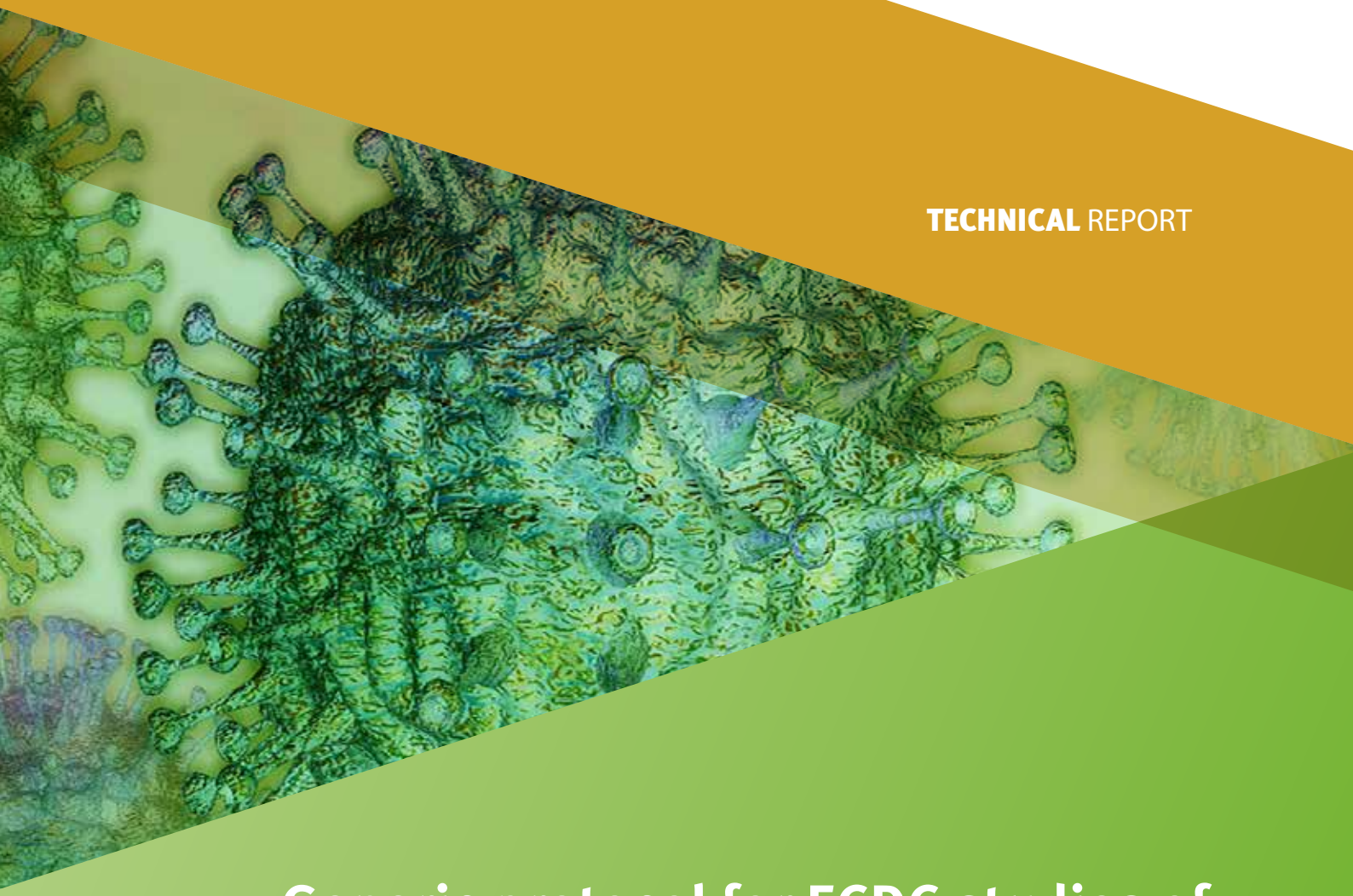

TECHNICAL REPORT

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

Version 1.0

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ECDC TECHNICAL REPORT

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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 review by ECDC and possible study sites.

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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 virus associated with a 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, ECDC started building infrastructure to perform COVID-19 vaccine effectiveness (VE) studies at the end of 2020, utilising the lessons learned from other 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). Many critical questions remain about the effectiveness of COVID-19 vaccines in real-world settings. These questions can only be answered in post-marketing VE 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 vaccine 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 a 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 whether to be vaccinated. 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 swab should be collected from participants.

