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

WHO-AFRO Guidance Document

Adapted from the WHO/EURO Guidance document (version 2 March 2021)

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Abbreviations

COVID-19	Coronavirus disease 2019
HW	Health worker
IPC	Infection prevention and control
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
OR	Odds ratio
PCR	Polymerase chain reaction
PPE	Personal protective equipment
RR	Rate Ratio
VE	Vaccine Effectiveness
WHO	World Health Organization

1. Executive Summary

Many critical questions remain about the effectiveness of COVID-19 vaccines in real-world settings. It is important to carry out post-introduction vaccine effectiveness studies in selected countries to address these questions.

This guidance document outlines the methods of a prospective six-month cohort study of hospital-based healthcare workers (HWs) to evaluate the effectiveness of COVID-19 vaccine in preventing laboratory-confirmed SARS-CoV-2 infection (against any infection or against symptomatic infection only). HWs should be enrolled ideally prior to or simultaneous with the implementation of the COVID-19 vaccination campaign, after the study protocol is approved by the local ethical review committee. All HWs eligible to be vaccinated with COVID-19 vaccine can be enrolled in the study, including those who intend to get vaccinated, those who don't plan on getting vaccinated, and those who are not sure whether or not they will be vaccinated.

At enrolment, study participants should complete a baseline enrolment questionnaire about demographics, clinical comorbidities, and work- and community-related behaviours related to infection risk. In addition, a baseline serology and a respiratory swab for RT-PCR testing for SARS-CoV-2 should be collected from participants at enrolment.

During the course of the study, participants should be actively followed up for suspected SARS-CoV-2 infection. Symptomatic participants who meet a suspected case definition should provide a respiratory sample , collected by a trained HW or by self-swab (following training), which should be tested for SARS-CoV-2 by RT-PCR.

When resources allow to measure vaccine effectiveness against any infection, during the course of the study, all participants regardless of their symptoms should be asked to provide a respiratory sample, weekly or fortnightly, in order to evaluate asymptomatic infection. Alternatively, a saliva sample can be provided weekly. Samples should be tested by RT-PCR for SARS-CoV-2.

Finally, during the course of the study, serology could be conducted periodically (e.g. every 6-8 weeks or longer), for all participants to identify asymptomatic cases that could have been infected during the study period. If possible, serology should be tested for antibodies to SARS-CoV-2 by tests that can distinguish between vaccine-induced antibodies and antibodies that result from natural infection (note: currently distinction cannot be made when inactivated vaccine used. In addition, if resources allow, sera can undergo additional laboratory testing for correlates of disease protection (when known), and additional blood can also be collected and tested for markers of cell-mediated immunity.

Vaccine effectiveness should be analysed as described in the analysis section below. In addition to the final analysis at the end of the study period, interim analyses at different points during the study can be undertaken.

2. Introduction

In late 2019 a novel 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 27 April 2021, 3,244,774 cases and 81,785 deaths had been reported to the World Health Organization (WHO) AFRO region[1]. International collaborative efforts have accelerated the development of COVID-19 vaccines. As of April 23, 2021, 91 candidate vaccines were in clinical development and 184 were in preclinical development[2].

Health workers (HWs) are at a higher risk of infection. In addition, HW can transmit the infection to susceptible patients at high risk of severe COVID-19. The WHO SAGE roadmap for prioritizing uses of COVID-19 vaccines in the context of limited vaccine supply includes HW as a priority group for vaccination.

Evaluating the real-world COVID-19 vaccine performance is critical for understanding the risks and benefits of vaccination programs. Many factors impact real-world vaccine effectiveness (VE), including vaccine transportation and storage and how patients are vaccinated. In addition, the people who get the vaccine in clinical trials are often young and healthy, and therefore different from those who will receive vaccines in the real world[3].

Real-world vaccine effectiveness 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 one dose vs. two doses, and effectiveness of the vaccine against new variant strains of SARS-CoV-2.

This document provides guidance for a prospective cohort study to evaluate the effectiveness of COVID-19 vaccines in HWs, with a focus on hospital-based HWs (**Annex 1**). This document can be used by countries and institutions that are interested in conducting COVID-19 vaccine effectiveness studies in HWs. Research should be conducted only after site-specific protocols are developed and approved by the relevant local ethical review committee(s). The site-specific protocols should be aligned with WHO interim guidance on evaluation of COVID-19 vaccine effectiveness[4,5].

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[1] World Health Organization AFRO COVID-19 Dashboard.
Available at: https://www.afro.who.int/health-topics/coronavirus-covid-19 (accessed 12 March 2021).
[2] Draft landscape of COVID-19 candidate vaccines. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines (accessed 27 April 2021).
[3] Patel MM, Jackson ML, Ferdinands J. Postlicensure evaluation of covid-19 vaccines. *JAMA - J Am Med Assoc*. 2020;324(19):1939-1940. doi:10.1001/jama.2020.19328
[4] World Health Organization. Regional Office for Europe. (2021). Cohort study to measure COVID-19 vaccine effectiveness among health workers in the WHO European Region: guidance document. World Health Organization. Regional Office for Europe. Available at: https://apps.who.int/iris/handle/10665/340217 (accessed 27 April 2021).
[5] Interim guidance: Evaluation of COVID-19 Vaccine Effectiveness. World Health Organization. March 2021. Available at:https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccine_effectiveness-measurement-2021.1 (accessed 27 April 2021).

3. Objectives

3.1. General objective

To measure **product-specific** COVID-19 vaccine effectiveness (VE) amongst hospital health workers **eligible for vaccination** against:

(a) Any laboratory-confirmed SARS-CoV-2 infection *(for sites able to test periodically all enrolled patients irrespective of symptoms, see section 4.12 below),*
OR
(b) Symptomatic laboratory-confirmed SARS-CoV-2 infection only

3.2. Secondary objectives

Depending on sample size and resources to measure COVID-19 VE, possible secondary objectives are outlined in table 1. If these objectives cannot be addressed by individual countries, data could be pooled from multiple countries. For definitions relating to VE, see section 6.3 below.

Table 1. Secondary Objectives

Secondary Objective	Description/Notes
1. What is VE against symptomatic laboratory-confirmed SARS-CoV-2 infection	If not used as primary objective. Outcome is symptomatic infection defined by accepted case definition for suspected COVID-19
2. What is VE against asymptomatic laboratory-confirmed SARS-CoV-2 infection?	To respond to this objective, respiratory samples should be collected on a weekly (or fortnightly) basis. Symptoms are not reported in relation to positive SARS-CoV-2 infection
3. What is the VE against severe laboratory-confirmed SARS-CoV-2 infection?	Severe infection can be defined by WHO case definition (see 6.6).
4. What is the duration of protection conferred by the vaccine?	VE by time since vaccination
5. What is the VE in different age groups?	Age group categories can be determined in relation to number and age distribution of participants
6. What is the VE in persons with different high-risk co-morbidities?	High-risk comorbidities can be defined according to known risk factors for severe COVID-19 disease. HW are typically young and therefore not an ideal population to study this objective.
7. What is the VE in persons with reports of previous SARS-CoV-2 infection?	Previous infection can be defined by prior PCR-confirmed infection or serology attesting to prior infection

8. What is the VE by health worker occupation?	The analysis can also relate to hospital ward (e.g medical adult vs. paediatric vs. surgical) rather than profession (see question 47 in Form A, **Annex 3**)
9. What is the VE in patient-facing health workers compared to non-patient-facing HWs?	Patient-facing status should be determined through questionnaires
10. What is the VE in partially vaccinated health workers compared to fully vaccinated health workers?	This question is only relevant in vaccines that require two doses for full protection.
11. What is the VE against specific variants of SARS-CoV-2?	Answering this question would require a certain minimum number of circulating variants, and for most variants also assumes genomic characterization is being conducted for study samples

4. Methods

4.1. Study setting

The study is designed to be conducted among HWs based in hospitals, because of the convenience of follow-up of a centralized study population.
Depending on the setting, this could include urban healthcentres with inpatient facilities to increase the available population.

