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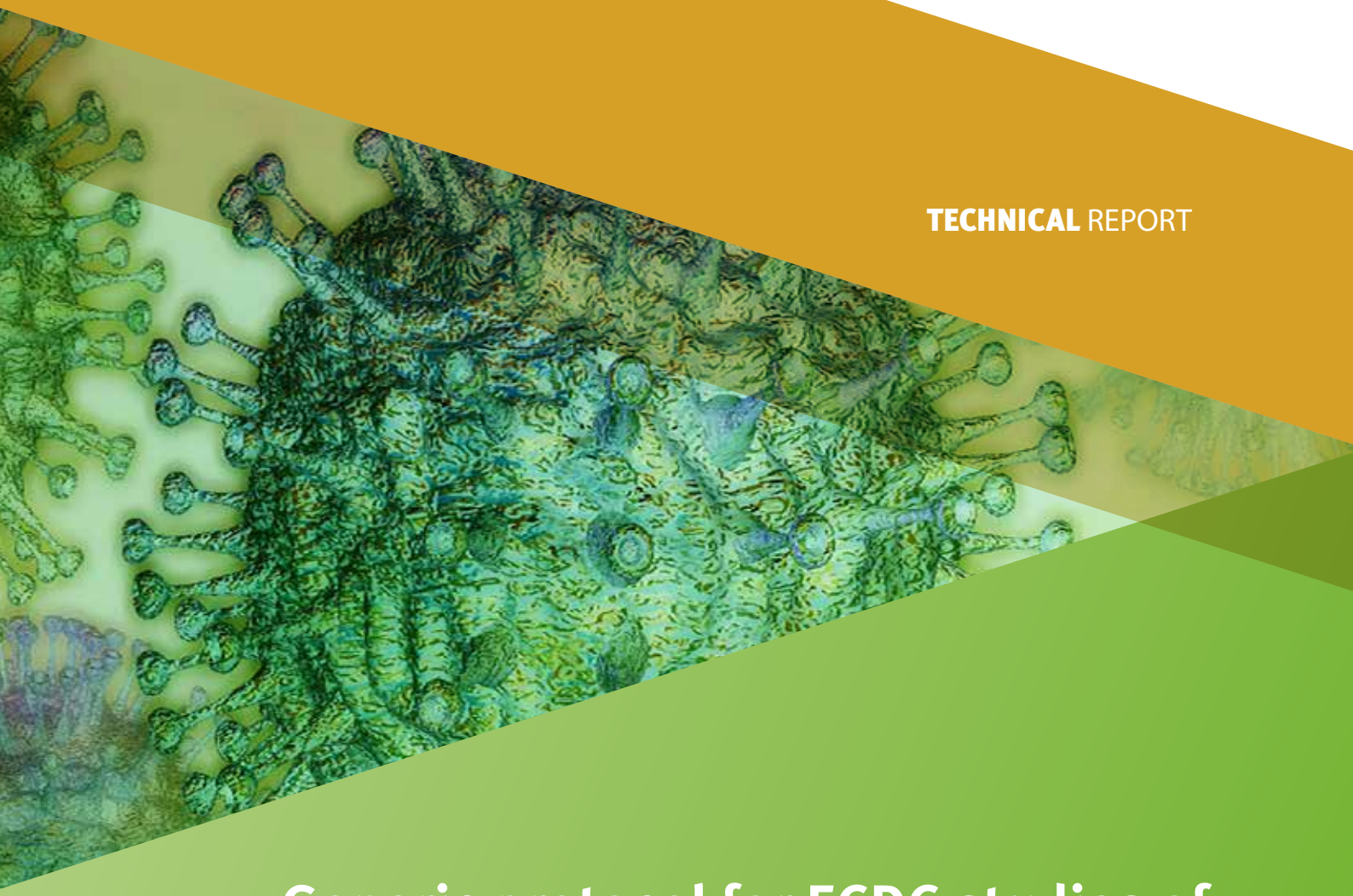

TECHNICAL REPORT

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

Version 3.0

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These updated generic protocols were 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 and version 2.0 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. Version 3.0 includes updates of the data collected on symptoms, community exposures and harmonises the serology data collection.