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

- **Molecular testing:** participants should provide a weekly sample, either a nasopharyngeal 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. Alternative sampling schedules (e.g. bi-weekly nasopharyngeal swabs) are discussed in the protocol, but these will limit the sensitivity of detecting infection and hence estimates of VE against asymptomatic infection. 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 brief weekly survey reporting the appearance of any COVID-19-related symptoms and any changes in high-risk exposures to infection (both professional and personal).
- **Serology:** serum samples should be collected periodically (at enrolment and thereafter every 6–8 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 generic 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.

This document presents the first version of the protocol, which relates to the implementation of the study during 2021; the protocol has been updated and revised over the first year of implementation of the study (see version 2.0).

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 22 July 2022, 169 candidate vaccines were in clinical development and 198 were in preclinical development [3]. Within the EU/EEA, as of 7 November 2022, six vaccines, of which five are spike-protein-based and one inactivated vaccine, have been given marketing authorisation by the European Medicine Agency (EMA). In addition, four adapted mRNA vaccines have also been authorised for use in the EU/EEA. These bivalent vaccines contain the original strain plus either Omicron subvariant BA.1 or BA.4-5. [2]. In the 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 affect 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 [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 the ECDC 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 during the first year. This document outlines standardised methods for establishing the study, collecting data and undertaking analysis as well as allowing for necessary local adaptions.

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 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 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 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 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 ECDC's protocol is presented in this document, is a multi-country study aimed at estimating COVID-19 VE against confirmed SARS-CoV-2 infection, by assessing it in hospital-based HCWs.

1.3 Aim of the protocol

This ECDC generic protocol for studies of COVID-19 VE against confirmed SARS-CoV-2 in HCWs covers the main elements of a hospital-based study of COVID-19 VE in HCWs, outlining the standardised methods for collecting data related to COVID-19 and SARS-CoV-2 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 Coordinatori 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 first 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.

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 ECDC's protocol.

[i] 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 HCWs eligible for vaccination against all 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
- 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 patient-facing vs. non-patient-facing HCWs

    - *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 within which HCW cohorts are recruited, including type and size of hospital (e.g. number of wards and beds), number of COVID-19 patients admitted since the beginning of the pandemic, at the start of and during the study, incidence in the area, etc.*
- *Data on each study site/hospital/country, including local and national incidence of COVID-19, implementation of public health and social measures, as well as infection and prevention control measures and their coverage.*

3.2 Study design

This is a prospective longitudinal 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 HCW in hospitals can be included. HCWs are defined as all staff in the healthcare facility involved in the provision of care for patients: 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, cleaners, 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 3.7).

- *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.

HCWs who have already been vaccinated against COVID-19 vaccine in clinical trials will be excluded.

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

Vaccine documentation should include for each dose:

- COVID-19 vaccination received and date of vaccination
- Vaccine brand
- Vaccine batch
- Ascertainment (e.g. self-reported, documented, vaccine registry etc)

➢ *Each study site/hospital/country to describe how vaccination status will be ascertained*

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 ECDC's 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 conforms 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 either admittance to an intensive care unit and/or intubation or mechanical ventilation.

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 and assuming 4 months follow up.

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 calculates 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), assuming four months follow-up

Yearly hazard rate in unvaccinated	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
		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.

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 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 (T0). 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 4.4).

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. A minimum information should be collected from the HCWs declining participation (age, sex, occupation, vaccination).

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 Section 7 for more details). Study staff should describe the study in detail, answer all questions, and review the informed consent form with the potential participant 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 for RT-PCR;
- Provide a blood sample for serology;
- 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 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. **Molecular (RT-PCR and genomic sequencing) testing:** Samples are to be collected from participants every week, 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 HW which have been shown to perform well in comparison to naso- or oropharyngeal swabs, particularly in the early stages of infection [10-14].

Participants diagnosed with SARS-CoV-2 infection should be followed-up for outcomes including disease severity. Site investigators should select for genetic sequencing samples from all or a proportion of SARS-CoV-2 confirmed infections in participants.

2. **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.
3. **Serology:** Blood samples are to be taken regularly during the follow up at intervals of 6–8 weeks, to identify asymptomatic cases that could have been infected during the study period and to assess antibody levels over time (see Section 5.3.2).