4.2. Study design

Prospective cohort design

This is a prospective longitudinal cohort study among HWs eligible for vaccination, comparing SARS-CoV-2 incidence among COVID-19 vaccinated and unvaccinated HWs.

4.3. Study population

The study population will be composed of HWs (see **Annex 1**) in participating hospitals, eligible for vaccination, with no contraindication to receive COVID-19 vaccine.

4.4. Inclusion Criteria

HWs may include all categories of staff working in the hospitals who are eligible for vaccine.
Ideally, HWs should be included either before vaccination or within 7 days of vaccination.
If it cannot be avoided, HWs who have already been vaccinated against COVID-19 as part of the routine COVID-19 vaccine rollout can be included, as long as information can be collected (and ideally verified, see 4.7 below) about the date and type of the vaccine that was administered.

4.5. Exclusion Criteria

- HWs who are not eligible for COVID-19 vaccination should not be eligible to participate in the study.
- HWs who have already been vaccinated against COVID-19 in COVID-19 vaccine clinical efficacy trials should be excluded.
- HWs who know at study onset that they cannot remain under follow-up for the duration of the study
- *Other criteria may be considered according to country setting.*

4.6. Study period and recruitment

The study period should ensure a **minimum follow-up of 6 months** for all individuals enrolled. Ideally the study should be started before or early in the vaccination campaign.
The study should be conducted only after the study protocol is approved by the relevant ethical review committee (if applicable).

After the protocol is approved, the study should be publicized within participating hospitals. Study staff should approach healthcare workers at designated sites in hospitals to make HWs aware of the study and solicit interest in participation in the study. Study staff should describe the study in detail, answer all questions, and review the informed consent form (**Annex 2**) with the potential participant in a private area designated for study use. This study requires individual consent and this consent cannot be given by the employer on behalf of the Health worker.

4.7. Exposure

Vaccination status documentation

Precise vaccination status documentation is essential for this study. Vaccine ascertainment will depend on how the vaccination is delivered and registered in each setting.
Self-reported vaccination status should be verified and confirmed through vaccine registry, vaccination card or any potential data source. Participants should be informed in the inform consent form that these additional sources will be accessed, when relevant, in order to confirm their vaccination status.

Vaccine documentation should include (to allow for product-specific VE estimates):

- **COVID-19 vaccination received and date of vaccination (for each vaccine dose)**
- **vaccine brand**
- **vaccine batch / lot**

4.8. Definitions of outcomes

The primary outcome should be SARS-CoV-2 laboratory confirmation by RT- PCR in:

1. any participant, regardless of symptoms *(for sites able to test periodically all enrolled participants, see section 4.12 below)*
   OR
2. any *symptomatic* participant who meets the following case definition (taken from the WHO COVID-19 Suspected Case Definition[6],[7])*:
   a. acute onset of fever and cough OR
   b. acute onset of any three or more of the following symptoms in the previous 10 days: Fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnoea, anorexia/nausea/vomiting, diarrhoea, altered mental status, anosmia, ageusia**

*Consideration can be given to implementing broader, more sensitive case definitions
**The last two symptoms are in addition to the existing WHO case definition (to provide a sensitive enough definition)

4.9. Minimum variables to be collected from participants

The minimum data that should be collected include the following. Data could be collected in an enrolment questionnaire (**Annex 3**) or from electronic medical records, when available, or through a combination of both approaches:

At enrolment:

- age
- sex
- presence of chronic disease(s) /co -morbidities
- previous SARS-CoV-2 infection (clinical or laboratory-confirmed)
- hospital exposure to SARS-CoV-2 (job exposure to COVID-19 patients, use of PPE, compliance with Infection Prevention and Control measures, involvement in aerosol-generating procedures)
- community exposure
- knowledge, attitudes and practices questions about COVID-19 and COVID-19 vaccine could be considered

For symptomatic illness arising during the study period

- symptoms
- date of onset of symptoms
- date of PCR testing and PCR results
- clinical course of illness (including outpatient and inpatient visits)

[6] WHO COVID-19 Case definition. https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2020.2 (accessed 27 April 2021)

[7] Interim guidance: Evaluation of COVID-19 Vaccine Effectiveness. World Health Organization. March 2021. https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccine_effectiveness-measurement-2021.1 (accessed 27 April 2021)

4.10. 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 (defined as a full course) in the population, the assumed VE, the estimated incidence of SARS-CoV-2 infection over the follow-up time in the unvaccinated study population and the desired precision.

Table 2 presents a varying incidence of SARS-CoV-2 infection among unvaccinated participants during a 6 months study and measures 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).

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 HWs may choose to get vaccinated.

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

As an example, if for a study, it was estimated that 10% of unvaccinated people would be infected with SARS-CoV-2 over a period of 6 months (Yearly rate-unvacc = 0.1), and the expected VE were 70%, and the expected coverage among HWs were 70%, the study would need to recruit 912 participants. However, if there was an expected drop-out rate of about 20%, then the study would need to recruit 1140 participants.

Note that if the length of follow up is longer, the required sample size would be smaller (i.e. for a 1 year follow up using the same assumptions of 0.1 yearly rate, 70% VE, 70% vaccine coverage, 20% drop-out, the sample size estimate would be 598 participants.

Table 2: Sample size estimation (for one stratum), assuming 6 months follow up.

Yearly hazard rate in unvaccinated	VE (%)	Vaccine coverage (%)	Total sample size	Unvaccinated N	Unvaccinated Number events	Vaccinated N	Vaccinated Number events
0.2	90	90	388	39	4	349	3
		80	258	52	5	206	2
		70	222	67	6	155	2
		60	214	86	8	128	1
	80	90	609	61	6	548	11
		80	383	77	7	306	6
		70	319	96	9	223	4
		60	300	120	11	180	4
	70	90	939	94	9	845	25
		80	570	114	11	456	13
		70	464	139	13	325	10

