
- contact or exposure to a possible or confirmed case(s) SARS-CoV-2 at LTCF in the previous seven days;
- personal exposure (number of external visitors, visits outside LTCF) in the previous seven days.

Where participants receive a confirmed diagnosis of SARS-CoV-2 infection, the site investigators should collect the following data during follow-up:

- symptoms with date of onset;
- date of PCR testing and PCR results;
- clinical course of infection (including out-patient and in-patient visits);
- changes in vaccination status;
- risk of exposure for other LTCF residents.

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

Table 5. Data collection of common variables (key variables that should be collected, optional variables recommended) and questionnaires to be used

Categories	Variable	Key/optional variable	Enrolment questionnaire T1	Follow-up questionnaire
Socio Demographic	Age	Key	✓	X
	Sex	Key	✓	X
	Ethnicity	Optional	✓	X
Individual behaviour	Smoking (current/past/never)	Key	✓	X
	BMI (height and weight)	Key	✓	X
	Alcohol use	Optional	✓	X
COVID-19 vaccination	Vaccine offered	Key	✓	✓ (if status changes)
	Vaccine dose (i.e. first, second, third, fourth)	Key	✓	✓ (if status changes)
	Vaccination date(s) (for each dose)	Key	✓	✓ (if status changes)
	Vaccine product (for each dose)	Key	✓	✓ (if status changes)
	Vaccine batch (for each dose)	Key	✓	✓ (if status changes)
	Source used for vaccine ascertainment	Key	✓	✓ (if status changes)
Other vaccinations	Influenza (vaccine type/brand and date)	Key	✓	✓ (if status changes)
	Pneumococcal (year)	Optional	✓	✓ (if status changes)
SARS-CoV-2 infection	Laboratory confirmed/clinical/self-reported	Key	✓ (last episode)	✓ (If reported)
	List of symptoms	Key	✓ (last episode)	✓ (If reported)
	Date of onset	Key	✓ (last episode)	✓ (if reported)
	Severity	Key	✓ (last episode)	✓ (if reported)
Contact with SARS-CoV-2 in LTCF	Contact with possible COVID-19 cases and confirmed SARS-CoV-2 infections	Key	✓	✓ (if status changes)
Clinical history	Frailty score	Key	✓	X
	Diagnosis chronic conditions (see Annex 1)	Key	✓	X
	Medication for chronic conditions (see Annex 1)	Optional	✓	X
Individual behaviours	Number of visitors external to LTCF	Key	✓	✓
	Number of external visits	Key	✓	✓
Laboratory results	PCR	Key	✓	✓ (if reported)
	Variant	Key	✓ (if reported)	✓ (if reported)

➢ Each individual study site should list variables collected at enrolment and during follow-up.

4.9.1 Data sources

Data can be collected through questionnaires completed by the study monitors or study participants, electronic medical records, vaccine registries or other relevant sources. Once collected, data should be entered into a centralised on-line platform which conforms with international standards (e.g. ISO 027001), General Data Protection Regulation (GDPR) and national legislation and regulations for the hosting of personal medical data.

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

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

5. Laboratory methods

5.1 Specimen collection

Respiratory samples, including nasal, naso- or oropharyngeal swabs, are to be taken by a trained healthcare worker (e.g. research nurse or LTCF staff). Where saliva specimens are being collected for testing, these should either be collected by a trained healthcare worker or by the participant, being observed by a trained healthcare worker (with instruction provided to ensure good sample collection).

All biological sampling for SARS-CoV-2 RNA will follow WHO COVID-19 technical guidance documents on the proper handling and processing of potentially infectious specimens (Laboratory biosafety guidance related to coronavirus disease (COVID-19), published 28 January 2021 and Laboratory testing for coronavirus disease (COVID-19) in suspected human cases, published 19 March 2020), as well as WHO's general laboratory guidance (General guidance of laboratory biosafety- third edition, updated 2004).

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

Note: Given that guidance related to SARS-CoV-2 may be subject to rapid change, it is recommended that investigators check for updates to these documents before initiating the study to ensure that current recommendations are being followed.

5.2 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 WHO's website.[2]

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

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

If participants consent, the samples can be entered into a biobank for future research projects.

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

5.3 Specimen testing

- Each study site should describe all the laboratory procedures:
  - samples taken, storage, transport
  - kits used and performance
  - participation in quality assurance/quality control schemes
  - selection of specimens for sequencing.

5.3.1 Molecular testing

Laboratory guidance for molecular testing for COVID-19 can be found on the WHO and ECDC websites. Several assays that detect SARS-CoV-2 have recently been developed and the protocols or standard operating procedures (SOPs) can also be found on WHO's website. Quality assurance of assay performance at sites should be undertaken using international, national or research standards [18].

Testing for SARS-CoV-2 with RT-PCR should be undertaken as followings and at the specified points in time:

- upon enrolment, with specimens collected using nasal, naso- or oropharyngeal swab;
- for all symptomatic participants who meet the ECDC suspected case definition, with a specimen collected using nasal, naso- or oropharyngeal swab.

[2] WHO technical guidance publications: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance-publications

If possible, where individuals are symptomatic, RT-PCR should also be performed for other respiratory pathogens, such as influenza and respiratory syncytial virus (RSV), at the same time as COVID-19.

As described in Section 4.8, samples collected from asymptomatic residents should be molecularly tested if screening or testing is being performed at the LTCF as a result of national policies or in response to one or more possible or confirmed COVID-19 cases having been identified in the facility [14].

