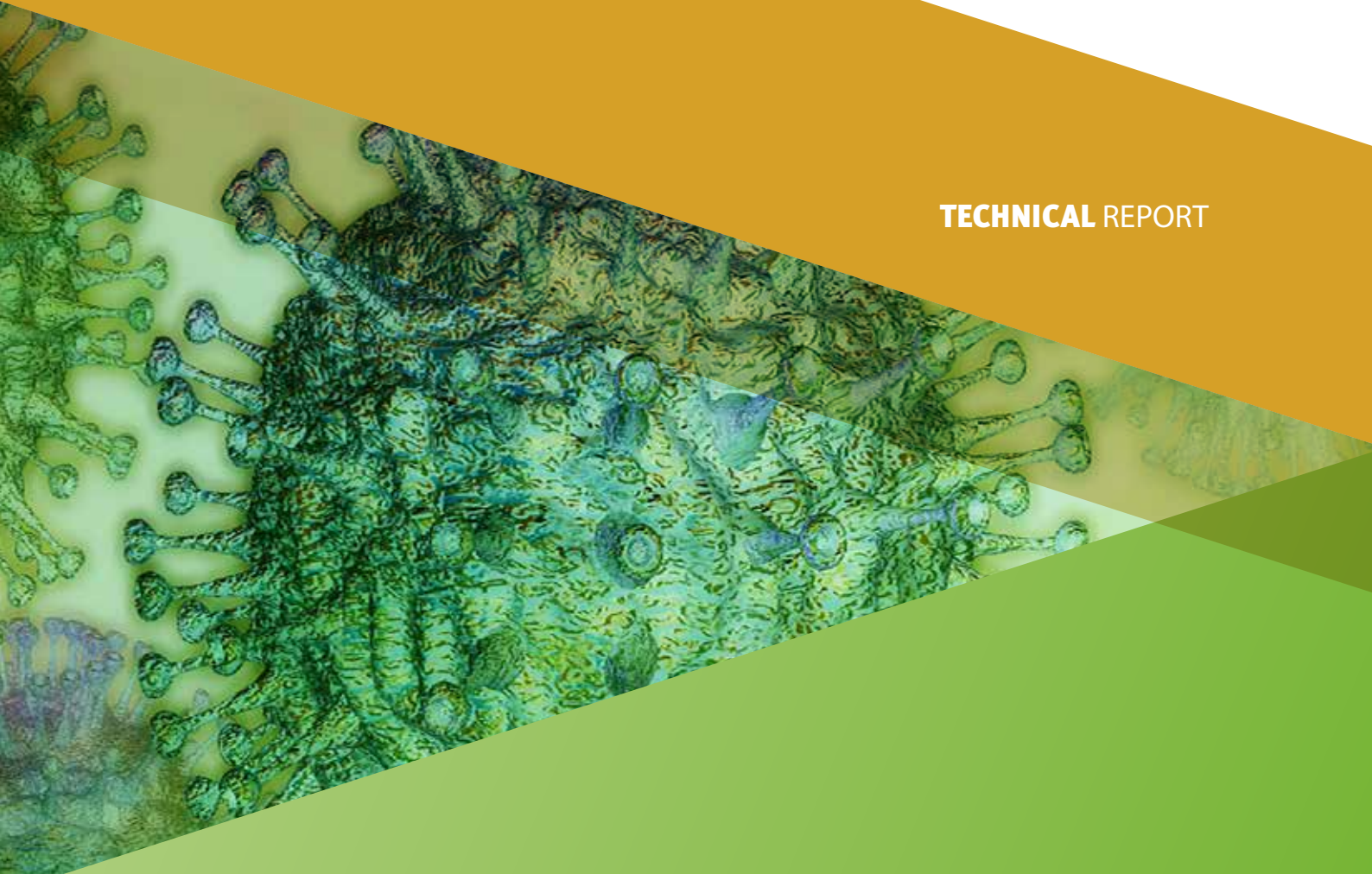


**TECHNICAL** REPORT



**Generic protocol for ECDC studies of  
COVID-19 vaccine effectiveness against  
confirmed SARS-CoV-2 using healthcare  
worker cohorts  
Version 2.0**

**ECDC TECHNICAL REPORT**

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This generic protocol was commissioned by the European Centre for Disease Prevention and Control (ECDC), as part of the activities referring to Framework contract N. ECDC/2021/017 'Vaccine Effectiveness, Burden and Impact Studies (VEBIS) of COVID-19 and Influenza, Lot 2', coordinated by Kim Brolin.

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This generic protocol is based on: current literature, WHO Europe Guidance document: Cohort study to measure COVID-19 vaccine effectiveness among health workers (<https://www.who.int/publications/i/item/WHO-EURO-2021-2141-41896-57484>; WHO/EURO:2021-2141-41896-57484), ECDC expert panel meeting (26 January 2021) and version 1.0 of the protocol, as well as review by ECDC and study sites implementing the study.

Specifically, the version 1.0 of this core protocol corresponds to the version used to implement the Direct Contracts ECD.11486 and ECD.12175. Version 2.0 updated version 1.0 to include recommendations of the First and Second Technical meetings of the VEBIS Lot 2 project and lessons learned from the implementation of the study up to 31 July 2022.

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# Abbreviations

COVID-19	Coronavirus disease 2019
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
HCW	Healthcare worker
IPC	Infection prevention and control
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
PCR	Polymerase chain reaction
PPE	Personal protective equipment
VE	Vaccine effectiveness
WHO	World Health Organization

## Executive summary

The end of 2019 saw the emergence of a novel severe acute respiratory syndrome: coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19). As of 20 July 2022, 157.6 million cases and 1.1 million deaths have been reported in the European Union (EU) and the European Economic Area (EEA) [1].