		60	429	172	16	257	8
	60	90	1,468	147	14	1,321	52
		80	872	175	17	697	27
		70	697	209	20	488	19
		60	637	255	24	382	15
	50	90	2,380	238	23	2,142	104
		80	1,392	279	27	1,113	54
		70	1,098	330	31	768	37
		60	992	397	38	595	29
0.1	90	90	765	77	4	688	765
		80	508	102	5	406	508
		70	437	131	6	306	437
		60	420	168	8	252	420
	80	90	1,199	120	6	1,079	1,199
		80	753	151	7	602	753
		70	626	188	9	438	626
		60	589	236	12	353	589
	70	90	1,850	185	9	1,665	1,850
		80	1,123	225	11	898	1,123
		70	912	274	13	638	912
		60	843	337	16	506	843
	60	90	2,888	289	14	2,599	2,888
		80	1,714	343	17	1,371	1,714
		70	1,369	411	20	958	1,369
		60	1,250	500	24	750	1,250
	50	90	4,678	468	23	4,210	4,678
		80	2,733	547	27	2,186	2,733
		70	2,155	647	32	1,508	2,155
		60	1,945	778	38	1,167	1,945
0.05	90	90	1,518	152	4	1,366	3
		80	1,008	202	5	806	2
		70	866	260	6	606	2
		60	832	333	8	499	1
	80	90	2,380	238	6	2,142	11
		80	1,493	299	7	1,194	6
		70	1,242	373	9	869	4
		60	1,167	467	12	700	3
	70	90	3,672	368	9	3,304	25
		80	2,227	446	11	1,781	13
		70	1,809	543	13	1,266	9
		60	1,672	669	17	1,003	7
	60	90	5,729	573	14	5,156	51
		80	3,399	680	17	2,719	27
		70	2,714	814	20	1,900	19
		60	2,475	990	24	1,485	15
	50	90	9,274	928	23	8,346	104
		80	5,417	1,084	27	4,333	54
		70	4,270	1,281	32	2,989	37
		60	3,853	1,541	38	2,312	29

Note: 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)

4.11. Study procedures

4.11.1. T0. Study Preparation

After the study has been approved by the relevant ethical review committee, a list of all HW eligible for vaccination in the hospital should be obtained. All HWs or a random selection of HW eligible for vaccination should be invited to participate in the study, be provided with written information explaining the study, and sign an informed consent form (**Annex 2**).
HWs should be invited to participate in the study regardless of their intention to be vaccinated.

To ensure that participants with diverse characteristics (socio-demographic, occupational responsibilities) are included, a stratified sampling scheme can be used to randomly select HW in each pre-defined group (e.g. age-group, sex, occupation, COVID/non-COVID wards). Alternatively, all HWs at a site can be recruited for enrolment.

4.11.2. T1 Enrolment: questionnaire, respiratory sample, and serology sample

On or near the day of vaccination, participants who choose to be vaccinated should be enrolled. On the day of enrolment, participants who are **not** immediately planning to be vaccinated should also be enrolled.

All those enrolled should:

- provide a respiratory specimen for RT-PCR testing, and
- a blood sample for serology, and
- complete an enrolment questionnaire (**Form A, Annex 3**) that includes demographic, clinical, and epidemiological information, information about vaccination history, and occupation- and community-related behaviour.

For sites in which HW vaccination has already started, on the day of enrolment, **all study participants** should provide the above samples and questionnaire .

If feasible, anonymous basic demographic information should be collected from HWs who do not wish to participate to assess non-response/non-participation bias.

4.12. Active follow-up

The objective of the follow-up is to identify among the cohort of participant HWs: new cases, changes in vaccination status (e.g. unvaccinated receive the vaccine, vaccinated one dose receive the second dose) and changes in potential exposures (e.g. HW working in different wards, contacts with COVID-19 cases).

Study participants need to be **actively** followed up and how this will be done should be defined in national protocols (i.e. via hospital visits, telephone calls, SMS, online questionnaire etc.).

Approaches to active follow-up will likely depend on available resources and the study objective. The following approaches to study follow-up of participants could be used, independently or combined (see also table 3):

1. Participants are followed up **weekly** with active surveillance questions (including about new symptoms and changes in vaccine status) using a **follow-up questionnaire** (**Form C, Annex 3**), ideally electronically. Any participant who develops symptoms compatible with the suspected case definition should have a **respiratory swab collected** and tested for SARS-CoV-2 by RT-PCR as soon as possible. In addition, study participants should be instructed to report to study staff if they are symptomatic, rather than wait to report these symptoms through the weekly follow-up questionnaire.

2. Routine testing of HW:
    - If resources allow to measure VE against any infection: respiratory samples should be collected from all participants **every week or every two weeks**, irrespective of symptoms, and tested by RT-PCR. Alternatively, saliva samples could be collected every week[8].
    - Blood samples can be taken periodically during the follow up (if possible), at intervals of 6–8 weeks or longer (e.g. every 3 months), to identify asymptomatic cases that could have been infected during the study period that are not identified by weekly swabbing (see section 5.3 below for test requirements). This would be only possible if the serological test used distinguishes between infection-induced and vaccine induced antibodies and vaccines in use are not inactivated. Those with infection-induced immunity would be excluded from the denominator in the analysis.

Active surveillance for symptomatic illness could involve the following approaches:

- Study staff can contact study participants periodically between the weekly follow-ups to ask if they have developed COVID-19 symptoms and whether they have had any changes in exposures (e.g. new COVID-19 vaccination, changes in occupation-related tasks).
- Every time participants develops symptoms consistent with the COVID-19 suspected case definition they should notify the study coordinator and (i) provide a respiratory specimen, (ii) fill-in the follow-up questionnaire.

For all participants who develop symptoms that meet the case definition for suspected COVID-19 case, a respiratory swab should be collected as soon as possible. Self-swabbing can be considered (training required). All swabs should be tested for SARS-CoV-2 by RT-PCR.

[8] As an alternative, to improve acceptability and feasibility of the weekly follow-up, self-taken saliva swabs can also be provided by HW which perform well in comparison to naso or oropharyngeal swabs, particularly in the early stages of infection (see section 5.1)

In addition, if routine sampling of study participants is conducted, all participants who test positive for SARS-CoV-2 should complete a follow-up questionnaire (**Form C, Annex 3**) about their symptoms and clinical course of illness. This can be requested when the participant is informed about their test result. This information will be critical to inform whether the patient should be considered an asymptomatic, presymptomatic, or symptomatic COVID-19 case-patient.

Routine local protocols for HW suspected case management and contact tracing should be followed for all suspected cases. HW should be notified of their COVID swab result in a timely manner.

Table 3: Timing of questionnaires and specimen collection

Timing in the study	**Baseline**	**Weekly (or every two weeks for respiratory sample collection)**	**For symptomatic participants who meet the COVID-19 case definition**	**Every 6–8 weeks (or longer)**
Enrolment questionnaire T1 (Form A, Annex 3)	X			
Follow-up questionnaire (Form C, Annex 3)		X		
Respiratory (or saliva) sample for RT-PCR testing	X	X (essential for studies measuring VE against any infection)*	X	
Serology	X			X (optional)*

*For studies measuring VE against any infection (including RT-PCR-confirmed SARS-CoV-2 in asymptomatic persons and IgM/IgG-positive serology results regardless of symptoms)

Note: irrespective of participation in the VE study, HW 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 HW providing care for possible and confirmed COVID-19 cases. These HWs should be trained in reporting procedures and report any symptoms, and if developing fever or any 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 recommendations in place (See also WHO guidelines on Prevention, identification and management of health worker infection in the context of COVID-19. https://www.who.int/publications/i/item/10665-336265)

4.13. Data collection and Data sources

Table 4 summarises the data that should be collected during the study. A more detailed list of variables with definitions is provided in **Annex 4** and questionnaires are provided in **Annex 3**. Variables are marked as key (essential) or optional. All key variables should be collected to facilitate both in-country and multiple country pooled analysis were possible.

Table 4: Data collection: variables and questionnaires to be used (to be adapted to country setting).