- Although nasal, naso- or oropharyngeal swabs are proposed in the study protocol, investigators may wish to consider the use of saliva swabs/specimens. Saliva swabs/specimens can be used in some, but not all, European countries for the diagnosis of SARS-CoV-2 infections [19]. Although saliva samples have a lower sensitivity than nasal, naso- or oropharyngeal swabs [20], both types of swabs are considered to have similar performance [21], especially in the acute phases of infection [22].

5.3.2 Genetic sequencing

All, or a random sample of SARS-CoV-2 RT-PCR positive specimens collected from study participants should be further characterised using genetic sequencing [18, 23]. It is particularly important to undertake genetic sequencing during the study to understand whether changes in vaccine effectiveness could be due in part to mutations in the circulating virus. Investigators should also ensure genetic sequences are uploaded into the appropriate sequencing data platform (for example, the GISAID or ENA platform).

6. Limitations

- **Laboratory tests:** misclassification of the outcome can occur due to problems with the test performance. In the analysis, it is possible to adjust for sensitivity and specificity of the tests. Sites will employ different tests and therefore investigators should seek to use common international, national or research standards to address possible variation in test performance at sites. At present, the UK National Institute of Biological Standards and Control offers international standards for molecular and serological testing [24].
- **Selection bias:**
  - **Previous infections:** the study population may have been highly exposed to SARS-CoV-2 infection. Individuals previously infected may be less likely to accept vaccination and may have some immunity. This will result in an underestimation of the VE.
  - In the absence of serology, the previous infection status of residents will need to be ascertained through self-reporting or documented evidence. As all residents will be screened for possible SARS-CoV-2 infection if one or more confirmed COVID-19 cases are reported at an LTCF, documented evidence of previous infection will have a similar validity to that of serology [25].
  - **Frailty bias**: individuals who are in a state of 'extreme frailty', many of whom will be resident in LTCFs, may not be offered vaccination and yet, if infected, are more likely to have severe disease. In this situation, the VE will be over-estimated.
  - **Negative confounding:** conversely, individuals who have a high risk of developing severe disease (i.e. those with chronic conditions) may be more likely to be vaccinated and therefore VE will be underestimated.
- **Reporting bias:** vaccinated cases may be more or less likely to report symptoms and VE against symptomatic SARS-CoV-2 may be overestimated or underestimated accordingly.
- **High vaccine coverage:** sites that have very high vaccine coverage in residents may find:
  - The validity of the study is reduced due to an insufficient number of outcomes in the unvaccinated study population. If vaccine coverage is very high, alternative methods may be required to estimate vaccine effectiveness (e.g. retrospective cohort study designs);
  - selection bias as those study participants who remain unvaccinated may have very different exposures and/or precedents to those who have been vaccinated.
- **Sample size/power:** inadequate sample sizes may limit the power of some stratified or secondary analyses. Furthermore, if vaccine coverage is very high in the study population, the validity of the study may be reduced (see above). In such circumstances, retrospective analysis of data collected at enrolment will be employed to estimate VE.
- **Unmeasured or residual confounding** between vaccinated and unvaccinated may occur – e.g. risky behaviour, beliefs affecting exposure and vaccine acceptancy.
- **The quality of self-reporting information** may vary between the vaccinated and unvaccinated.
- **Differences of incidence and vaccination policy and coverage over time or between LTCFs:** the risk of exposure to the virus and the vaccination coverage will differ among LTCFs (if several LTCFs are included), between regions/countries (if a multicentre study is conducted) and over time. Multi-level analysis and adjustment by time will be required to minimise the effect of this differences in exposure.

7. Ethical considerations

Studies of COVID-19 vaccine effectiveness at a LTCF should be approved by the relevant local ethics review committee.

All residents approached about enrolment should be informed that participation is voluntary and that they will be able to withdraw from the study, without justification, at any time without consequences.

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

The informed consent form should include a description of the methods and frequency for collecting respiratory samples, and clinical and epidemiological data for the intended purpose of the investigation. Informed consent should also mention how the data collected will used (for example, if pooling across study sites or countries is planned) and that samples may be shipped outside of the country for additional testing (if applicable) and used for future research purposes (if applicable).

➢ Each study site should obtain ethics review committee approval and collect informed consent.

8. Data governance

Biological materials and related data should only be collected and stored in cooperation with local health authorities. The governance structure of any such data collection should represent the original setting. All governance systems should follow the principle of accountability and maintain good stewardship of stored biological materials and related data. None of the regulations concerning the storage, use and fate of biological samples should contradict or overrule conditions originally stated in (broad) informed consent documents and agreed to by research participants.

Site-specific protocols, along with informed consent forms, should address governance issues surrounding biological materials and data. Data governance statements should state the length of time for which data will be stored, when data will be destroyed, who will have access to data during and after the study and how participants can withdraw permission for use of their data.

All points relating to governance of biological samples and data should be addressed in the informed consent form. For more information, please see International Ethical Guidelines for Health-related Research Involving Humans[3].

9. Prevention of SARS-CoV-2 infection in investigation personnel

Study staff should be trained in IPC procedures (standard contact, droplet, contact and airborne precautions, as determined by national or local guidelines). These procedures should include proper hand hygiene and the correct use of medical or respiratory face masks, if necessary. Investigators should review ECDC guidance for IPC in healthcare settings [17]. Furthermore, investigators can complete WHO's online training course 'Infection Prevention and Control (IPC) for Novel Coronavirus (COVID-19)'[4].

10. Risks and benefits for subjects

This study poses minimal risk to participants, involving the simple collection of respiratory specimens in response to symptoms compatible with a SARS-CoV-2 infection which would be carried out as part of routine healthcare. 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 timely detection of SARS-CoV2 infection, which would then allow for appropriate monitoring and treatment. The primary benefit of the study is indirect in that the data collected will help to measure the effectiveness of the COVID-19 vaccines and guide vaccination policies.