As of week 45 2022, six vaccines (Comirnaty, Spikevax Vaxzevria, Jcovden (previously COVID-19 Vaccine Janssen), Valneva and Nuvaxovid) have been authorised by the European Commission based on the scientific opinion of the European Medicines Agency (EMA) for use in the European Union, and others are under rolling review. In addition, four adapted bivalent vaccines are authorised for use (Comirnaty Original/Omicron BA.1, Comirnaty Original/Omicron BA.4-5, Spikevax bivalent Original/Omicron BA.1, and Spikevax bivalent Original/Omicron BA.4-5 [2]).

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. In November 2020, the European Commission proposed to the European Parliament and the Council of the EU a change to the mandates of EMA and ECDC in the context of its COVID-19 lessons learned package and the creation of a European Health Union, empowering the two agencies to jointly coordinate independent vaccine monitoring studies.

As a result, at the end of 2020, utilising the lessons learned from other vaccine effectiveness (VE) studies, ECDC started building infrastructure to perform COVID-19 VE 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). The studies have been embedded in a project called VEBIS (Vaccine Effectiveness, Burden and Impact Studies).

This generic protocol for ECDC studies describes the design and methods for a prospective multi-country cohort study of hospital-based healthcare workers (HCWs) to evaluate the effectiveness of COVID-19 vaccines in preventing laboratory-confirmed SARS-CoV-2 infection. The combination of data from multiple sites aims at providing sufficient statistical power to meet both the overarching primary objective and a range of more specific secondary objectives. This protocol has been adapted to the rapid vaccine roll-out for COVID-19 in many countries and accommodates the establishment of HCW cohorts subsequent to the implementation of vaccination programmes.

All HCWs eligible to be vaccinated with COVID-19 vaccine can be enrolled in the study, including those who have already been vaccinated with a primary COVID-19 vaccination course, those who have received booster dose(s), those who intend or do not intend to be vaccinated, and those who are not sure. At enrolment, study participants complete a baseline enrolment survey about demographics, clinical comorbidities, and work- and community-related behaviours related to infection risk. In addition, a baseline serology sample and a respiratory specimen should be collected from participants.

During the course of the study, participants should be actively followed for suspected COVID-19 SARS-CoV-2 infection through regular monitoring:

- **Molecular testing:** participants should provide a weekly sample, either a nasopharyngeal, nasal or oropharyngeal swab collected by trained HCWs (or self-swab following training) or a self-taken saliva sample, which should be tested for SARS-CoV-2 by RT-PCR. A less frequent sampling schedule of bi-weekly nasopharyngeal swabs is also allowed to improve acceptability among study participants. Site investigators should select for genetic sequencing all or a representative proportion of SARS-CoV-2 confirmed infections in participants.
- **Questionnaire survey:** participants should complete a weekly survey reporting the occurrence of any COVID-19-related symptoms and any changes in high-risk exposures to infection (both professional and in the community).
- **Serology:** serum samples should be collected periodically (at enrolment and thereafter every 6-12 weeks) from participants. Serum samples should be tested for antibodies against SARS-CoV-2 by serological testing algorithms that can distinguish between vaccine-induced and infection-induced antibodies.

This protocol is primarily intended to guide the implementation of ECDC-funded studies. However, ECDC encourages the active endorsement and implementation of this protocol beyond ECDC-funded studies to strengthen the evidence base for future policy decisions. The use of consistent protocols will facilitate the comparability of study results across studies, countries, and study sites.

The second version of the protocol includes the lessons learnt from the studies performed until end of July 2022, comments from the site investigators and recommendations from the first technical meetings of the VEBIS HCW project.

## Changes in version 2.0

The main changes in this version compared to version 1.0 include the restriction by circulation of different variants of concern, relative VE analysis comparing booster dose and primary course, adjusted analysis, hybrid protection analysis, time since the administration of the last dose of vaccination. The first version of this protocol (see version 1.0) was used until March 2022 and also thereafter for those sites that only obtained their ethical permit after March 2022.

### 1. Background

#### 1.1 Context

In late 2019, a novel virus associated with a severe acute respiratory syndrome – coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), emerged. On 11 March 2020, the World Health Organization declared COVID-19 a pandemic. As of 20 July 2022, 157.6 million cases and 1.1 million deaths have been reported in the European Union (EU) and the European Economic Area (EEA) [1].

International collaborative efforts have accelerated the development of COVID-19 vaccines. As of 27 September 2022, 177 candidate vaccines were in clinical development and 199 were in preclinical development [3]. Within the EU/EEA, as of 25 July 2022, six vaccines, of which five are spike-protein-based and one inactivated vaccine, have been given (conditional) marketing authorisation by the European Medicines Agency (EMA) [2]. In the initial context of limited vaccine supplies, target groups for the prioritisation of COVID-19 vaccination were established. Many countries included healthcare workers (HCWs) as a priority group for COVID-19 vaccination as they are considered at a higher risk of SARS-CoV-2 infection [4] can transmit the infection to susceptible patients at high risk of severe COVID-19 and in order to maintain essential healthcare services [4-6].

Evaluating the real-world COVID-19 vaccine performance is critical for understanding the risks and benefits of vaccination programmes. Many factors impact real-world VE, including vaccine transportation and storage and delivery of vaccination to population. In addition, people recruited to vaccine clinical trials may have different characteristics from those who will receive vaccines in the real world [7]. Real-world VE studies can also answer questions about effectiveness by age group and risk factors, duration of vaccine protection, protection against transmission, relative effectiveness of different vaccines, relative effectiveness of different number of doses and their timings, and effectiveness of the vaccine against SARS-CoV-2 variants of concern.