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Abbreviations

ARI	Acute respiratory infection
COVID-19	Coronavirus disease 2019
Ct	Cycle threshold
CVE	COVID-19 vaccine effectiveness
EEA	European Economic Area
EU	European Union
GDPR	General Data Protection Regulation
HCW	Healthcare worker
HR	Hazard ratio
IPC	Infection prevention and control
ICF	Informed consent form
ILI	Influenza-like illness
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
OR	Odds ratio
PCR	Polymerase chain reaction
PPE	Personal protective equipment
RR	Rate ratio
rVE	Relative vaccine effectiveness
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 December 2023, eight vaccines (Comirnaty, Spikevax, Vaxzevria, Jcovden Valneva, Nuvaxovid, VidPrevtyn, and Bimervax) have been authorised for use in the European Union (EU) by the European Commission, based on the scientific opinion of the European Medicines Agency (EMA). Updated formulations of Comirnaty and Spikevax to protect against the original and BA.4-5 strains were authorised in 2022. Adapted versions using the Omicron XBB.1.5 strain were authorised on 31 August (Comirnaty), 15 September (Spikevax), and 31 October (Nuvaxovid) 2023 [1].

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 studies, ECDC started building infrastructure to perform COVID-19 vaccine effectiveness studies. The infrastructure aims to build a system to regularly monitor vaccine effectiveness and perform studies in different settings, and depending on the setting, to provide information on different outcomes (severe disease, moderate disease, infection, transmission, etc). The studies have been embedded in a project called VEBIS (Vaccine Effectiveness, Burden and Impact Studies).

This generic protocol 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 vaccines can be enrolled in the study, including those who have already been vaccinated with a primary COVID-19 vaccination course, those that 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 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. 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 at enrolment and thereafter every 12 weeks (three samples during the winter season) 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 also 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 included 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. This updated version 3.0 includes recommendations for COVID-19 surveillance after the pandemic phases as well as recommendations from participating sites until end of May 2023.

Changes in version 3.0

The main changes in this version compared to version 2.0 include data collection on clinical characteristics to reconstitute the acute respiratory infection (ARI) and influenza-like illness (ILI) case definitions according to the current recommendations for respiratory diseases surveillance, and additional clarifications on serology data collection section and community exposures, as well as additional analyses: restrictions by circulation of different sub-lineages of Omicron VOC, relative vaccine effectiveness analysis comparing the second and first booster doses and first booster dose and primary course, adjusted analysis and inclusion of re-infections. The second version of this protocol (see version 2.0) was used until 21 May 2023.

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.

International collaborative efforts have accelerated the development of COVID-19 vaccines. As of 30 March 2023, 183 candidate vaccines were in clinical development and 199 were in preclinical development [2]. Within the EU/EEA, as of December 2023, eight vaccines, of which seven are spike-protein-based and one inactivated vaccine, have been given the marketing authorisation by the European Commission based on an opinion by the European Medicine Agency (EMA) [1]. In the initial context of limited vaccine supplies, target groups for the prioritisation of COVID-19 vaccination were established. Healthcare workers (HCWs) were included among the priority groups for COVID-19 vaccination [3] 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]. The vaccination recommendations evolved over time, but HCWs remained among priority groups for booster vaccination in many EU/EEA countries [7] and at the global level in order to maintain the healthcare systems' resilience [8].

Evaluating the real-world COVID-19 vaccine performance is critical for understanding the risks and benefits of vaccination programmes. Many factors impact real-world vaccine effectiveness (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 [9]. 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 the European Centre for Disease Prevention and Control (ECDC) generic protocol version 3.0 for a prospective multi-country cohort study to evaluate the effectiveness of the COVID-19 vaccine in hospital-based health workers, which will be used to implement the study starting 1 October 2023. This document outlines standardised methods for establishing the study, collecting data and undertaking analysis as well as allowing for necessary local adaptions. Version 2.0 of this protocol was used for the sites that started the study after March 2022. 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 before 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 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 vaccine effectiveness studies, ECDC started building infrastructure to perform COVID-19 vaccine effectiveness studies. The infrastructure aims to build a system to regularly monitor vaccine effectiveness and perform studies in different settings, and depending on the setting, to provide information on different outcomes (severe disease, moderate disease, 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 characterizes the studies, with a foreseen progressive inclusion of more countries over time.

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

1.3 Aim of the protocol

This ECDC protocol for studies of COVID-19 vaccine effectiveness against confirmed SARS-CoV-2 in healthcare workers covers the main elements of a hospital-based study of COVID-19 vaccine effectiveness 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 vaccine effectiveness 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 vaccine effectiveness. Specifically, each study site has been identified through a process involving the countries' relevant National Coordinator[1] 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 **version 3.0** of the generic 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, and statistical analysis plan that are available upon request by emailing vpd.vpd@ecdc.europa.eu or adminepidemio@epiconcept.fr

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.