11. Dissemination of results

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

12. Organisation of study

12.1 Study leader

At each study site, a principal investigator will coordinate the study and the investigators involved.

12.2 Human resources

At each LTCF or network of LTCFs, an investigator will be in charge of monitoring data collection at LTCF level. Study investigators at the LTCF will ensure proper information documentation for the study at the site (e.g. ethical approval, archiving of informed consent) and undertake and/or oversee the collection of information from participants.

12.3 Standard operating procedures

Standard operating procedures (SOPs) should be used by investigators at all stages of the study for identification of study subjects, data collection, specimen collection, laboratory methods, data entry, monitoring, etc.

- Each study site should develop (or adapt pre-existing) study SOPs to be used by the study team

[3] 'International Ethical Guidelines for Health-related Research Involving Humans' available at: https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf

[4] WHO online training course 'Infection Prevention and Control (IPC) for Novel Coronavirus (COVID-19)' available at: https://openwho.org/courses/COVID-19-IPC-EN

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Annex 1. Questionnaire

Note: personal information should be kept confidential in accordance with local data security.

Example of variables, definitions and coding of study data

List of questionnaires:

1. Pre-enrolment questionnaire (to be completed by study monitor)
2. Enrolment questionnaire (to be completed by resident, staff or study team)
   a. Identifier and contact details
   b. Socio-demographic information
   c. Individual behaviours
   d. Vaccination history: COVID vaccine
   e. Vaccination history: Other vaccines
   f. Previous history of COVID-19
   g. Admission date
   h. Contact with confirmed/possible SARS-CoV-2 case in the last 14 days
   i. Clinical history: general health and chronic health conditions
   j. Treatment/medications(s)
   k. Possible exposures
3. Laboratory questionnaire (to be completed by study team)
4. Follow-up questionnaire (to be completed by resident, staff or study team)
   a. Administration
   b. Vaccination history: COVID vaccine
   c. Vaccination history: Other vaccines
   d. Possible COVID-19 infection
   e. Contact with possible/confirmed COVID-19 cases
   f. Possible exposure to COVID-19
5. Medical attention for COVID-19 (to be completed by study team)

Part 1. Pre-enrolment questionnaire (to be completed by study monitor)		
Form completion date	dd/mm/yyyy	Date Date should be the date on which the participant was approached.
Country		Text
Name/code of long-term health care facility		Text
Participant unique ID		Alphanumeric. Generated by study tool.
Does the participant report any contra-indication for the COVID-19 vaccine?	o Yes o No o Unknown	Numeric
Accepts participation in the VE study	o Yes o No o Unknown	
Informed consent given	o Yes, by participant o Yes, by guardian o No, by participant o No, by guardian	Categorical A copy of informed consent should be provided to the participant and a copy kept in study records.
Nature of relationship of guardian		Text
If invitee does not agree to participate:		
What are your reason(s) for not participating		Text
What sex are you?	☐ Male ☐ Female	Numeric (binary)
How old (in years) are you?		Integer (continuous)

Part 2. Enrolment questionnaire		
2.a. Identifier and contact details		
1. First name		Text
2. Surname		Text
3. Room number (residents only)		Alphanumeric
2.b. Socio-demographic information		
4. What sex are you?	☐ Male ☐ Female	Numeric (binary)
5. How old are you? (years)		Integer (continuous)
6. What ethnicity do you consider yourself to be?	Categories to be determined according to setting	Categorical
2.c. Individual behaviour		
7. What is your height?		Numeric with limits
8. What is your weight?		Numeric with limits
9. If height and weight are not collected: BMI		Numeric
10. Do you smoke or have you ever smoked (any smoking: cigarettes, cigars, vaping)?	o I have never smoked o I stopped smoking more than one year ago o I stopped smoking within the last year o Yes, I currently smoke o I do not know	Categorical
11. Do you drink alcohol?	o No, I do not drink o Yes, I drink rarely (a few times a year) o I drink occasionally (once per month) o Yes, I drink regularly (once a week) o Yes, I drink more than once a week, but not every day o Yes, I drink every day o I do not know.	Categorical
2.d. Vaccination history: COVID vaccine		
12. Have you been offered the COVID-19 vaccine?	o Yes o No o Unknown	Categorical If responds: No or Unknown, go to next section
13. Have you received the first dose of any COVID-19 vaccine?	o Yes o No o Unknown	Categorical If responds: • Yes, go to question 14 • No, go to question 13 and then next section • Unknown, go to next section
14. If no, what were your reason(s)? (Please tick all that apply)	o I have not had time o I do not believe in vaccination o I am concerned about possible side-effects o Declined by resident's guardian o Other, please specify ____	Categorical
15. If yes, on what date did you receive the first dose?	dd/mm/yyyy	Date
16. Which vaccine did you receive for the first dose?	☐ Astra Zeneca (Vaxzevria) ☐ Janssen (Jcovden) ☐ Moderna	Categorical Product names to be updated