Categories	**Variable**	**Key /optional variables**	**Enrolment Questionnaire T1**	**Follow-up weekly questionnaire**
COVID-19 vaccine	Vaccine dose received (for each dose) Yes/no	Key	Yes	Yes (for unvaccinated at T1)
	Vaccination date(s) (for each dose)	Key	Yes	Yes (for unvaccinated at T1)
	Vaccine product	Key	Yes	Yes (for unvaccinated at T1)
	Vaccine dose (first or second)	Key	Yes	Yes (for unvaccinated at T1)
	Vaccine batch	Key	Yes	Yes (for unvaccinated at T1)
	Source used for vaccine ascertainment	Key	Yes	Yes (for unvaccinated at T1)
Socio Demographic	Age	Key	Yes	
	Sex	Key	Yes	
	Ethnicity	Optional	Yes	
	Blood group	Optional	Yes	
	Socioeconomic status	Optional	Yes	
Clinical	List of symptoms	Key	Yes	Yes
	Date of onset	Key	Yes	Yes
	Severity (list)	Key	Yes	Yes
Chronic conditions	List	Key	Yes	
Medication for chronic condition	List	Optional	Yes	
Previous SARS-CoV-2 infection	Laboratory/clinical/ confirmed	Key	Yes	
Previous vaccinations (when applicable)	Influenza, pneumococcal, (month, year of last vaccination)	Optional	Yes	Yes
Hospital exposures (in last 14 days)	Occupation	Key	Yes	Yes
	Wards	Key	Yes	Yes
	Use of PPE	Key	Yes	Yes
	Questions about IPC compliance	Key	Yes	Yes
	Contact with suspected and confirmed COVID-19 patients	Key	Yes	Optional

	Contact SARS-CoV-2-positive HWs	Key	Yes	Optional
	Involvement in aerosol generating procedures (list)	Key	Yes	Optional
	Non-aerosol generating procedures (list)	Key	Yes	Optional
Community exposures (in last 14 days)	Contact with confirmed COVID-19 cases outside the hospital (list)	Key	Yes	Optional
	Household size	Key	Yes	No
	Travel outside the country/region	Optional	Yes	Optional
	Frequency of wearing mask	Key	Yes	Optional
	Frequency of respecting 2 meters distance in indoors space	Key	Yes	Optional
	Frequency of participating in indoor gatherings	Key	Yes	Optional
	Use of public transport	Key	Yes	Optional
Individual behaviours/attitude	Smoking (current/past/never)	Optional	Yes	
	BMI (collect height and weight)	Key	Yes	
	Alcohol use	Optional	Yes	
	Attitude towards vaccination	Optional	Yes	
Laboratory results	PCR	Key	Yes	Yes
	Serology	Key	Yes	

4.13.1. Data sources

Data can be collected through questionnaires (**Annex 3**) completed by the HW for the study, electronic medical records, vaccine registries, occupational health registries, or other relevant sources. For each variable, possible and optimal data sources should be identified.

4.13.2. Data Management and ensuring Data Confidentiality

Each participant should be allocated a unique study ID number at enrolment that will be subsequently use as the identifier in all documents. No personal identifiers, such as name or national ID number, should be included in study databases. Personal Identifying information should be maintained only by the responsible person(s) in each study site in accordance with regulatory agencies requirements.

5. Laboratory Methods

5.1. Specimen collection

Respiratory samples: can be taken by a dedicated medical staff (i.e. research nurse) or by participants themselves (self-swab) if they undergo a brief training.

Saliva samples: As an alternative to improve acceptability and feasibility of the weekly follow-up, self-taken saliva swabs can also be provided by HW which perform well in comparison to naso or oropharyngeal swabs, particularly in the early stages of infection.[9,10,11,12,13]

Blood: 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 including "Laboratory biosafety guidance related to coronavirus disease (COVID-19)"[14], "Laboratory testing for coronavirus disease (COVID-19) in suspected human cases"[15] as well as WHO's general laboratory biosafety guidance[16].

All collection tubes will be labelled with a coded study ID number that will also be recorded on the laboratory form and interview questionnaires (**Annex 3**). The time and place of collection, and the name of the person who collected the sample should also be recorded.

[9] To KK, Tsang OT, Leung WS, Tam AR et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infect Dis doi:10.1016/s1473-3099(20)30196-1.

[10] Williams E, Bond K, Zhang B, Putland M et al. Saliva as a Noninvasive Specimen for Detection of SARS-CoV-2. J Clin Microbiol. 2020 Jul 23;58(8):e00776-20. doi: 10.1128/JCM.00776-20.

[11] Brotons P, Perez-Argüello A, Launes C, Torrents F et al. Validation and implementation of a direct RT-qPCR method for rapid screening of SARS-CoV-2 infection by using non-invasive saliva samples. MedRxix Pre-print. DOI: https://doi.org/10.1101/2020.11.19.20234245

[12] Haute Autorite de Sante. La HAS amorce la réévaluation des tests RT-PCR salivaires à la lumière de nouvelles données. Availlable at : https://www.has-sante.fr/jcms/p_3234225/fr/la-has-amorce-la-reevaluation-des-tests-rt-pcr-salivaires-a-la-lumiere-de-nouvelles-donnees (accessed 27 April 2021)

[13] Infectious Disease Society of America. PCR testing. https://www.idsociety.org/covid-19-real-time-learning-network/diagnostics/RT-pcr-testing/ (accessed 27 April 2021)

[14] WHO. Laboratory biosafety guidance related to coronavirus disease (COVID-19). Available at: https://www.who.int/publications/i/item/laboratory-biosafety-guidance-related-to-coronavirus-disease-(covid-19) (accessed 27 April 2021)

[15] WHO. Laboratory testing for coronavirus disease (COVID-19) in suspected human cases. Available at: https://www.who.int/publications/i/item/10665-331501 (accessed 27 April 2021)

[16] WHO. General guidance of laboratory biosafety- 3rd edition. Available at: https://www.who.int/publications/i/item/9241546506 (accessed 27 April 2021)

Note: Given the rapidly developing guidance related to SARS-CoV-2, it is recommended that investigators check for updates to these documents on the WHO website prior to study initiation to ensure that current recommendations are being followed (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance).

5.2. Specimen storage, shipment and transport

All those involved in collecting and transporting specimens should be trained in safe handling practices and spill decontamination procedures. For details regarding the transport of samples collected and infection control advice, please refer to the case management algorithm and laboratory guidance in the country, or to WHO laboratory guidance, available on the WHO website (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance).

For each biological sample collected, the time of collection, the conditions for transportation and the time of arrival at the laboratory will be recorded (**Form B, Annex 3**). 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 on 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 the WHO "Guidance on regulations for the transport of infectious substances 2019–2020"[17].

5.3. Specimen testing

5.3.1. Serology

Serology at enrolment (T1) should measure total antibodies, IgM or IgG (depending on tests used) to a panel of SARS-CoV-2 antigens and define serological status of enrolled patients.

[17] WHO. Guidance on regulations for the transport of infectious substances 2019–2020. Available at: https://www.who.int/ihr/publications/WHO-WHE-CPI-2019.20/en/ (accessed 27 April 2021)

Follow up serologies periodically (every 6–8 weeks or longer), as resources permit, using a serological test distinguishing infection and vaccine-induced antibodies (note: currently, distinction cannot be made for inactivated vaccines).