Alternative sampling schedules: The protocol proposes a weekly follow-up of participants with samples and questionnaire which sites may find difficult to achieve. Thus, alternative schedules which may be employed include:

- Biweekly collection, in which case it should not include saliva samples and include only nasal, naso- or oropharyngeal swabs for RT-PCR testing, even though this may mean that some infections will only be detected at the extremes of the range of sensitivity of RT-PCR [12].
- Collection of nasal, naso- or oropharyngeal swabs only when participants report COVID-19 related symptoms and/or contact with confirmed case. This sampling schedule will only allow VE against symptomatic disease to be calculated. Sites proposing to undertake only sampling of symptomatic HCWs should ensure a cohort of HCWs of a minimum size is recruited with more frequent sampling to allow estimation of VE against infection.

Table 2. Timing of questionnaires and specimen collection

Timing in the study	Questionnaire	Molecular testing	Serology
Enrolment			
	Enrolment questionnaire	Nasal, naso- or oropharyngeal swab	Serum
Follow-up			
Weekly	Weekly update	Nasal, naso- or oral-pharyngeal swab or saliva sample	-
Every 6-8 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]*

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

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].*

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 on-line 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);
- Previous SARS-CoV-2 infection (clinical- or laboratory-confirmed);
- Vaccination status for COVID-19 and other respiratory pathogens (influenza, pneumococcus);

- Molecular and serological testing results;
- Hospital exposure to SARS-CoV-2 (professional exposure to COVID-19 cases, use of personal protective equipment (PPE), compliance with infection prevention and control measures, involvement in aerosol-generating procedures);
- Community exposure to SARS-CoV-2 (household make up, personal exposure to confirmed COVID-19 cases, and use of PPE in social situations).

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 participant or the 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);
- 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.

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) Yes/no	Key	✓	✓ (if status changes)
	Vaccination date(s) (for each dose)	Key	✓	✓ (if status changes)
	Vaccine product	Key	✓	✓ (if status changes)
	Vaccine dose (first or second)	Key	✓	✓ (if status changes)
	Vaccine batch	Key	✓	✓ (if status changes)
	Source used for vaccine ascertainment	Key	✓	✓ (if status changes)
Previous vaccinations	Influenza (with date of vaccination), pneumococcal vaccination	Key	✓	✓ (if status changes)

Categories	Variable	Key/optional variable	Enrolment questionnaire T1	Follow-up questionnaire
Previous vaccinations	Pneumococcal vaccination date, (month, year)	Optional	✓	✓ (if status changes)
SARS-CoV-2 infection	Laboratory/clinical/self-reported confirmed	Key	✓	X
(Last episode)	List of symptoms	Key	✓	✓ (If reported)
	Date of onset	Key	✓	✓ (if reported)
	Severity (symptomatic, hospitalisation, ICU admission)	Key	✓	✓ (if reported)
Hospital exposures	Occupation	Key	✓	✓ (if status changes)
	Wards	Key	✓	✓ (if status changes)
	Contact with suspected and confirmed COVID-19 patients	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 (list)	Key	✓	✓ (if status changes)
	Household size	Key	✓	X
	Frequency of wearing mask	Key	✓	✓ (if status changes)
	Frequency of respecting two metres distance in indoors space	Key	✓	✓ (if status changes)
	Frequency of participating in indoor gatherings	Key	✓	✓ (if status changes)
	Frequency of use of public transport	Key	✓	✓ (if status changes)
Laboratory results	PCR	Key	✓	✓
	Serology	Key	✓	✓

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

3.12 Data analysis

Data analysis and secondary studies are described in Annex 1.

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 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°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°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.

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
- Kits used and performance
- Participation in quality assurance/quality control schemes
- Selection of specimens for sequencing.

4.3.1 Molecular testing

Laboratory guidance for **molecular testing** for COVID-19 can be found on WHO's and ECDC's websites. 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 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 (T1) using a specimen collected with nasal, naso- or oropharyngeal swab;
- 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]. 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 6–8 weeks or more 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 Serological tests detecting SARS-CoV-2 spike (S) and nucleocapsid (N) antibodies could 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 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.

5. Limitations

- **Laboratory tests:** Misclassification of the outcome can occur due to the test performance. Sensitivity and specificity of the tests can be adjusted for in the analysis. Sites will employ different tests, so investigators should seek to use common international, national, or research standards to address possible variation in test performance at sites. The National Institute of Biological Standards and Control currently 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. This potential bias will be adjusted in the analysis using information collected on the potential exposures.
  - **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:** 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 (e.g. retrospective cohort study designs or prospective analysis using various comparison groups). This could include comparing individuals that have received a booster dose with those that have not, or incidence of infection with different variants in vaccinated individuals.
  - 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 Annex 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 have an impact on 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 carried out on behalf of ECDC. The privacy statement on vaccine effectiveness studies can be used for this 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 issues 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'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 measure the effectiveness of COVID-19 vaccines and guide vaccination policies.