[1] 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 COVID-19 vaccine effectiveness (VE) amongst 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 infection by SARS-CoV-2 variants of interest/concern;
- against symptomatic laboratory-confirmed COVID-19 infection and according to different case definitions;
- against asymptomatic laboratory-confirmed COVID-19 infection;
- against severe laboratory-confirmed COVID-19 infection;
- 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 (pre-enrolment) 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 HCWs 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 HCWs in participating hospitals, eligible for vaccination, with no contraindication to receive COVID-19 vaccine.

3.4 Inclusion criteria

All categories of HCWs 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 the patient but who have had contact with the patient's 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 adapted from the WHO definition [10] 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 eligible for vaccination 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 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 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
- 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 outcome** 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 meet the ECDC/WHO ARI/ILI case definition [11]:

Clinical characteristics ILI

- sudden onset of symptoms AND
- at least one of the following four systemic symptoms: fever- of feverishness, malaise, headache, myalgia, AND
- at least one of the following three respiratory symptoms: cough, sore throat, shortness of breath/dyspnoea

Clinical characteristics ARI:

- sudden onset of symptoms AND
- at least one of the following four respiratory symptoms: cough, sore throat, shortness of breath/dyspnoea, coryza, AND
- a clinical judgement that the illness is due to an infection.

Specific symptoms previously used for COVID-19 case definition will be collected but are not included in the general case definition.

- 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/WHO ARI/ILI case definition positive for 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/WHO ARI/ILI case definition positive for COVID-19 requiring hospitalisation and oxygen treatment;
- **Very severe disease:** reported symptoms consistent with the ECDC/WHO ARI/ILI case definition positive for 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 vaccine effectiveness, 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 /reference group (Table 1). 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 e.g. exclusion of this group from the main analysis and use other reference groups (see 3.13).

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 HCWs will change the vaccination status.

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 the reference group	VE (%)	Vaccine coverage (%)	Total sample size	Unvaccinated		Vaccinated	
				N	Number events	N	Number 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

Yearly hazard rate in the reference group	VE (%)	Vaccine coverage (%)	Total sample size	Unvaccinated		Vaccinated	
				N	Number events	N	Number events
		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
	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. The HCWs who participated in the first rounds of the study can also be invited.

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, making information available to HCWs at the selected hospitals. Investigators should make themselves available to HCWs to describe the study, 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 Annex 1 for 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 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) and changes in potential exposures (e.g. HCWs working in different wards, contacts with COVID-19 cases) among the cohort of participating HCWs.

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

- **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.
- **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, as these have been shown to perform well in comparison to naso- or oropharyngeal swabs, particularly in the early stages of infection [12–16] (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).

- **Serology:** Blood samples are to be taken regularly during the follow-up at intervals of 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).

Table 2. Timing of questionnaires and specimen collection

Timing in the study	Questionnaire	Molecular testing	Serology
Enrolment			
	Enrolment questionnaire	Nasal, naso- or oropharyngeal swab or saliva specimen (case by case basis)	Serum
Follow-up			
Weekly	Weekly update	Nasal, naso- or oro-pharyngeal swab or saliva specimen	-
Every 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/WHO ARI/ILI case definition [11].*

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

Note: *The objective of this study is to estimate vaccine effectiveness against infection which requires regular (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 vaccine effectiveness against symptomatic disease to be calculated.*
Note: *Irrespective of participation in the vaccine effectiveness study, HCWs developing the respiratory symptoms should comply with the local or national recommendations in place regarding infections prevention and control (See also the updated ECDC guidance 'Considerations for infection prevention and control in relation to respiratory viral infections in healthcare settings' [17]).*

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 on-line 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 on-line 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
Socio Demographic	Age	Key	✓	X
	Sex	Key	✓	X
	Ethnicity	Optional	✓	X
	Blood group	Optional	✓	X
	Socioeconomic status	Optional	✓	X
Chronic conditions (includes pregnancy)	Diagnosis chronic condition	Key	✓	X
	Medication for chronic condition	Optional	✓	X
Individual behaviours/attitude	Smoking (current/past/never)	Key	✓	X
	BMI (collect height and weight)	Key	✓	X
	Alcohol use	Optional	✓	X
COVID-19 vaccination	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 brand	Key	✓	✓ (if status changes)
	Source used for vaccine ascertainment	Key	✓	✓ (if status changes)
Previous vaccinations	Influenza vaccination/ Influenza vaccination date	Key	✓	✓ (if status changes)
	Pneumococcal vaccination	Key	✓	✓ (if status changes)
	Pneumococcal vaccination (month, year)	Optional	✓	✓ (if status changes)
SARS-CoV-2 infection (Last episode)	Laboratory/clinical/self-reported confirmed	Key	✓	X
	Updated list of symptoms to reconstitute ARI and ILI case definitions	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	✓	✓
Hospital exposures	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)
Community exposures	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 participating in indoor gatherings	Key	✓	✓ (if status changes)
	Use of public transport	Key	✓	✓ (if status changes)
Laboratory results	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. An infected HCW will be re-entered in the analysis at 60 days since the first positive PCR test. Vaccination effectiveness (VE) should be calculated using Cox regression (VE = 1 – hazard ratio [HR]) or Poisson regression (VE = 1 - 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.