Specific serology tests to be used should be determined by each study. Consideration should be given to using serology tests that can distinguish between natural infection and vaccine-related antibodies. If HWs have already been vaccinated when the study starts, it will be more important to differentiate natural and vaccine related immunity at baseline. If the study starts at or prior to the time of vaccination, this would be less critical at baseline.

5.3.2. Molecular testing

RT-PCR for SARS-CoV-2 to be conducted on all respiratory specimens collected at enrolment (T1) and for all symptomatic participants who meet the WHO suspected case definition.

If resources allow to study VE against any infection (symptomatic and asymptomatic particpants): weekly or fortnightly respiratory (or weekly saliva) specimens to be tested by RT-PCR for SARS-CoV-2.

If possible, RT-PCR should also be performed for other respiratory pathogens such as influenza and RSV.

Laboratory guidance for **molecular testing** for COVID-19 can be found on the WHO website[18]. Several assays that detect SARS-CoV-2 have been recently developed and the protocols or standard operating procedures (SOPs) can also be found on the WHO website[19].

If resources allow, all or a random sample of RT-PCR positive specimens collected among HW should undergo genomic characterization. Genetic sequencing is important to undertake during the study in order to understand whether changes in VE could be due in part to mutations in the circulating virus. Even if resources do not allow for sufficient numbers to undergo genomic characterization, it is important to have an understanding of virus variants circulating in the context of the study to help with interpretation of the results.

6. Analysis Plan

6.1 Participation

The study participants should be described in terms of: total number of eligible HWs, and number and proportion of total who participated and who refused participation.

[18] https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance-publications (accessed 27 April 2021)
[19] https://www.who.int/publications-detail/laboratory-testing-for-2019-novel-coronavirus-in-suspected-human-cases-20200117 (accessed 27 April 2021)

6.2 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
- pregnancy
- obesity
- smoking history
- history of other vaccines (influenza, hepatitis B, pneumococcal, other)
- HW category
- COVID-19 vaccination history
- previous SARS-CoV-2 infection
    - test performed
- occupational and community-related exposures

6.3 Vaccine effectiveness

The cohort design allows direct calculation of the rate of disease in vaccine recipients versus non-vaccine recipients, leading to estimation of risk reduction of disease among vaccinated persons. The greater the percentage of risk reduction of disease in the vaccinated group, the greater the vaccine effectiveness.

The basic formula is written as:

$$\frac{\text{Rate among unvaccinated group} - \text{rate among vaccinated group}}{\text{Rate among unvaccinated group}}$$

Vaccination status will be considered a time-varying exposure, because the vaccination status of individuals may change over time from unvaccinated to vaccinated and from one dose to two doses (for two-dose vaccines).

Vaccine product recommendations should be observed. For one-dose vaccines, an individual should be considered fully vaccinated 14 days after receiving the vaccine. For two-dose vaccines, 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.

Sensitivity analyses may be performed to evaluate the effectiveness of the vaccine after different intervals (including after first and second dose for two-dose vaccines) following vaccination.

Vaccination effectiveness (VE) should be estimated using Cox regression (VE = 1 – hazard ratio [HR]) or Poisson regression (VE = 1 - rate ratio [RR]), where the rate ratio is defined as the incidence rate in the exposed (vaccinated) divided by the incidence rate in the unexposed (unvaccinated). Follow-up will be from baseline to the earliest of outcome or study exit.

Both unadjusted and adjusted estimates of vaccine effectiveness should be presented. Adjustment should be made in the multivariable regression model for all potential confounders – variables that could be associated with both the exposure (in this case, COVID-19 vaccine) and the outcome (infection). Confounders should be identified a-priori.

Effect modification can occur when the degree of the effect of the exposure (in this case, COVD-19 vaccine on the outcome (SARS-CoV-2 infection) varies by the extent of the presence of a third variable.

The analysis of this study should include an analysis of potential effect modifiers.

Depending on the sample size, analysis should be stratified according to:

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

Effect modifiers should be assessed one by one, comparing the estimates across the baseline characteristics listed above. Confounding factors should be assessed by comparing crude and adjusted estimates for each baseline characteristic.

The proportional hazards assumption of Cox regression should be assessed using graphical approaches and tests. If the assumption is not met, then survival models with random effects will be explored to take into account unmeasured heterogeneity.

6.4 Controlling for clustering by health facility

In studies that involve more than one health facility, in order to control for a clustering effect by health facility, a mixed model could be considered, including health facility as a random intercept.

6.5 Missing data

Missing data should be categorised and an appropriate approach to handle missing data chosen. Depending on assumptions that can be made about the missing variables this may be a complete case or multiple imputation approach.

6.6 Secondary Analyses

As a secondary analysis vaccine effectiveness should be assessed in subgroups and against multiple infections as indicated in Table 5.

Table 5: Research questions and corresponding HW cohorts

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

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

Secondary outcomes can also be considered and may include (according to what is feasible in country setting):

- SARS-CoV-2 laboratory confirmation by RT-PCR in any severely ill HW participating in the study, where RT-PCR positive cases are defined as one or more of:
  - being hospitalised
  - requiring supplementary oxygen therapy
  - intubated
  - requiring mechanical ventilation
  - admitted to ICU
  - in-hospital death
  - death within 30 days of a positive SARS-CoV-2 test
  - clinical signs of pneumonia
  - severe respiratory rate > 30 breaths/min

- severe respiratory distress
- acute respiratory distress syndrome (ARDS)
- oxygen saturation <90% on room air
- sepsis
- septic shock

Severe cases should ideally meet one of WHO's severe COVID-19 case definitions:

(1) WHO COVID-19 case management definition for severe or critical disease: Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) plus one of the following:

- respiratory rate > 30 breaths/min
- severe respiratory distress
- SpO2 < 90% on room air
- acute respiratory distress syndrome (ARDS)
- sepsis
- septic shock
- death

OR

(2) WHO surveillance case definition for Severe Acute Respiratory Illness Infection (SARI): A hospitalized person with acute respiratory infection, with a history of fever or measured fever of ≥ 38°C and cough with onset within the last 10 days

- SARS-CoV-2 asymptomatic or mild infection: Any HW participating in the study who tested RT-PCR positive for SARS-CoV-2 or had a positive serology test indicating infection-induced immunity (either as part of active surveillance or other screening activity) during the study period, and did not present with symptoms required to meet the case definition for suspected COVID-19 case.

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

- Previous clinical COVID-19: HW reporting having had the symptoms required to meet the case definition for WHO probable COVID-19 case before enrolment in the VE study but who did not have a SARS-CoV-2 diagnostic test during the period he or she was symptomatic.

- Previous SARS-CoV-2 infection with detectable antibodies at enrolment and history of clinical COVID-19: HW testing positive 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 detectable antibodies at enrolment and no previous COVID-19: HW testing positive at enrolment (the time of inclusion in the study) with no past clinical history or laboratory confirmation of COVID-19.

- Previous clinical SARS-CoV-2 infection without detectable antibodies at the start of the study: HW who report having had COVID-19 (meeting the WHO suspected case definition, clinically confirmed or self-reported) with a negative serology at the time of inclusion in the study.