This document presents ECDC's generic protocol for a prospective multi-country cohort study to evaluate the effectiveness of the COVID-19 vaccine in hospital-based health workers, which was used to implement the study from March 2022. This document outlines standardised methods for establishing the study, collecting data and undertaking analysis as well as allowing for necessary local adaptations. The first version of this protocol (see version 1.0) was used up until March 2022, and also thereafter for those sites that obtained their ethical permit only after March 2022.

#### 1.2 ECDC COVID-19 vaccine effectiveness studies

In 2018, the Council recommendation on Strengthened Cooperation against Vaccine-preventable Diseases (2018/C 466/01) called on the European Commission to work with the Member States with the support of the European Medicines Agency (EMA) and in cooperation with ECDC to '*continuously monitor the benefits and risks of vaccines and vaccinations at EU level including through post-marketing authorisation studies*'.

In 2020, the European Commission emphasised the importance of continuously monitoring the safety and effectiveness of vaccines in EU/EEA and called on ECDC and EMA to develop a structured post-authorisation monitoring platform for vaccines, prioritising COVID-19 vaccines. In November 2020, the European Commission proposed to the European Parliament and the Council of the EU an addition to the EMA's and ECDC's mandates as part of the European Health Union package, proposing to empower the two agencies to jointly coordinate independent vaccine post-authorisation studies, and proposing additional EU funds to conduct such studies.

As a result, at the end of 2020, utilising the lessons learned from other VE studies, ECDC started building infrastructure to perform COVID-19 VE 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, transmission, etc). The studies have been embedded in a project called VEBIS (Vaccine Effectiveness, Burden and Impact Studies). The multi-country approach of the

effectiveness studies is also one of the key features that characterises the studies, with a foreseen progressive inclusion of more countries over time.

One of the first studies implemented, and for which the first update of the ECDC protocol is presented in this document, is a multi-country study aimed at estimating COVID-19 vaccine effectiveness (VE) against confirmed SARS-CoV-2 infection, by assessing it in hospital-based healthcare workers.

### 1.3 Aim of the protocol

This ECDC protocol for studies of COVID-19 VE against confirmed SARS-CoV-2 in healthcare workers covers the main elements of a hospital-based study of COVID-19 VE in healthcare workers, outlining the standardised methods for collecting data related to COVID-19 and SARS-CoV-2 infection and includes a plan for a pooled analysis. The combination of data from multiple sites will allow for studies with more statistical power to meet both the overarching primary objective and a range of more specific secondary objectives. If there are large sample sizes available within a country, this protocol is also suitable for analysis on national level.

With the final aim of putting in place a system for the regular monitoring of VE, ECDC has worked closely with EU Member States to recruit hospitals capable of applying the generic protocol and therefore contributing to the EU-level monitoring of COVID-19 VE. Specifically, each study site has been identified through a process involving the countries' relevant National Coordinator<sup>1</sup> designated for coordination of activities with ECDC.

This protocol therefore is primarily intended to guide the implementation of ECDC-funded studies. However, ECDC encourages the active endorsement and implementation of this protocol beyond ECDC-funded studies to strengthen the evidence base for future policy decisions. The use of consistent protocols will facilitate the comparability of study results across studies, countries, and study sites.

This document presents a second version of the protocol, which is planned to be updated and revised on a regular basis.

This protocol is complemented by a questionnaire template, a list of variables to be collected and their coding, all of which are available upon request at [vpd.vpd@ecdc.europa.eu](mailto:vpd.vpd@ecdc.europa.eu).

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

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<sup>1</sup> <https://www.ecdc.europa.eu/sites/portal/files/media/en/aboutus/governance/competent-bodies/Documents/COORDINATING-competent-bodies-structures-terms-of-reference-and-interactions-w-Annexes.pdf>



## 2. Objectives

### 2.1 Primary objective

The primary objective of this study protocol is to measure product-specific COVID-19 VE among hospital healthcare workers (HCWs) eligible for vaccination against laboratory-confirmed SARS-CoV-2 infection.

### 2.2 Secondary objectives

Depending on sample size, the secondary objectives are to measure COVID-19 VE:

- against asymptomatic laboratory-confirmed COVID-19 infection;
- against symptomatic laboratory-confirmed COVID-19 infection and according to different case definitions;
- against severe laboratory-confirmed COVID-19 infection;
- against SARS-CoV-2 variants of interest/concern;
- by vaccination status;
- by vaccine product and by combination of different products;
- by time since vaccination and between vaccine doses;
- by different age groups;
- by sex;
- by different high-risk comorbidities;
- in those with previous SARS-CoV-2 infection;
- by HCW occupation and/or ward type;
- by re-infection with SARS-CoV-2 during the study period.

➤ *Each study site/hospital/country to specify the secondary objectives of their study.*

## 3. Methods

### 3.1 Study setting

The study is designed to be conducted among HCWs based in hospitals, because of the convenience of follow-up of a congregated study population.

- *Each study site/hospital/country to describe the hospitals recruiting HCW cohorts including type and size of hospital (e.g. number wards and beds), laboratory capacity, and vaccination coverage at the hospital level.*

### 3.2 Study design

This is a prospective longitudinal dynamic cohort study among healthcare workers eligible for vaccination, comparing SARS-CoV-2 incidence among HCWs with different vaccination status.

### 3.3 Study population

The study population will be composed of healthcare workers in participating hospitals, eligible for vaccination, with no contraindication to receive COVID-19 vaccine.