	☐ Pfizer/Biotech (Comirnaty) ☐ Other, please specify ___ ☐ Do not know	
17. What was the batch number of the first dose vaccine received? *Please provide the batch number from documents or state 'Unknown'		Text
18. How was vaccination with the first dose ascertained (tick all that apply)?	o Vaccination card o Vaccination registry o Medical record o Other, please specify _____ o Not documented	Categorical
19. Have you received a second dose of the COVID-19 vaccine?	o Yes o No o Unknown	Categorical If responds: • Yes, go to question 21 • No or unknown, go to question 28
20. If yes, on what date did you receive the second dose?	dd/mm/yyyy	Date
21. Which vaccine did you receive for the second dose?	☐ Astra Zeneca (Vaxzevria) ☐ Janssen (Jcovden) ☐ Moderna ☐ Pfizer/Biotech (Comirnaty) ☐ Other, please specify _____ ☐ Do not know.	Categorical Product names to be updated
22. What was the batch number of the second dose vaccine you received? *Please provide the batch number from documents or state 'Unknown'		Text
23. How was vaccination with the second dose ascertained (tick all that apply)?	o Vaccination card o Vaccination registry o Medical record o Other, please specify _____ o Not documented.	Categorical
24. Have you received a third dose of the COVID-19 vaccine?	o Yes o No o Unknown	Categorical If responds: • Yes, go to question 25 • No or Unknown, go to question 28
25. If yes, on what date did you receive the third dose?	dd/mm/yyyy	Date
26. Which vaccine did you receive for the third dose?	☐ Astra Zeneca (Vaxzevria) ☐ Janssen (Jcovden) ☐ Moderna ☐ Pfizer/Biotech (Comirnaty) ☐ Other, please specify _____ ☐☐Do not know.	Categorical Product names to be updated
27. What was the batch number of the third dose of vaccine you received? 28. *Please provide the batch number from documents or state 'Unknown'		Text
29. How was vaccination with the third dose ascertained (tick all that apply)?	o Vaccination card o Vaccination registry o Medical record o Other, please specify _____ o Not documented.	Categorical
30. Have you received a fourth dose of the COVID-19 vaccine?	o Yes o No o Unknown	Categorical If responds: • Yes, go to question 25 • No or Unknown, go to question 28
31. If yes, on what date did you receive the	dd/mm/yyyy	Date

fourth dose?		
32. Which vaccine did you receive for the fourth dose?	☐ Astra Zeneca (Vaxzevria) ☐ Janssen (Jcovden) ☐ Moderna ☐ Pfizer/Biotech (Comirnaty) ☐ Other, please specify _____ ☐ Do not know	Categorical Product names to be updated
33. What was the batch number of the fourth dose vaccine you received? *Please provide the batch number from documents or state 'Unknown'		Text
34. How was vaccination with the fourth dose ascertained (tick all that apply)?	o Vaccination card o Vaccination registry o Medical record o Other, please specify _____ o Not documented	Categorical
2.e. Vaccination history: other vaccines		
35. Have you received an influenza vaccine in the last 12 months?	☐Yes ☐ No ☐ Unknown	Categorical If responds: No or Unknown, go to question 37
36. If yes, when did you receive the influenza vaccine?	dd/mm/yyyy	Date
37. What was the product name of the influenza vaccine received?		Text
38. Have you received a pneumococcal vaccine?	☐ Yes ☐ No ☐ Unknown	Categorical If responds: No or Unknown, go to next section
39. What type of pneumococcal vaccine did you receive?	o PPSV23 o PCV13 o Other, please specify _____ o Do not know	Categorical
40. In which year did you last receive a pneumococcal vaccine?	yyyy	Date
2.f. Previous history of COVID-19		
41. Since the beginning of the pandemic, have you ever been diagnosed (or self-diagnosed) as having COVID-19?	☐ Yes ☐ No ☐ Unknown	Categorical If responds: No or Unknown, go to next section
42. How many distinct episodes of illness did you have?		Numeric (integer)
43. Please specify the date of onset of the last episode COVID-19	dd/mm/yyyy	Date
44. Which, if any, test was used for confirmation of the COVID-19 during that episode?	o No test was done o Rapid Antigen Test o PCR o Serology o I do not remember what kind of test was done.	Categorical
45. Please specify the date of test:	dd/mm/yyyy	Date
46. During the last episode, did you have any COVID-like symptoms?	☐ Yes ☐ No ☐ Unknown	Categorical If responds: No or Unknown, go to question 44
a) Fever (≥ 38 °C) or history of fever	o Yes o No o Unknown	Categorical
b) If yes to fever, please specify maximum temperature		Numeric

c) Cough	o Yes o No o Unknown	Categorical
d) General weakness/fatigue	o Yes o No o Unknown	Categorical
e) Dyspnoea/shortness of breath	o Yes o No o Unknown	Categorical
f) Loss of smell (anosmia)	o Yes o No o Unknown	Categorical
g) Loss of taste (ageusia)	o Yes o No o Unknown	Categorical
h) Other (please specify)		Text
i) On what date did the first symptoms appear?	dd/mm/yyyy	Date
47. Did you have radiological evidence of lesions compatible with COVID-19 (e.g. by chest X-ray or computed tomography scan)?	o Yes o No o Unknown	Categorical
48. Did you seek or receive any medical attention for that episode?	o Yes o No o Unknown	Categorical If responds: Yes: clinical monitor to complete hospitalisation questionnaire
2.g. Admission date		
49. What was the admission date of the resident?	__/__/____	Date (dd/mm/yyyy) Enter the first date of admission to the LTCF, disregarding shorter periods of absence because of hospitalisation or other reasons, unless the resident was administratively considered discharged, and their room/bed was assigned to another person.
2.h. Contact with confirmed/possible SARS-CoV-2 case in the last 14 days		
50. In the past 14 days, have you been in contact with a person with confirmed COVID-19 or COVID-19 symptoms (possible case) within the long-term care facility?	o Yes o No o Unknown	Categorical If responds: No or Unknown, go to next section
51. How many people with possible/confirmed COVID-19 have you been in contact with in the last 14 days?		
52. What was the date of your last contact with a possible/confirmed case?	dd/mm/yyyyy	Date
53. Were you in close (<2 metres) contact with any of the people with possible/confirmed COVID-19?	o Yes o No o Unknown	Categorical If responds: No or Unknown, go to next section
54. Was the persons with possible/confirmed COVID-19 (please tick all that apply):	o Another resident o Staff member o External visitor o Other, please specify _____	Categorical
2.i. Clinical history: General health and chronic health conditions		
55. Are you (or is the resident) disorientated?	o No o Mild o Moderately o Severely	Categorical Residents who suffer from periods of confusion especially as to time, place,