- HWs who did not have baseline serology at enrolment, regardless of previous documentation of SARS-CoV-2 infection by clinical or laboratory diagnosis

6.8 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 intervals between symptom onset and specimen collection
- Using different intervals between vaccination and suspected immunity for defining vaccination status (time period after vaccination)
- Calculating E-values to quantify the potential for bias due to unmeasured confounding
- VE by time since vaccination ; including Farrington /Longini/ Halloran methods[20,21] for analysing / correcting for biases due to cumulative incidence **risk**; stable or variable incidence **rate** over time.

6.9 Additional analysis: test-negative design

Within the cohort study, a nested test-negative design (TND) can be conducted in which cases are HW who RT-PCR positive for SARS-CoV-2 and controls those RT-PCR negative. Cases and controls should be matched at a minimum by health facility and time. The TND may address the differential reporting of symptoms (e.g. asymptomic, Acute Respiratory Infection (ARI), severe e.g. SARI) 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 – OR)*100. The 95% Confidence Interval will be calculated around the estimate.

[20] Kanaan, Mona N., and C. Paddy Farrington. "Estimation of Waning Vaccine Efficacy." *Journal of the American Statistical Association*, vol. 97, no. 458, 2002, pp. 389–397. *JSTOR*.Available at: https://www.jstor.org/stable/3085652 (accessed 21 April 2021)

[21] Jerome I Tokars, Manish M Patel, Ivo M Foppa, Carrie Reed, Alicia M Fry, Jill M Ferdinands, Waning of Measured Influenza Vaccine Effectiveness Over Time: The Potential Contribution of Leaky Vaccine Effect, *Clinical Infectious Diseases*, Volume 71, Issue 10, 15 November 2020, Pages e633–e641, https://doi.org/10.1093/cid/ciaa340

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.

7. 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.

- **Selection bias**
  - **Previous infections:** HW are a population highly exposed 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 addressed in the analysis using potential exposures collected.

  - **Healthy vaccinee effect**: vaccinated HW 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 PPE use variables collected.

- **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.

- **Sample size/power**
  - may be limited for some for stratified or secondary analyses.
  - if vaccine coverage is very high among HW, the study may lack of power

- **Unmeasured confounding** between vaccinated and unvaccinated may be present like risky behaviours, beliefs affecting exposure and vaccine acceptance.

- **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 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.

8. Ethical considerations

Studies of COVID-19 vaccine effectiveness in healthcare workers should be approved by the relevant local Ethics Review Committee.

All HWs approached for enrolment should be informed that participation is voluntary and that he/she will be able to withdraw from the study, without justification, at any time during the without consequences. It should be clearly stated that participation to this study will not impact on offer for vaccination or on their employment.

The Informed consent form (**Annex 2**) should include a description of the methods and frequency of collecting blood, respiratory samples, clinical and epidemiological data (through questionnaires (**Annex 3**), and, when applicable, database queries) 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).

9. Data Governance

Biological materials and related data should only be collected and stored in collaboration with local health authorities. The governance structure of such collection should have representation of the original setting. 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.

Site-specific protocols should also address the question of sponsorship of long-term storage; ownership of the samples (e.g., sponsor, participant, investigator, or biorepository); and should address the subject of who will benefit from potential downstream commercialisation derived from sample use (e.g., if new diagnostic equipment is tested on the samples leading to commercialisation of the equipment).

*All points relative to governance of biological samples and data should be addressed in the informed consent form (***Annex 2***).*
(For more information, please see International Ethical Guidelines for Health-related Research Involving Humans[22])

[22] International Ethical Guidelines for Health-related Research Involving Humans. Fourth Edition. Geneva. Council for International Organizations of Medical Sciences (CIOMS); 2016. Available at: https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf (accessed 27 April 2021)

10. 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 or respiratory face masks, if necessary. Investigators can complete WHO's online training course on Infection Prevention and Control (IPC) for Novel Coronavirus (COVID-19): https://openwho.org/courses/COVID-19-IPC-EN and refer to WHO interim guidance[23].

11. 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. The direct benefit to the participant will be the potential detection of SARS-CoV-2 infection, which would then allow for appropriate monitoring and treatment. The primary benefit of the study is indirect in that the data collected will help to measure the effectiveness of the COVID-19 vaccine and guide vaccination policies.

Site-specific protocols should consider how study-related activities may impact on service delivery and patient care if conducted during work time.

12. Dissemination of results

Results of PCR tests and serology will be shared with participants as soon as they are available. A summary of the study results should be fed back to the participant HW.

[23] Prevention, identification and management of health worker infection in the context of COVID-19. Interim guidance 30 October 2020. Available at: https://www.who.int/publications/i/item/10665-336265 (accessed 27 April 2021)

Annex 1: Classification of Health Workers

Health workers are defined by WHO as all people engaged in actions with the primary intent of enhancing health, including social care workers who often have roles in the provision of care in long-term care facilities and in community settings[24].

Health workers can be classified into health service providers (those facing patients) and health management and support workers (those not facing patients).

HW facing patients:

- Health professionals (except nursing)
- Nursing and midwifery professionals
- Modern health associate professionals (except nursing)
- Nursing and midwifery associate professionals
- Traditional medicine professionals (acupuncturist, phytotherapist, etc.)

HW not facing patients:

- Computing professionals
- Social science and related professionals
- Administrative associate professionals
- Secretaries and keyboard operating clerks
- Painters, building structure cleaners and related trades workers

[24] The World Health Report 2006: Working Together for Health. Geneva, Switzerland. Geneva; 2006. Available at: https://apps.who.int/iris/handle/10665/43432 (accessed 27 April 2021)

Annex 2: Informed consent form

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

Notes to implementers:
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.**

Informed Consent Form - Cohort Study to measure COVID-19 Vaccine Effectiveness Among Health Workers in XXX

[YOUR INSTITUTIONAL LETTER HEAD]	
Participant ID:	

CONSENT FORM
Cohort Study to measure COVID-19 Vaccine Effectiveness Among Health Workers in XXX

Hello,

I am _____, and I am helping to conduct study run by the XXX. The purpose of the study is to understand how effective the COVID-19 vaccine is in preventing infection in health workers in XXX. We are approaching you because you are a health worker at XXX Hospital, which is participating in this study.

This study is approved by the Ministry of Health of XXX. It is a collaborative study between the XXX and XXX.

If you choose to participate in the study, we will ask you to do a few things. First, on the day you enroll, we will ask you to fill out an initial questionnaire that will take approximately 10-15 minutes. Also, blood specimens will be collected for lab testing, and we will ask you to provide a respiratory specimen.

During the 6-month study, we will ask you to:

- complete a weekly questionnaire, which will take 1-2 minutes,
- inform the study staff if you get ill and complete a brief 1-2 minute questionnaire and provide a respiratory specimen. The specimen will be tested by the lab, and the results will be shared with you as soon as they are available.

In addition to the blood sample that you give on the day of enrollment, we will collect blood from you XX more times, after XX months, XX months, XX months and XX months.

Because of the respiratory sample, you may experience temporary discomfort.

To ensure your safety during collection of the blood sample, venipuncture and specimen collection will be performed by trained staff in compliance with all infection control requirements and use of sterile disposable materials for blood collection. Very uncommon complications that could occur include a small subcutaneous hematoma (hemorrhage) at the puncture site, inflammation at the puncture site, local phlebitis (inflammation of vein section) at the puncture site, nerve injury by the puncture.

In addition, in order to confirm your COVID-19 vaccination history, if you grant us permission, we will access your vaccination records in the XXX national database.