### 3.4 Inclusion criteria

All categories of HCW in the hospitals may be included.

HCWs are defined as all staff in the healthcare facility involved in the provision of care for patients, both those providing direct care to patients, those who may not have provided direct care to patients but who have had contact with patients' body fluids, potentially contaminated items or environmental surfaces present, as well as those who may have been in the same area as patients. This is based on WHO's definition [8] and is intended to be broad to include healthcare professionals, allied health workers and auxiliary health workers. The definition encompasses roles such as cleaning and laundry personnel, X-ray physicians and technicians, clerks, phlebotomists, respiratory therapists, nutritionists, social workers, physical therapists, laboratory personnel, admission/reception clerks, patient transporters, catering staff, etc.

All HCWs who are vaccinated against COVID-19 can be included as long as information can be collected about the vaccine brand(s), number of doses, and dates of vaccination (see Section 3.11).

- *Each study site/hospital/country to describe categories of staff to be included.*

### 3.5 Exclusion criteria

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

### 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 begins any time after COVID-19 vaccines became available in each of the participating countries. The study period is defined initially for each priority vaccination group and begins for each vaccination group when the vaccination campaign in this group begins. **The study period should ensure for all individuals enrolled a minimum follow up of three months and longer if feasible.** Follow-up time will also depend on the level of viral circulation.

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

### 3.7 Exposure

#### Vaccination status documentation

Precise vaccination status documentation is essential for this study. Vaccination status ascertainment will depend on how the vaccination is delivered and registered in each setting.

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

Vaccine documentation should include for each dose:

- COVID-19 vaccination received and date of vaccination;
  - vaccine brand;
  - vaccine batch;
  - ascertainment (e.g. self-reported, documented, vaccine registry, etc).
- *Each study site/hospital/country to describe how vaccination status will be ascertained. Ideally, study sites should ensure that vaccination status is documented.*

### 3.8 Definitions of outcomes

The **primary outcomes** should be a confirmed SARS-CoV-2 infection detected by laboratory RT-PCR in any participant, regardless of symptoms.

**Secondary outcomes** include symptomatic COVID-19, defined as participants with confirmed SARS-CoV-2 infection detected by laboratory RT-PCR who report one or more of the following clinical criteria to conform with the ECDC possible case definition of COVID-19 [9]:

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

Secondary outcomes of COVID-19 disease severity are defined as participants who conform to the definition of a primary outcome measure of SARS-CoV-2 infection with the following stages:

- **Asymptomatic:** no reported symptoms consistent with the ECDC definition of COVID-19.
- **Mild disease:** reported symptoms consistent with the ECDC definition of COVID-19 requiring attendance at a medical service but requiring no further assistance for activities of daily living.
- **Moderate disease:** reported symptoms consistent with the ECDC definition of COVID-19 requiring either hospitalisation but not requiring oxygen treatment or not hospitalised but requiring assistance for activities of daily living.
- **Severe disease:** reported symptoms consistent with the ECDC definition of COVID-19 requiring hospitalisation and oxygen treatment.
- **Very severe disease:** reported symptoms consistent with the ECDC definition of COVID-19 requiring hospitalisation and any of the following: admittance to an intensive care unit and/or intubation or mechanical ventilation and/or additional systems/organs support (vasopressors, dialysis, ECMO) or death.

### 3.9 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 VE, the estimated incidence of SARS-CoV-2 infection over the follow-up time in the unvaccinated study population (or other chosen denominator), and the desired precision.

Table 1 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) according to different levels of incidence of SARS-CoV-2 infection among unvaccinated participants during a one-year study. As the vaccination coverage of HCWs has been beyond 90% in most EU settings and in the study sites including also the first months of the study, Table 1 is presented for illustrative purposes. The unvaccinated group might be affected by selection bias and therefore other approaches in the analysis should be explored (see 3.13,) e.g. exclusion of this group from the main analysis.

The sample size calculation does not account for any study dropouts. It also does not account for the fact that during the course of the study some of the unvaccinated HCWs may choose to get vaccinated.

In the real-world study setting, the sample size could be increased to account for study dropout rates, stratification and adjustment variables, and to increase precision (particularly for the higher VE estimates).

The estimates presented in Table 1 were calculated using the following command in STATA statistical software:

```
power exponential (0.05 0.1 0.2), 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 fperiod)
```

**Table 1. Sample size estimation (for one stratum)**

Yearly hazard rate in unvaccinated	VE (%)	Vaccine coverage (%)	Total sample size	Unvaccinated		Vaccinated	
				N	Number of events	N	Number of events
0.2	90	90	550	55	4	495	3
		80	365	73	5	292	2
		70	314	94	6	220	2
		60	302	121	8	181	1
	80	90	863	87	6	776	11
		80	542	109	7	433	6
		70	450	135	9	315	4
		60	423	169	11	254	4
	70	90	1 330	133	9	1 197	25
		80	808	162	11	646	13
		70	656	197	13	459	10
		60	607	243	16	364	8
60	90	2 077	208	14	1 869	52	
	80	1 233	247	17	986	27	
	70	985	296	20	689	19	
	60	899	360	24	539	15	
50	90	3 365	337	23	3 028	104	
	80	1 967	394	27	1 573	54	
	70	1 550	465	31	1 085	37	
	60	1 400	560	38	840	29	
0.1	90	90	1 088	109	4	979	3
		80	722	145	5	577	2
		70	620	186	6	434	2
		60	597	239	8	358	1
	80	90	1 706	171	6	1 535	11
		80	1 070	214	7	856	6
		70	890	267	9	623	4
		60	837	335	12	502	4
	70	90	2 630	263	9	2 367	25
		80	1 597	320	11	1 277	13
		70	1 296	389	13	907	9
		60	1 198	479	16	719	8
60	90	4 106	411	14	3 695	51	
	80	2 437	488	17	1 949	27	
	70	1 946	584	20	1 362	19	
	60	1 775	710	24	1 065	15	
50	90	6 648	665	23	5 983	104	
	80	3 883	777	27	3 106	54	
	70	3 062	919	32	2 143	37	
	60	2 763	1 105	38	1 658	29	
0.05	90	90	2 165	217	4	1 948	3
		80	1 435	287	5	1 148	2
		70	1 235	371	6	864	2
		60	1 187	475	8	712	1
	80	90	3 393	340	6	3 053	11
		80	2 128	426	7	1 702	6
		70	1 769	531	9	1 238	4
		60	1 662	665	12	997	3