	o Unknown	or identification of persons (e.g. cognitive impairment) due to a chronic disease or condition diagnosed by a specialist or according to the mental evaluation scale used at the LTCF.
56. Are you (or is the resident) mobile?	o Ambulant (independent) o Ambulant (assisted) o Wheelchair o Bedridden o Unknown	Categorical The resident is independently ambulant (he/she can walk alone), assisted (he/she can walk alone with or without canes, crutches, walkers, etc), he/she needs a wheelchair for his/her movement or he/she is bedridden at the start of the follow-up period.
57. Are you (or is the resident) incontinent?	o Yes o No o Unknown	Categorical Presence of urinary and/or faecal incontinence. Lack of control of the sphincter from bladder or bowel resulting in an uncontrolled loss of urine or faeces and necessitating the use of diapers. A resident with a urinary catheter should not be considered as incontinent for urine.
58. Do you have (or does the resident have) a urinary catheter?	o Yes o No o Unknown	Presence of urinary catheter at the start of the follow-up period. Any tube system placed in the body to drain and collect urine from the bladder, e.g. an in-dwelling urinary catheter, suprapubic or abdominal wall catheter, cystostomy. External catheters not draining urine directly from the bladder (e.g. condom catheters) should not be included.
59. Do you have (or does the resident have) a vascular catheter?	o Yes o No o Unknown	Presence of a vascular catheter at the start of the follow-up period. Any tube system placed in the body to access the vascular (venous, arterial) system, (e.g. a peripheral intravenous catheter, an implanted vascular access system or any other intravascular access system, including arteriovenous fistulae).
60. Do you have a chronic health condition?	o Yes o No o Unknown	Categorical If responds: No or Unknown, go to next section
If yes, please specify:		
a) Diabetes	o Yes o No o Unknown	Categorical
b) Cardiovascular disease (excluding	o Yes	Categorical

hypertension)	o No o Unknown	
c) Hypertension	o Yes o No o Unknown	Categorical
d) Immunodeficiency/organ transplant	o Yes o No o Unknown	Categorical
e) Lung disease	o Yes o No o Unknown	Categorical
f) Asthma	o Yes o No o Unknown	Categorical
g) Cancer	o Yes o No o Unknown	Categorical
h) Renal disease	o Yes o No o Unknown	Categorical
i) Liver disease	o Yes o No o Unknown	Categorical
j) Rheumatological disease	o Yes o No o Unknown	Categorical
k) How many times have you been hospitalised for the chronic condition(s) in the last 6 months		Numeric Hospitalisation if the resident has been admitted to hospital for one or more nights. Combine hospitalisations for all chronic conditions.
61. Has the resident (or have you) been assessed for any type of clinical frailty score?	o Yes o No o Unknown	Categorical If responds: • Yes, go to question 60 • No or Unknown, go to next section.
a. Which scale has been used to assess the resident's (or your) frailty?	o Barthel Index o Clinical Frailty Score o ADL Score o Other scale or index o Unknown	Categorical
b. If Barthel Index, please specify the score		Numeric Maximum 100
c. If Clinical Frailty Score, please specify the score		Numeric Maximum 9
d. If ADL Score, please specify the score		Numeric Maximum 16
If other scale:		
• Please specify the scale		Text
• Please specify the score		Numeric
• Please specify the maximum score for the scale		Numeric
2.j. Treatment/medications(s)		
62. Are you taking regularly any medication(s)?	o Yes o No o Unknown	Categorical If responds: • Yes, go to question 66a-i • No or Unknown, go to next section
If yes, please specify		
a) Statins	o Yes	Categorical

	o No o Unknown	
b) Angiotensin-converting enzyme inhibitors	o Yes o No o Unknown	Categorical
c) Angiotensin II receptor blockers	o Yes o No o Unknown	Categorical
d) Non-steroidal anti-inflammatory drugs	o Yes o No o Unknown	Categorical
e) Corticosteroids	o Yes o No o Unknown	Categorical
f) Anti-rheumatic drugs	o Yes o No o Unknown	Categorical
g) Antithrombotic/platelet aggregation inhibitors	o Yes o No o Unknown	Categorical
h) Anti-diabetic (e.g. Metformin)	o Yes o No o Unknown	Categorical
i) Other, please specify		Text
2.k. Possible exposures		
63. Do you (or does the resident) share your room with other residents?	o Yes o No o Unknown	Categorical If responds: No or Unknown, go to question 60
a. If yes, with how many other residents do you share your room?		Number
64. In the last 14 days, have you had any external visitors?	o Yes o No o Unknown	Categorical If responds: No or unknown, go to question 61
a. How many visitors have you had?		Number
b. Were they (tick all that apply):	o Family/friends (adult) o Family/friends (children) o Health professional o Others	Categorical Children are under 18 years of age. Health professionals includes allied health professionals (e.g. chiropractor, dietician)
65. In the last 14 days, have you made any visits outside of the facility?	o Yes o No o Unknown	Categorical If responds: No or unknown, end the enrolment questionnaire.
a. How many visits have you made in the last 14 days?		Numeric
b. Were the visits to (tick all that apply):	o Home of family/friends o Social event with family/friends o Trip arranged by facility o Hospital clinic o Other health service o Others	Categorical Social venue includes eateries (bar, restaurant) or other venues (cinema, theatre, park) but excludes any trips arranged by the facility. Other health service includes premises of allied health professions (e.g. opticians, physiotherapist).