Your participation in the study is voluntary.

The study staff will process all collected information with utmost confidentiality. Your participation will remain unidentified and no names of participants will appear in study reports or publications.

Your blood samples and respiratory samples will be sent to laboratories in XX and may be sent outside of the country for advanced testing. If they are sent outside of the country, all personal identifying data will be removed beforehand.

Any test (serology or PCR) which is found to be positive for COVID-19 will be reported to the local public health authorities in accordance with the national standard operating procedures in XXX.

You will be contacted via phone by the local public health authorities about any test result of a respiratory sample or a blood sample that is positive for SARS-CoV-2, the virus that causes COVID. In addition to follow up from the public health authorities, study staff will contact you with the results of any nasal swab or blood which is obtained during the study.

Your blood and respiratory samples will be stored for a maximum of XX years in order to ensure that there is adequate time for testing, including genetic sequencing of respiratory samples.

Data we collect from you will be stored securely at the hospital and in a secure data management system. The data will be stored for a maximum of 5 years and will only be accessed by study investigators and study staff. All data will be used in order to answer questions related to the objectives of the study in according to consensus decisions by study investigators.

You may withdraw from the study at any time without any explanation. Refusal to participate will not affect your rights to get a COVID-19 vaccine and will not impact any aspect of your employment.

If you decide to withdraw from the study, your data and samples will be maintained in accordance with study guidelines unless you request for your data and samples to be destroyed

If you have any questions about the study at any time during the study, please call the study manager at your hospital (contact information for study manager at hospital should be listed here)

We hope you will be able to participate in the study because your participation is important, and the study's findings will be very useful for public health decision-making in XXX and the world. If you have any questions please contact investigators of this project:

Investigators:	

Do you have any questions? Can I start the survey? Please let me know if at some point during the study you decide to withdraw, - you can withdraw at any time.

Thank you.

If you agree please tick the boxes:

1. I confirm to have read and understood the information about this study. I was able to review this information, ask questions and I have received satisfactory answers ☐

2. I understand that the blood sample may cause discomfort and sensation of pain at the puncture site. ☐

3. I was made aware that after blood collection the following complications may occur:
- emergence of subcutaneous hematoma (hemorrhage) at the puncture site
- soft tissue inflammation at the puncture site as a result of infection
- development of local phlebitis (inflammation of vein section) at the vein puncture site
- nerve injured by puncture or pressing by hematoma. ☐

4. I was made aware of potential repeated venipuncture due to technical difficulties occurring during blood collection from vein. ☐

5. I was made aware of the benefits to participating in the study. The data collected will help to measure the effectiveness of the COVID-19 vaccine and will inform decisions in XXX and all over the world about vaccination policies. ☐

6. I confirm that I will provide my full history of all diseases, illnesses and conditions in the questionnaire. I confirm that I will answer all questions honestly and will not conceal any information about my health. ☐

7. I grant the study staff permission to access my vaccination records in the XXX database ☐

8. In case I become infected with COVID-19 during the course of the study, I grant the study staff permission to access my laboratory records and my hospital records related to the course of my illness for COVID-19 (if relevant) ☐

9. I agree that my blood samples and respiratory samples from this study may be sent to laboratories outside of the XXX for advanced testing, and respiratory virus samples may undergo genetic sequencing. If samples are sent outside of the country, all personal identifying data will be removed beforehand. ☐

10. I understand that my participation is voluntary and I am free to withdraw at any time without any explanation. ☐

11. I understand that any information provided by me may be used in future reports, articles and presentations made by the investigation team. ☐

12. I understand that my name will not be identified in any report, article or presentation. ☐

13. I agree to take part in the above study. ☐

_____ _____

Participant signature Date

_____ _____

Investigator signature Date

Annex 3: Questionnaires

Form A: Enrolment questionnaire

***Note**: personal information should be kept confidential according to local data security procedures.*

Note: questions in grey are optional.

Pre-enrolment questionnaire: (To be completed by study staff)	
Unique health worker ID	
Accepts to participate in the VE study	□ Yes □ No
Has consent been provided by HW?	□ Yes □ No
For HW who do not agree to participate, basic demographics (age, sex, occupation)	
Name/code of health care facility	
Form completion date (dd/mm/yyyy)	___/___/___

Enrolment questionnaire (to be completed by participant)	
Part 1. Identifier and HW characteristics	
Contact details:	
1. First name	
2. Surname	
3. Email address	
4. Phone number	
Info to be collected for all HW approached	
5. Sex	□ Male □ Female
6. Date of birth (dd/mm/yyyy)	___/___/___
7. How old are you? (years)	
8. What district do you live in?	
9. What is your nationality? If more than one, provide the one you currently use.	
10. What is your highest level of education?	□ None □ Primary □ Secondary □ University □ Prefer not to answer
11. Ethnicity	Categories to be determined according to setting
HW characteristics	
12. What is your height?	
13. What is your weight?	
14. What is your blood group	□ A □ B □ O

15. Do you have a chronic condition?	☐ Yes ☐ No ☐ Unknown/Non-disclosure If yes, specify:
a) Diabetes	□ Yes □ No □ Unknown/Non-disclosure
b) Heart disease	□ Yes □ No □ Unknown/Non-disclosure
c) Hypertension	□ Yes □ No □ Unknown/Non-disclosure
d) Immunodeficiency or organ transplant	□ Yes □ No □ Unknown/Non-disclosure
e) Lung disease	□ Yes □ No □ Unknown/Non-disclosure
f) Asthma	□ Yes □ No □ Unknown/Non-disclosure
g) Cancer	□ Yes □ No □ Unknown/Non-disclosure
h) If height and weight are not collected: BMI (if available)	
i) Renal disease	□ Yes □ No □ Unknown/Non-disclosure
j) Liver disease	□ Yes □ No □ Unknown/Non-disclosure
k) Rheumatological disease	□ Yes □ No □ Unknown/Non-disclosure
l) How many times have you been hospitalised for the chronic condition in the last 12 months	
16. Are you currently pregnant?	□ Yes □ No □ Unknown/Non-disclosure
a) If pregnant, specify trimester	□ First □ Second □ Third □ Unknown/Non-disclosure
17. Do you smoke or have you ever smoked (any smoking: cigarettes, cigars, vaping)?	□ I've never smoked □ I stopped smoking more than one year ago □ Yes, I currently smoke
Treatment/medications(s)	
18. Are you taking regularly any medication(s)?	□ Yes □ No □ Unknown /Non-disclosure If yes, please specify:
a) Statins	□ Yes □ No □ Unknown/Non-disclosure
b) Angiotensin-converting enzyme inhibitors	□ Yes □ No □ Unknown/Non-disclosure
c) Angiotensin II receptor blockers	□ Yes □ No □ Unknown/Non-disclosure
d) Non-steroidal anti-inflammatory drugs	□ Yes □ No □ Unknown/Non-disclosure
e) Corticosteroids	□ Yes □ No □ Unknown/Non-disclosure
f) Anti-rheumatic drugs	□ Yes □ No □ Unknown/Non-disclosure
g) Antithrombotic/ platelet aggregation inhibitors	□ Yes □ No □ Unknown/Non-disclosure
h) Metformin	□ Yes □ No □ Unknown/Non-disclosure
i) Other, specify	
Vaccination history **COVID-19 vaccine**	
19. Do you have a contraindication for the COVID-19 vaccine?	□ Yes □ No □ Unknown/Non-disclosure