Yearly hazard rate in unvaccinated	VE (%)	Vaccine coverage (%)	Total sample size	Unvaccinated		Vaccinated	
				N	Number of events	N	Number of events
	70	90	5 232	524	9	4 708	25
		80	3 174	635	11	2 539	13
		70	2 577	773	13	1 804	9
		60	2 382	953	17	1 429	7
	60	90	8 165	817	14	7 348	51
		80	4 843	969	17	3 874	27
		70	3 867	1 160	20	2 707	19
		60	3 527	1 411	24	2 116	15
	50	90	13 213	1 322	23	11 891	104
		80	7 717	1 544	27	6 173	54
		70	6 082	1 825	32	4 257	37
		60	5 489	2 196	38	3 293	29

- *Each study site/hospital/country to define the expected sample size.*

## 3.10 Study procedures

### 3.10.1 Study preparation

After the study has been approved by the relevant ethical review committee, a list of all HCWs eligible for vaccination in the hospital should be obtained. All HCWs or a random selection of HCWs eligible for vaccination should be invited to participate in the study and sign an informed consent form.

HCWs should be invited to participate in the study regardless of their intention to be vaccinated or of their vaccination status.

To ensure that participants with diverse characteristics (socio-demographic, occupational responsibilities) are included, either all HCWs at a study site can be recruited or a stratified sampling scheme can be used to randomly select HCWs in each pre-defined group (e.g. age group, sex, occupation, COVID-19/non-COVID-19 wards). A list of all HCWs in the hospital or wards of interest will be obtained at the beginning of the study, constituting the sample frame at the start of the study. If a random sample, rather than all hospital HCWs is used, then it should be selected to be proportionally representative for:

- HCWs working in COVID-19 and non-COVID-19 wards; and
- HCWs facing and HCWs not facing patients (see definition of HCW in Section 3.4).

All HCWs in the hospital can be invited to participate in the study. If a sample of HCWs is invited, the HCWs could be selected through random sampling from the list of all HCWs. The HCWs refusing participation will be replaced by the HCWs next in the list. If possible, a minimum information will be collected from the HCWs declining participation (age, sex, occupation, COVID-19 vaccination status).

After the protocol is approved, investigators should actively promote participation in the study by widely publicising it, making information available to HCWs at the selected hospitals. Investigators should make themselves available to HCWs to describe the study, and answer all questions with potential participants either individually or in groups.

- *Each study site/hospital/country to define selection procedure employed to establish HCW cohort.*

### 3.10.2 Enrolment: questionnaire, respiratory sample, and serology sample

All participants should provide informed consent prior to their enrolment into the study (see Supplementary document 1 for further details). Study staff should describe the study in detail, answer all questions, and review the informed consent form with the potential participant in a private area designated for study use. If feasible, study staff will administer a short set of anonymous questions to identify reasons(s) that HCWs do not wish to participate to assess non-response/non-participation bias.

Once informed consent has been obtained, HCWs should be enrolled regardless of their individual vaccination status and should:

- Provide a nasal, naso- or oropharyngeal swab, or a saliva sample for RT-PCR testing;
- Provide a blood sample for serology testing;
- Complete an enrolment questionnaire that includes demographic, clinical, and epidemiological information, information about vaccination history, and occupation- and community-related behaviour.

### 3.10.3 Active follow-up

The objective of the follow-up is to identify among the cohort of participating HCWs new cases of SARS-CoV-2 infection, changes in vaccination status (e.g. unvaccinated people who received the vaccine, those vaccinated with one dose who received the second dose) and changes in potential exposures (e.g. HCWs working in different wards, contacts with COVID-19 cases).

Study participants should be regularly and actively followed up to perform:

1. **Monitoring:** Participants are followed up with a weekly survey to report changes in health or vaccination status as well as likely professional and personal exposures. The questionnaire can be completed directly by the HCWs or by a study site monitor as part of regular weekly contacts.
2. **Molecular (RT-PCR and genomic sequencing) testing:** Samples are to be collected from participants weekly, irrespective of symptoms, and tested by RT-PCR. Samples can be either nasal, naso- or oropharyngeal swabs which can be taken by a trained study monitor or by the HCWs themselves after suitable training. As an alternative, to improve acceptability and feasibility of the weekly follow-up, self-taken saliva samples can also be provided by HCWs which have been shown to perform well in comparison to naso- or oropharyngeal swabs, particularly in the early stages of infection [10-14] (see Section 4).  
Participants diagnosed with SARS-CoV-2 infection should be followed-up for outcomes including disease severity and re-infection. Study site investigators should select for genetic sequencing samples from all or a proportion of specimens of SARS-CoV-2 confirmed infections in participants (see Section 4).
3. **Serology:** Blood samples are to be taken regularly during the follow up at intervals of 6-12 weeks, to identify asymptomatic cases that could have been infected during the study period and to assess antibody levels over time (see Section 4).