Part 3. Laboratory questionnaire		
Laboratory identification number		Alphanumeric
Participant ID number		Alphanumeric
Timing of virology test	o Enrolment o Development of symptoms	Categorical

	o Other, please specify o Unknown	
Date sample collected	dd/mm/yyyy	Date
Date sample received	dd/mm/yyyy	Date
Type of sample (virology)	o Nasal swab o Throat swab o Nasopharyngeal swab o Saliva o Oropharyngeal o Other	Categorical
Virology test brand		Text
Virology test result	o Positive o Negative o Inconclusive/Equivocal o Unknown	Categorical
CT value		Numeric
Date virology result	dd/mm/yyyy	Date
Was sequencing performed?	o Yes o No o Unknown	Categorical
If yes:	Variant	
Result of sequencing *(Note: please use the Pango dynamic nomenclature for lineages)*	Variant	
Methodology to sequence	o RT-PCR o Next-generation sequencing o Unknown	
Were other respiratory pathogens tested?	o Yes o No o Unknown	Categorical
If yes, which pathogens?	o Influenza (no type available) o Influenza A (not subtyped) o Influenza A(H1) o Influenza A(H3) o Influenza B o RSV o BoV o RhV o ADV o MPV o PIV o CoV o *Sp. Pneumoniae* o Other	Categorical
Which respiratory pathogens were detected?	As above	Categorical
Specimens shipped to other laboratory for confirmation/sequencing?	o Yes o No o Unknown	Categorical
If yes, specify date of shipment	dd/mm/yyyy	Date
Name of laboratory		Text

Part 4. Follow-up questionnaire		
4.a. Administration		
1. Participant ID number		Alphanumeric
2. Date of completion	dd/mm/yyyy	Date Date is date on which questionnaire was administered.
4.b. Vaccination history: COVID vaccine		
3. Have you received a further dose of a COVID-19 vaccine since enrolment?	o Yes o No o Unknown	Categorical If responds: No or Unknown, go to next section
a. Which dose of the COVID-19 vaccine did you receive?	o First o Second o Third o Fourth o Unknown	Categorical
b. On what date did you receive the dose?	dd/mm/yyyy	Date
c. Which vaccine did you receive?	☐ Astra Zeneca (Vaxzevria) ☐ Janssen (Johnson&Johnson) ☐ Moderna ☐ Pfizer/Biotech (Comirnaty) ☐ Other, please specify _____ ☐ Do not know	Categorical Product names to be updated
d. What was the batch number of the vaccine received? e. *Please provide the batch number from documents or state 'Unknown'		Text
f. How was vaccination ascertained (tick all that apply)?	o Vaccination card o Vaccination registry o Self-report o Other, please specify _____ o Not documented	Categorical
4.c. Vaccination history: Other vaccines		
4. Have you received any other vaccination in the last 7 days?	☐ Yes ☐ No ☐ Unknown	Categorical If responds: No or Unknown, go to next section
a. If yes, which vaccine did you receive	☐ Influenza ☐Other ☐ Unknown	
b. When did you receive the influenza vaccine?	dd/mm/yyyy	Date
c. What was the product name of the influenza vaccine received?		Text
d. If other, please specify the vaccine		Text
4.d. Possible COVID-19 infection		
5. In the last seven days have you had any test for confirmation of COVID-19?	o No test was done o Rapid Antigen Test o PCR o Serology	Categorical

	o I do not remember what kind of test was done.	
a. If yes, what was the test result?	o Positive o Negative o Inconclusive/Equivocal o Unknown	Categorical
6. In the last seven days, have you developed any COVID-like symptoms?	☐ Yes ☐ No ☐ Unknown	Categorical If responds: No or Unknown, go to next section
a. Fever (≥ 38°C) or history of fever	o Yes o No o Unknown	Categorical
b. If yes to fever, please specify maximum temperature		Numeric
c. Cough	o Yes o No o Unknown	Categorical
d. General weakness/fatigue	o Yes o No o Unknown	Categorical
e. Dyspnoea/shortness of breath	o Yes o No o Unknown	Categorical
f. Loss of smell (anosmia)	o Yes o No o Unknown	Categorical
g. Loss/distortion of taste (ageusia/dysgeusia)	o Yes o No o Unknown	Categorical
h. Other (please specify)		Text
i. On what date did the first symptom appear?	dd/mm/yyyy	Date
j. Radiological evidence of lesions compatible to COVID-19 (e.g. by chest X-ray or computed tomography scan)?	o Yes o No o Unknown	Categorical
k. Did you seek or receive any medical attention for that episode?	o Yes o No o Unknown	Categorical If responds: Yes, clinical monitor to complete hospitalisation questionnaire
4.e Contact with possible/confirmed COVID-19 cases		
7. In the past seven days have you been in contact with a person with confirmed COVID-19 or COVID-19 symptoms within the long-term care facility?	o Yes o No o Unknown	Categorical If responds: No or Unknown, go to next section
a. How many people with possible/confirmed COVID-19 have you been in contact with in the last seven days?		Numeric
b. What was the date of your last contact with a possible/confirmed case?	dd/mm/yyyyy	Date
c. Who were the people with possible/confirmed COVID-19 (please tick all that apply):	o Another resident o Staff member o External visitor o Other, please specify _____	Categorical
d. Were you in close (<2 metres) contact with any of the people with possible/confirmed COVID-19?	o Yes o No o Unknown	Categorical If responds: No or Unknown, go to next section