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Annex 1. Outline analysis plan

The analysis plan presented below will be reviewed on a regular basis and may be updated as a result to take into account any new public health recommendations and changes in epidemiology. The main aim of the analysis is to provide a description of the pooled dataset as well as an analytical approach. However, country-specific descriptive analysis will be conducted as a preparatory step for the pooled analysis.

Participation

The study participants should be described in terms of total number of eligible HCWs, and total number and proportion of HCWs who refused participation by reason for refusal.

Baseline characteristics

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

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

Vaccine effectiveness

Vaccination status will be considered a time-varying exposure (vaccination status of individuals may change over time from unvaccinated to vaccinated; one to two doses). An individual should be considered vaccinated with the first dose 14 days after receiving the first vaccine and fully vaccinated 14 days after receiving the second dose of the vaccine (for those vaccines requiring a two-dose schedule). Sensitivity analyses may be performed to evaluate the effectiveness of the vaccine after different intervals following vaccination.

VE should be estimated using Cox regression (VE = 1 – hazard ratio) or Poisson regression (VE = 1 - rate ratio). Follow-up will be from baseline to the earliest of outcome or study exit.

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

Effect modification should be explored. Depending on the sample size, analysis will be stratified according to:

- vaccine dose (if relevant: unvaccinated, partially vaccinated, fully vaccinated);
- type of HW and wards;
- age groups;
- sex;
- presence or absence of high-risk conditions;
- week or weeks of the year;
- COVID-19 vaccination history;
- time since vaccination;
- any other effect modifier identified.

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

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

Controlling for clustering by health facility

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

Missing data

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

Secondary analyses

As a secondary analysis, VE should be assessed by subgroups and against multiple infections, as indicated in Table 1.

Table 4. Research questions and corresponding HCW cohorts

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

** Different definitions of previous infection can be used: positive PCR, positive serology, clinically confirmed COVID-19 (or any combination of the three).*
Note: VE can be measured against SARS-CoV-2 positive RT-PCR (primary outcome) or against different clinical outcomes.

Secondary studies

Sites may wish to employ the established cohorts to address other related research objectives in secondary studies. Study investigators should ensure that ethical approval is obtained for any secondary studies to be conducted. Possible secondary studies that study investigators may wish to consider are:

- **Transmission study.** Assessment of indirect vaccine effects (i.e. transmission) through a related evaluation of household transmission should be considered. In such a secondary study, household members of study participants could be recruited and followed prospectively according to vaccination status, exposures, and SARS-CoV-2 infection. The household secondary attack rates can be compared between households where the index case was vaccinated against COVID-19 to households with an unvaccinated index case. Alternative methods of analysis in light of high vaccine coverage include comparing by vaccination status (partial, full vaccination, booster doses) and time from vaccination.

- **Immunological-related study.** The regular epidemiological, virological, and serological monitoring of HCWs provides an opportunity to investigate the impact of different timings of vaccination and infection on immunological responses.
- **Retrospective cohort study.** The present generic protocol proposes a prospective study design. However, if most HCWs will have been vaccinated before their enrolment into the study, the collation of data for this period may offer more information to estimate VE. At enrolment, the study would aim to collect retrospective information on date of vaccination(s) and most recent episode of SARS-CoV-2 infection. It will be more difficult to collect data regarding possible exposures in the preceding time period. Nonetheless, these data collected at enrolment can be employed to obtain crude estimates of VE based on risk rather than rates of infection. Whether the estimates of VE are for protection against infection or disease will depend on site-specific screening policies of HCWs.
- Sites/hospital/country conducting secondary studies to include the protocol of the secondary study.

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

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

Sensitivity analyses

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

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

Additional analysis: test-negative design

Within the cohort study, a nested test-negative design (TND) can be conducted in which cases are HCWs who test RT-PCR positive for SARS-CoV-2 and controls those who tests RT-PCR negative. The TND may address the differential reporting of symptoms between vaccinated and unvaccinated individuals. The odds of vaccination will then be compared between cases and controls to compute the odds ratio. VE will be measured as (1 – odds ratio)*100. The 95% Confidence Interval will be calculated around the estimate.

All sub-analysis listed for the cohort design could be conducted using the TND. Logistic regression will be used to adjust for potential confounding factors. Time of specimen collection and hospital should be included in all models.

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