**Alternative sampling schedules:** The protocol proposes a weekly follow-up of participants with samples and questionnaire, which study sites may find difficult to achieve. Thus, alternative schedules which may be employed include biweekly specimen collection. This should not include saliva samples and include only nasal, naso- or oropharyngeal swabs for RT-PCR testing, even though this will be at the extremes of sensitivity [12].

**Table 2. Timing of questionnaires and specimen collection**

Timing in the study	Questionnaire	Molecular testing	Serology
<b>Enrolment</b>			
	Enrolment questionnaire	Nasal, naso- or oropharyngeal swab or saliva specimen (case by case basis)	Serum
<b>Follow-up</b>			
Weekly	Weekly update	Nasal, naso- or oro-pharyngeal swab or saliva specimen	-
Every 6-12 weeks	-	-	Serum
Onset of symptoms*	Update on symptoms	Nasal, naso- or oral-pharyngeal swab	-
Confirmed SARS-CoV-2 infection*	Update on symptoms and outcomes	Genetic sequencing of all or a sample of confirmed cases	-

\*Compatible with ECDC COVID-19 case definition [9]

**Note:** The objective of this study is to estimate VE against infection which requires regular (weekly or bi-weekly) swabbing and testing of participants. Thus, the protocol does not include swabbing (nasal, naso- or oropharyngeal) and testing of participants only when they report COVID-19 related symptoms and/or contact with confirmed cases. This latter sampling schedule will only allow VE against symptomatic disease to be calculated.

**Note:** Irrespective of participation in the VE study, HCWs providing care to COVID-19 patients should be actively followed up for development of symptoms and provided with occupational health support. Hospitals should maintain a record of all HCWs providing care for possible and confirmed COVID-19 cases. These HCWs should be trained in reporting procedures and report any symptoms, and if developing fever or any other symptoms compatible with COVID-19 within 14 days of their last exposure to a confirmed case, they should be tested and be relieved of their duties if they become unwell and quarantined according to the national recommendations in place (See also ECDC guidance "Infection prevention and control and preparedness for COVID-19 in healthcare settings" [15]).

- Each study site/hospital/country to describe precisely all the study procedures.

### 3.11 Data collection and data sources

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

- age;
- sex;
- smoking status, body mass index (BMI);
- presence of chronic disease(s): at least one chronic condition, specific conditions;
- previous SARS-CoV-2 infection (clinical or laboratory-confirmed);
- vaccination status for COVID-19 and other respiratory pathogens (influenza, pneumococcus);
- hospital exposure to SARS-CoV-2 (professional exposure to COVID-19 cases, use of PPE, compliance with Infection Prevention and Control measures, involvement in aerosol-generating procedures);
- community exposure to SARS-CoV-2 (household makeup, personal exposure to confirmed COVID-19 cases and use of PPE in social situations);
- molecular and serological testing results.

The weekly monitoring form can be completed by the participant either online or using a mobile-enabled platform. Where participants receive a confirmed diagnosis of SARS-CoV-2 infection, the participants or study site investigators should complete the online questionnaire. The minimum data that should be collected during follow-up are:

- absence or presence of symptoms with date of onset of symptoms;
- date of PCR testing and PCR results;
- clinical course of infection (including outpatient and inpatient visits);
- additional vaccinations (COVID-19, influenza or pneumococcal);
- changes in professional exposure;
- changes in community exposure.

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

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

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

The table below summarises the data to be collected. For each variable, possible and optimal data sources should be identified.

**Table 3. Data collection of 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
<b>Socio Demographic</b>	Age	Key	✓	X
	Sex	Key	✓	X
	Ethnicity	Optional	✓	X
	Blood group	Optional	✓	X
	Socioeconomic status	Optional	✓	X
<b>Chronic conditions (includes pregnancy)</b>	Diagnosis chronic condition	Key	✓	X
	Medication for chronic condition	Optional	✓	X
<b>Individual behaviours/attitude</b>	Smoking (current/past/never)	Key	✓	X
	BMI (collect height and weight)	Key	✓	X
	Alcohol use	Optional	✓	X
<b>COVID-19 vaccination</b>	Vaccine dose received (for each dose: first, second, booster doses) Yes/no	Key	✓	✓ (if status changes)
	Vaccination date(s) (for each dose)	Key	✓	✓ (if status changes)
	Vaccine product	Key	✓	✓ (if status changes)
	Vaccine batch	Key	✓	✓ (if status changes)
	Source used for vaccine ascertainment	Key	✓	✓ (if status changes)
<b>Previous vaccinations</b>	Influenza vaccination/Influenza vaccination date	Key	✓	✓ (if status changes)
	Pneumococcal vaccination	Key	✓	✓ (if status changes)
	Pneumococcal vaccination (month, year)	Optional	✓	✓ (if status changes)
<b>SARS-CoV-2 infection (Last episode)</b>	Laboratory/clinical/self-reported confirmed	Key	✓	X
	List of symptoms	Key	✓	✓ (if reported)
	Date of onset	Key	✓	✓ (if reported)
	Severity (symptomatic, hospitalisation, ICU admission)	Key	✓	✓ (if reported)
	Type of the test used for confirmation	Key	✓	✓
<b>Hospital exposures</b>	Occupation	Key	✓	✓ (if status changes)
	Wards	Key	✓	✓ (if status changes)
	Contact with suspected and confirmed COVID-19 patients	Key	✓	✓ (if status changes)
	Contact with a symptomatic or asymptomatic HCW who tested positive	Key	✓	✓ (if status changes)
	Involvement in aerosol generating procedures (list)	Key	✓	✓ (if status changes)
	Use of PPE	Key	✓	✓ (if status changes)
	Compliance with IPC measures	Key	✓	✓ (if status changes)
<b>Community exposures</b>	Contact with confirmed COVID-19 cases outside the hospital (Yes/no, date)	Key	✓	✓ (if status changes)
	Household size and make-up	Key	✓	X
	Frequency of wearing mask and type of mask	Key	✓	✓ (if status changes)
	Frequency of respecting 2 meters distance in indoors space	Key	✓	✓ (if status changes)
	Frequency of participating in indoor gatherings	Key	✓	✓ (if status changes)
	Use of public transport	Key	✓	✓ (if status changes)
<b>Laboratory results</b>	PCR	Key	✓	✓
	Genomic variant for positive cases	Key	✓	✓
	Serology	Key	✓	✓