4.f. Possible exposure to COVID-19		
8. In the last seven days, have you had any external visitors?	o Yes o No o Unknown	Categorical If responds: No or unknown, go to question 72
a. How many visitors have you had?		Number
b. Were they (tick all that apply):	o Family/friends (adult) o Family/friends (children) o Health professional o Others	Categorical Children are under 18 years of age Health professionals includes allied health professionals (e.g. chiropractor, dietician)
9. In the last seven days, have you made any visits outside of the facility?	o Yes o No o Unknown	Categorical If responds: No or unknown, end the follow-up questionnaire
a. How many visits in the last seven days have you made?		Numeric
b. Were the visits to (tick all that apply):	o Home of family/friends o Social event with family/friends o Trip arranged by facility o Hospital clinic o Other health service o Others	Categorical Social venue includes eateries (bar, restaurant) or other venues (cinema, theatre, park) but excludes any trips arranged by the facility. Other health service includes premises of allied health professions (e.g. opticians, physiotherapist)

Part 5. Medical attention for COVID-19		
1. Symptomatic/asymptomatic status	o Asymptomatic; viral RNA detected o Symptomatic; viral RNA detected	Categorical
2. Did the resident receive any treatment at the long-term care facility?	☐ Regular monitoring ☐ Medication (antipyretic non-steroid anti-inflammatory) ☐ Medication (antipyretic other) ☐ Other medication (please specify) ☐ Oxygen treatment ☐ Other (please specify)	Categorical
3. Was the resident hospitalised?	o Yes o No o Unknown	Categorical
a) Date of hospitalisation	dd/mm/yyyy	Date
b) Date of discharge	dd/mm/yyyy	Date
c) Treatment in hospital	o Hospitalised; no oxygen therapy o Hospitalised; oxygen by mask or nasal prongs o Hospitalised; oxygen by NIV or high flow	Categorical
4. Was the resident admitted to an Intensive Care Unit (ICU) or High-Dependency Unit (HDU)?	o Yes o No o Unknown	Categorical
a) Admission date to ICU/HDU	dd/mm/yyyy	Date
b) Discharge date ICU/HDU	dd/mm/yyyy	Date
c) Treatment in ICU	o Intubation and mechanical ventilation, pO2/FiO2 >=150 or	Categorical

	SpO2/FiO2 >=200 o Mechanical ventilation pO2/FIO2 <150 (SpO2/FiO2 <200) or vasopressors o Mechanical ventilation pO2/FiO2 <150 and vasopressors, dialysis, or ECMO	
5. Has the resident died?	o Yes o No o Unknown	Categorical
a) Place of death	o Long-term care facility o Hospital o Other sites: please specify	Categorical
b) Date of death	dd/mm/yyyy	Date

Annex 2. Templates for informed consent

Informed consent

COMMENT: This template is given as an example which can be adapted for use in-country, if relevant and aligned with national ethical requirements.

Please note that this is a template developed to assist the investigators in the design of their informed consent forms (ICFs). It is important that investigators adapt their own ICFs to the requirements of their particular investigation and those of their national and institutional regulations. **The logo of the institution must be used on the ICF.**

1. The informed consent form consists of two parts: the information sheet and the consent certificate.
2. Do not be concerned by the length of this template. It is long because it contains guidance and explanations that you will not include in the informed consent forms you develop and provide to participants in your investigation.
3. This template includes examples of key questions that may be asked at the end of each section to ensure understanding of the information being provided, especially if the investigation is complex. These are just examples and suggestions, and the investigators can modify the questions depending upon their study.

In this template:

- square brackets indicate where specific information is to be inserted;
- bold lettering indicates sections or wording that should be included; and
- standard lettering is used for explanations to researchers only and must not be included in your consent forms.

TEMPLATE ON FOLLOWING PAGE

[YOUR INSTITUTIONAL LETTER HEAD]

Template for Informed Consent Form

Cohort study to measure COVID-19 vaccine effectiveness among residents of long-term care facility

[Name of principle investigator]

[Name of organisation]

[Name of sponsor]

[Name of project and version]

This informed consent form has two parts:

1. Information sheet (to share information on the study with you)
2. Certificate of consent (for signatures if you agree to participate)

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

Part 1: Information sheet

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

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

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

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

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

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

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

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

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

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

Confidentiality:
Explain how the investigation team will maintain the confidentiality of data, especially with respect to the information concerning the participant. Outline any limits to confidentiality.

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

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

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

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

PART 2: Certificate of consent
Certificate of consent

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

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

Print name of participant _____

Signature of participant _____

Date (day/month/year) _____

Or if signed by legal guardian

Print name of guardian _____

Signature of guardian _____

Specify nature of guardianship _____
Date (day/month/year) _____

Statement by the researcher/person taking consent

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

A copy of this informed consent form has been provided to the participant/guardian: ____

Print name of researcher/person taking the consent _____
Signature of researcher/person taking the consent _____

Date (day/month/year) _____

Annex 3. Outline analysis plan

An outline analysis plan is presented in this section.

Participation

The study participants should be described in terms of total number of eligible participants and total number and proportion refusing to participate, by reason for refusal.

Baseline characteristics

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

Baseline characteristics for participants tabulated should include:

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

Vaccine effectiveness

Vaccination status will be considered a time-varying exposure (vaccination status of individuals may change over time from unvaccinated to vaccinated; one to two to three or more doses).

We will measure vaccine effectiveness (VE) among those receiving any dose, one dose, two doses, three doses, or four/more doses. We define a person as having received a dose of vaccine if they received it at least ≥ 14 days before symptom onset. Consideration should be given in settings where the Janssen vaccine was used, as one dose of Janssen vaccine is considered equivalent to two doses of another vaccine.