Vaccine effectiveness should be measured comparing outcomes by person time at risk among vaccinated and unvaccinated groups. To date, participating study sites have reported very high vaccination uptake (>90%) among HCWs. Thus, the unvaccinated cohort may 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. Due to moving away from counting number of booster dose received and instead towards seasonal vaccination of groups at risk, the measurement of seasonal CVE should also be included in the analysis plan. Examples of analysis for CVE include:

1. HCWs who received vaccine primary schedule and those who have received first and second booster doses;
2. HCWs vaccinated with any COVID-19 vaccine in autumn/winter 2022/23 and those not vaccinated in autumn/winter 2022/23, nor in the six months preceding the autumn/winter 2022/23 campaign;
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 that 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 the Plan of Analysis specific to each analysis (to be obtained on request).

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 28 January 2021 and 'Laboratory testing for coronavirus disease (COVID-19) in suspected human cases,' published 19 March 2020), as well as WHO's general laboratory guidance ('General guidance of laboratory biosafety- 3rd edition,' updated 2004).

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

Note: *We recommend 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 the WHO website.

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

If a respiratory specimen is not likely to reach the laboratory within 72 hours, it should be frozen, preferably at –80 °C, and shipped on dry ice. It is recommended to aliquot samples prior to freezing, to minimize 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 °C or frozen to –20 °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 the 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 Annex 2. Several assays that detect SARS-CoV-2 have been developed and the protocols or standard operating procedures (SOPs) can also be found on the WHO website. Quality assurance of assay performance at study sites should be undertaken using international, national or research standards [18].

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;
- Regular follow-up for all participants, regardless of symptoms, using a specimen collected with nasal, naso- or oral-pharyngeal swab or saliva sampling.

If multiplex RT-PCR assay available, testing 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 [19]. 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 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[2]. 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-) [20].

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 vaccine effectiveness could be due in part to mutations in the circulating virus. Investigators should also ensure genetic sequences are uploaded into the appropriate GISAID and EMBL/ENA platforms.

[2] 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 [18].
- **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 vaccine effectiveness. 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 or vaccinated with primary course only. This may require alternative methods to estimate vaccine effectiveness (see section 3.12).
  - Selection bias as HCWs who remain unvaccinated or vaccinated with a primary course only 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. 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 virus circulation and vaccination.

6 Ethical considerations

Studies of COVID-19 vaccine effectiveness 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 biologic materials and data. Data governance statements should address how long data will be stored, when data will be destroyed, access to data during and after the study, and how participants can withdraw permission for use of their data.

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

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 guidance for IPC in healthcare settings [17,21] Furthermore, investigators can complete WHO's online training course 'Infection Prevention and Control (IPC) for Novel Coronavirus (COVID-19)' at 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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Annex 1. Informed consent form

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

Notes to study teams:

1. 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.**

2. The informed consent form consists of two parts: the information sheet and the consent certificate.

3. Do not be concerned by the length of this template. It is long only because it contains guidance and explanations that are for you and that you will not include in the informed consent forms that you develop and provide to participants in your investigation.

4. This template includes examples of key questions that may be asked at the end of each section, which could ensure understanding of the information being provided, especially if the investigation is complex. These are just examples and suggestions, and the investigators will have to modify the questions depending upon their study.

5. 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.

Annex 2. Template for Informed Consent Form

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

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

This Informed Consent Form has two parts:

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

You will be given a copy of the full Informed Consent Form

Part I: Information Sheet

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

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

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

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

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

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

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

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

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

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

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

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

Storage of tissue samples:
Explain that you are seeking permission to store their unused respiratory and blood samples for possible future use in either your own research or someone else's research, mainly the serology specimens (to check the protection for other respiratory pathogens). State that they need to make some decisions about storage and future use of their respiratory and blood samples because they gave you permission only to use it for the current research.

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

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

PART II: Certificate of Consent

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

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

Print Name of Participant _____

Signature of Participant _____

Date _____ **Day/month/year**

Statement by the researcher/person taking consent

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

A copy of this Informed Consent Form has been provided to the participant: ____

Print Name of Researcher/person taking the consent _____
Signature of Researcher/person taking the consent _____

Date _____ **Day/month/year**

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