➤ *Each study site/hospital/country to list variables collected.*



## 3.12 Data analysis

Data validation, cleaning, and verification will be carried out at study level.

For the pooled data, interim analyses will be conducted in different periods if appropriate and according to the available sample size. The timing to conduct each interim analysis will depend on the time needed to reach the appropriate sample size. This will depend mainly on COVID-19 incidence, vaccination coverage, the recruitment strategy within hospitals, and the number of participating hospitals/services per hospital.

The pooled analysis will be carried out in a similar way to the study site-specific analysis. The study participants should be described in terms of total number of eligible HCWs, and total number and proportion of HCWs who were lost to follow-up and reasons for loss of follow-up. Participants will be described according to the baseline characteristics.

Participants will be followed from baseline to censoring from the study, either due to detection of infection/disease (i.e. detection of outcome) or study exit. VE should be calculated using Cox regression ( $VE = 1 - \text{hazard ratio [HR]}$ ) or Poisson regression ( $VE = 1 - \text{rate ratio of vaccination [RR]}$ ). Country or study site will be included potentially as a fixed effect or as a random effect in a multilevel model. Statistical heterogeneity between study sites will be determined, using Q-test and the  $I^2$  index [8].

VE should be measured comparing outcomes by person's time at risk among vaccinated and unvaccinated groups. To date, participating study sites have reported very high vaccination uptake (>90%) among HCWs. The unvaccinated cohort may therefore not be a good reference group, both because of small numbers and also the representativeness of such a group. Thus, additional approaches should be employed to measure relative vaccine effectiveness (rVE) comparing the incidence rate of SARS-CoV-2 infection in HCWs who have received different COVID-19 vaccine regimens, or according to different vaccination and/or cases characteristics, including, for example:

1. HCWs who received the recommended primary vaccination schedule and those who have received primary and booster doses;
2. HCWs who did not comply with vaccination recommendations according to the number of doses, time elapsed between the doses, and type of the vaccine received compared to those who received the recommended vaccination schedule;
3. According to the time since vaccination;
4. According to the SARS-CoV-2 variant.

These different analysis approaches are detailed in Supplementary document 2, Statistical analysis plan.

## 4. Laboratory methods

### 4.1 Specimen collection

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

- **Respiratory samples:** to be taken by a dedicated medical staff (i.e. research nurse) or by study participants if they undergo a brief training;
- **Saliva samples:** to be taken by study participants after they undergo a brief training;
- **Blood samples:** venepuncture or dried blood samples can be used to obtain sera or plasma. The amount of blood drawn should be determined based on the specific requirements of the serological tests that will be carried out.

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 on 28 January 2021 and [‘Laboratory testing for coronavirus disease \(COVID-19\) in suspected human cases’](#), published on 19 March 2020), as well as WHO’s general laboratory guidance ([‘General guidance of laboratory biosafety – 3rd edition’](#), updated in 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 should also be recorded.

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

### 4.2 Specimen storage, shipment, and transport

All individuals 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](#).

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

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

Serum should be separated from whole blood and can be stored and shipped at  $4\text{ }^{\circ}\text{C}$  or frozen to  $-20\text{ }^{\circ}\text{C}$  or lower and shipped on dry ice.

An aliquot of Peripheral Blood Mononuclear Cells (PBMCs) can be stored for studies of cell-mediated immunity.

The samples can be entered into a biobank for future research projects if participants consent. All positive and inconclusive samples and proportion of the negative samples from pre/during/post epidemic wave should be stored and used for additional testing as approved under this study.

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](#).

### 4.3 Specimen testing

➤ *Each study site to describe all the laboratory procedures:*

- Samples taken, storage, transport;
- Laboratory platforms /assays used and performance;
- Participation in quality assurance/quality control schemes, accreditation (ISO/national standards);
- Selection of specimens for sequencing.

### 4.3.1 Molecular testing

Laboratory guidance for **molecular testing** for COVID-19 can be found on the [WHO](#) and [ECDC](#) websites and summarised in Supplementary document 3. Several assays that detect SARS-CoV-2 have been developed and the protocols or standard operating procedures (SOPs) can also be found on [WHO's website](#). Quality assurance of assay performance at study sites should be undertaken using international, national or research standards [16].

Testing for SARS-CoV-2 with RT-PCR should be undertaken on the following specimens and time points:

- At enrolment using a specimen collected with nasal, naso- or oropharyngeal swab or saliva specimen. Saliva specimen can be taken at enrolment if the procedure is validated at specific laboratory level with a good concordance compared to nasopharyngeal swabbing.
- For all symptomatic participants who meet the ECDC suspected case definition using a specimen collected with nasal, naso- or oropharyngeal swab or saliva sampling.
- Regular follow-up for all participants, regardless of symptoms, using a specimen collected with nasal, naso- or oral-pharyngeal swab or saliva sampling.