People will be considered to be 'unvaccinated' if they have not received any vaccine or were vaccinated on the day that symptoms appeared or after symptom onset. Those receiving their first dose of vaccine < 14 days before symptom onset will be excluded from the main analysis for VE after at least one dose or VE of one dose only. Those receiving their first dose of Janssen vaccine or second dose of other vaccines < 14 days before symptom onset will be excluded from the VE analysis for complete vaccination.

Sensitivity analyses may be performed to evaluate the effectiveness of the vaccine at different intervals following vaccination. If sample size allows, VE can be measured for varying time since vaccination. Intervals could include 14–90 days, 3–4 months, 5–6 months, depending on sample size.

Vaccination effectiveness (VE) should be estimated using Cox regression or a piece-wise exponential survival model (modelled through expanded Poisson regression) (VE = 1 – hazard ratio [HR]) or Poisson regression (VE = 1 - rate ratio [RR]). Follow-up will be from baseline to the earliest outcome or study exit.

Both unadjusted and adjusted estimates of VE should be presented. Adjustment should be made in the multivariable regression model for all potential confounders.

Effect modification should be explored. Analysis will be stratified, depending on the sample size, by:

- vaccine dose (if relevant: unvaccinated, partially vaccinated, fully vaccinated or by number of doses)
- age groups
- sex
- presence or absence of high-risk conditions
- any other effect modifier identified.

Effect modifiers will be assessed one by one, comparing the estimates across the strata of baseline characteristics. Confounding factors will be assessed by comparing crude and adjusted estimates for each baseline characteristic.

The proportional hazards assumption of the analysis will be assessed using graphical approaches and tests based on Schoenfeld residuals. If there is evidence of non-proportionality then a proportional hazards model may not be appropriate. A full set of frailty mixture models may be fitted to assess the appropriate method to measure VE.

Controlling for clustering by long-term care facility

To control for a clustering effect by long-term care facility, a mixed model could be considered, including health facility as a random intercept.

Missing data

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

Secondary analyses

As a secondary analysis, VE should be assessed by subgroups and against multiple infections, as indicated in Table 3.1.

Table 3.1. Research questions and corresponding cohorts of LTCF residents

Research question	Group for which VE is measured	Individuals included in the analysis	Follow up: contribution to the denominator
VE among residents eligible for vaccination **(primary analysis)**	All residents enrolled, irrespective of previous infection* at enrolment.	All residents enrolled.	Until participant tests positive for PCR: exclusion of 'post-onset' person-time of cases.
VE among residents eligible for vaccination **with no** SARS-CoV-2 infection before or at enrolment.	Residents enrolled with no previous infection* at enrolment.	All residents testing negative by PCR, serology and with no previous clinical infection.	Until participants tests positive for PCR: exclusion of 'post-onset' person-time of cases.
VE among residents eligible for vaccination **with** SARS-CoV-2 infection before or at enrolment.	VE among those with previous infection* at enrolment	All residents testing positive by PCR, serology or with previous clinical infection.	Excluded until at risk of reinfection. Included to identify reinfections until participant tests positive for PCR during the study period: exclusion of 'post-onset' person-time of cases.
VE against multiple infections among residents eligible for vaccination.	All residents enrolled, irrespective of previous infection* at enrolment.	All residents enrolled.	Excluded until at risk of reinfection. Included to identify reinfections until the end of the study.

** Different definitions of previous infection can be used: positive PCR, positive serology, clinically confirmed COVID-19 (or any combination of the three).*

Note: vaccine effectiveness can be measured against SARS-CoV-2 positive RT-PCR (primary outcome) or against different clinical outcomes.

Secondary outcomes can also be considered and may include:

- SARS-CoV-2 laboratory confirmation by RT-PCR in any severely-ill residents participating in the study, where severe RT-PCR positive cases are defined as:
  - requiring supplementary oxygen therapy;
  - intubated;
  - requiring mechanical ventilation;
  - admitted to ICU;
  - in-hospital death;
  - death within 30 days of a positive SARS-CoV-2 test.
- SARS-CoV-2 asymptomatic or mild or moderate infection: Any residents participating in the study who tested RT-PCR positive for SARS-CoV-2 during the study period, and did not present with symptoms required to meet the case definition for a suspected COVID-19 case.

Definitions used for secondary analyses measuring VE by previous SARS-CoV-2 infection

- Previous clinical COVID-19: residents reporting having had the symptoms required to meet the case definition for possible or probable COVID-19 case before enrolment in the VE study but who did not have a SARS-CoV-2 test during the period when they were symptomatic.
- Previous SARS-CoV-2 infection with detectable infection-induced antibodies at enrolment and history of clinical COVID-19: residents with a serologically positive result at enrolment (the time of inclusion in the study) with a history of past clinical confirmation of COVID-19.
- Previous SARS-CoV-2 infection with infection-induced detectable antibodies at enrolment and no previous COVID-19: residents with a serological positive result at enrolment (the time of inclusion in the study) without a history of past clinical confirmation of COVID-19.
- Previous self-reported clinical COVID-19 infection without infection-induced detectable antibodies at the start of the study: residents who report having had COVID-19 (meeting the definition of possible case) with a negative serology at the time of inclusion in the study (clinically confirmed or self-reported).
- Residents who did not have baseline serology at enrolment, irrespective of previous documentation of COVID-19 infection by clinical or laboratory diagnosis.

Sensitivity analyses

- Using different outcomes and combination of outcomes (PCR, serology);
  - Correcting for sensitivity and specificity of various outcomes;
- By previous infection using different definitions of previous infection;
- Using different delays for defining vaccination status;
- Calculating E-values to quantify the potential for bias due to unmeasured confounding.

VE by time since vaccination; including Farrington/Longini/Halloran methods for analysing/correcting for biases due to cumulative incidence risk; stable or variable incidence rate over time.

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