If possible, RT-PCR should be performed for other respiratory pathogens such as influenza and respiratory syncytial virus (RSV).

### 4.3.2 Serological testing

Specific serology tests to be used should be determined by each study site. Acceptable sensitivity and specificity for quantitative tests are 95% and 97% or above, with desirable parameters of 98% and 99% or above, respectively [17] (see Supplementary document 3 for guidelines). Serology for SARS-CoV-2 should be undertaken to measure total antibodies, IgM or IgG (depending on tests used) to a panel of SARS-CoV-2 antigens at the following time points:

- Serology at enrolment;
- Regular follow-up whether every 6-12 weeks as often as resources permit.

Consideration should be given to using serology tests that can distinguish between natural and vaccine-induced immunity. If a HCW has already been vaccinated when the study starts and depending on the vaccine type, it will be important to differentiate natural and vaccine-induced immunity at baseline. All vaccines currently used in the participating study sites are targeting the spike-protein<sup>2</sup>. Serological tests detecting SARS-CoV-2 spike (S) and nucleocapsid (N) antibodies should be used for distinguishing infection (i.e. S+/N+) from vaccine-acquired antibodies (i.e. S+/N-) [18].

### 4.3.3 Genetic sequencing

All or a random sample of SARS-CoV-2 RT-PCR positive specimens collected among HCWs with a Ct value less than 30 should be further characterised using genetic sequencing. Genetic sequencing is particularly important to undertake during the study to understand whether changes in VE could be due in part to mutations in the circulating virus. Investigators should also ensure genetic sequences are uploaded into the appropriate [GISAID](#) and EMBL/ENA platforms.

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<sup>2</sup> On 24 June 2022, the European Commission granted a [marketing authorisation](#) for COVID-19 Vaccine (inactivated, adjuvanted) Valneva for use in the primary vaccination of people from 18 to 50 years of age. COVID-19 Vaccine Valneva contains inactivated (killed) whole particles of the original strain of SARS-CoV-2 that cannot cause disease. However, this vaccine has so far not been used in the participating study sites. Serological assays might need to be adapted in case of including individuals vaccinated with Valneva.

## 5. Limitations

- **Laboratory tests:** Misclassification of the outcome can occur due to the test performance. In the analysis, sensitivity and specificity of the tests can be adjusted for. Study sites will employ different tests and thus investigators should seek to use common international, national or research standards to address possible variation in test performance at study sites. Currently the National Institute of Biological Standards and Control offers international standards for molecular and serological testing [16].
- Selection bias:
  - **Previous infections:** HCWs are a population at high risk of exposure to SARS-CoV-2 infection. With the current knowledge, it is difficult to determine the immunity conferred by natural infection. Individuals previously infected may be less likely to accept vaccination and may have some immunity. This will result in an underestimation of the VE. The analysis taking into account previous infection will address this potential selection bias.
  - **Indication bias:** there may be a different likelihood to be vaccinated according to professional exposure (activities) to the virus or due underlying conditions. This potential bias will be adjusted in the analysis using information collected on the potential exposures and underlying conditions.
  - **Healthy vaccinee effect:** individuals in better health conditions are more likely to get vaccinated, which could potentially lead to an underestimation of VE. In addition, vaccinated HCWs may be more (or less) likely to use PPE and less (or more) likely to be exposed to the virus. This potential bias will be addressed in the analysis using information collected on PPE use.
- **Reporting bias:** vaccinated cases may be more likely or less likely to report symptoms and VE against symptomatic SARS-CoV-2 may be overestimated or underestimated accordingly.
- **High vaccine coverage:** Study sites that have very high vaccine coverage in HCWs may find:
  - Reduced study power with insufficient number of outcomes in HCWs who are unvaccinated. If vaccine coverage is very high this may require alternative methods to estimate VE (see section 3.12).
  - Selection bias as HCWs 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 among HCWs, the study may lack power (see above). In such circumstances, retrospective analysis of data collected at enrolment will be employed to estimate VE or prospective analysis as described above (see Section 3.11 and 6.1).
- **Unmeasured or residual confounding** between vaccinated and unvaccinated may be present such as risky behaviours, beliefs affecting exposure and vaccine acceptancy.
- **The quality of self-reporting information** may be different between vaccinated and unvaccinated.
- **Differences of incidence and vaccination policy and coverage over time or between hospitals:** The risk of exposure to the virus and its variants and the vaccination coverage will be different between hospitals (if several hospitals included), between regions/countries (if multicentre study is conducted) and over time. Multilevel analysis and adjustment by time will be used to minimise the effect of this differences in exposures.

## 6. Ethical considerations

Studies of COVID-19 VE in HCWs should be approved by the relevant local Ethics Review Committee.

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

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

### 6.1 Personal data protection

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

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

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

## 7. Data governance

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

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

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

## 8. Prevention of SARS-CoV-2 infection in investigation personnel

Study staff should be trained in IPC procedures (standard, contact, droplet, and airborne precautions, as determined by national or local guidelines). These procedures should include proper hand hygiene and the correct use of medical respirators, if necessary. Investigators should review ECDC's guidance for IPC in healthcare settings [15]. Furthermore, investigators can complete WHO's online training course 'Infection Prevention and Control (IPC) for Novel Coronavirus (COVID-19)' [<https://openwho.org/courses/COVID-19-IPC-EN>].

## 9. Risks and benefits for subjects

This study poses minimal risk to participants involving the collection of a small amount of blood and the collection of respiratory specimens. Results of PCR tests and serology will be shared with participants as soon as they are available. The direct benefit to the participant will be the potential 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.



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