20. Have you received the first dose of any COVID-19 vaccine?	□ Yes □ No □ Unknown/Non-disclosure
21. If yes, what was the date of the first dose? (dd/mm/yyyy)	___/___/___
22. Which COVID-19 vaccine did you receive? (product name: provide list according to products available in country with "other" as an option)	List
23. Mode of COVID-19 vaccine ascertainment (to be the verified by study staff)	□ = vaccination card □ = vaccination registry □ = self-report □= other (specify_____) □ = not documented
24. What was the Batch/lot of the COVID-19 vaccine received?	Please provide the batch number from the above documents or state □ Unknown
25. Have you received a second dose of the COVID-19 vaccine?	□ Yes □ No □ Unknown
26. If yes, what day did you receive the second dose (dd/mm/yyyy)	___/___/___
27. Which kind of COVID-19 vaccine did you receive for the second dose (product name: provide list according to products available in country with "other" as an option)	
28. What was the Batch/lot number of the second dose vaccine you received?	Please provide the batch number from the ascertainment documents or state □ Unknown
29. Mode of vaccine ascertainment of the second dose (to be verified by study staff)	□ = vaccination card □ = vaccination registry □ = self-report □ = other (specify_____) □ = not documented
Other vaccines	
30. Have you received an influenza vaccine in the current influenza season? (when applicable)	□ Yes □ No □ Unknown
31. If yes, when did you receive the influenza vaccine (dd/mm/yyyy)	___/___/___
32. Name of influenza vaccine received (product name)	
33. Have you received a pneumococcal vaccine? (when applicable)	□ Yes □ No □ Unknown
34. If yes, type of vaccine	□ PPSV23 □ PCV13 □ Other, specify_____ □ Do not know

35. If yes, in which year did you last receive a pneumococcal vaccine?	
36. Have you taken any COVID-19 treatment in the last 14 days?	□ Yes □ No □ Unknown
37. If yes, date started treatment (dd/mm/yyyy)	___/___/___
38. If yes which treatment did you take?	
39. Since the beginning of the pandemic in January 2020, have you tested positive for SARS-CoV-2?	□ Yes □ No
40. If yes, which test was used?	□ Antigen □ PCR □ Serology □ I don't remember what kind of test was done
41. If yes, when was your (last) positive test? (dd/mm/yyyy) or (mm/yyyy)	___/___/___
42. If you've never had a positive test, has a doctor ever diagnosed you with a COVID-19?	□ Yes □ No
43. If yes, when was this?(dd/mm/yyyy)	___/___/___
44. If you've never had a positive COVID test and were never diagnosed with COVID-19 by a doctor, do you think you ever had a COVID-19 illness that wasn't tested or diagnosed?	□ Yes □ No
45. If yes, when was this? (dd/mm/yyyy)	___/___/___

Part 2. Exposures in the last 14 days	
2a. Work exposures in last 14 days	
46. What is your job?	□ Medical doctor □ Registered nurse (or equivalent) □ Nursing assistant, nurse technician (or equivalent) □ Radiology/x-ray technician □ Phlebotomist □ Physical therapist □ Nutritionist/dieticians □ Laboratory personnel □ Admission/reception clerk □ Patient transporter □ Catering staff □ Cleaner □ Administration □ Other [***specify***]:

47. Which ward(s) do you work in? (check all that apply)	□ Intensive Care Unit □ Surgery □ Medicine □ Emergency Department □ Pediatrics and/or Pediatric Specialties □ Gynecology and/or Obstetrics □ Oncology and/or Hematology □ Dentistry □ Radiology □ Outpatient clinic □ Pharmacy □ Laboratory □ Nutrition □ Social Assistance □ Physiotherapy □ Occupational therapy □ Other (specify) _____
48. In the last 14 days have you worked in more than 1 ward?	□ Yes If yes, please specify the wards: _____ □ No
49. Do you interact with COVID-19 patients as part of your job?	□ Yes □ No
50. In the past 14 days, which of the following aerosol-generating procedures have you been involved in?	□ Tracheal intubation □ Laryngeal mask airway (LMA) □ Non-invasive ventilation using mask or similar device □ Tracheotomy □ Cardiopulmonary resuscitation □ Manual ventilation □ Bronchoscopy □ Sputum induction with nebulized saline □ Autopsy procedures □ Other If other, specify _____ Number of each procedure □ None
51. How many COVID-19 patients have you been exposed to during your occupational duties in the last 14 days? (provide an appropriate scale according to size of facility i.e. 0, 1-10, 11-100, 100+ etc.)	Scale (to be defined)
52. Have you had close contact (within 1 metre) with the patient(s) since their admission in the last 14 days?	□ Yes □ No □ Unknown
53. Have you been involved in nebulizer treatment in the last 14 days?	□ Yes □ No □ Unknown

54. Have you been involved in administering respiratory support in the last 14 days?	□ Yes □ No □ Unknown If yes, please specify: ☐ O2 high flow ☐ O2 low flow ☐ High nasal cannula ☐ High pressure O2 ☐ Metered-dose inhaler ☐ not specified
2b. Exposures outside of your work in the last 14 days	
55. Outside of the hospital, have you been in close contact with a confirmed COVID-19 patient or a person with COVID-19 symptoms in the last 14 days?	□ Yes □ No □ Unknown
56. How many individuals live in your household (including yourself)? (a household is defined as a **group of people (two or more) living in the same residence**.)	□ 0 □ 1-2 □ 3-5 □ 6-8 □ 9 or more
57. In the last 14 days, how many times have you used public transportation besides a family car (public bus, shared van, train, subway/metro)?	□ 0 □ 1-2 □ 3-5 □ 6-8 □ 9 or more
58. In the last 14 days, how many times have you attended a social indoor event or gathering with MORE than 10 people? (This includes activities such as attending church, parties, weddings, and sporting events, or visiting a bar or restaurant).	□ 0 □ 1-2 □ 3-5 □ 6-8 □ 9 or more
59. How often have you worn a mask when in an indoor setting outside of your home?	□ always □ often □ sometimes □ rarely □ never □ did not go to indoor locations outside home

60. How often have you stayed at least 2 metres from other people in indoor spaces outside your home?	□ always □ often □ sometimes □ rarely □ never □ did not go to indoor locations outside home
61. In the last 14 days, how many times have people who do not live in your household visited your home?	□ 0 □ 1-2 □ 3-5 □ 6-8 □ 9 or more
62. In the last 14 days, how many times have you visited other people in their homes?	□ 0 □ 1-2 □ 3-5 □ 6-8 □ 9 or more

Part 3. Adherence to infection prevention and control (IPC) measures	
63. Do you follow recommended hand hygiene practices?	□ Always, as recommended □ Most of the time □ Occasionally □ Rarely □ Never
64. Do you use alcohol-based hand rub or soap and water before touching a patient?	□ Always, as recommended □ Most of the time □ Occasionally □ Rarely □ Never
65. Do you use alcohol-based hand rub or soap and water before cleaning/aseptic procedures?	□ Always, as recommended □ Most of the time □ Occasionally □ Rarely □ Never
66. Do you use alcohol-based hand rub or soap and water after (risk of) body fluid exposure?	□ Always, as recommended □ Most of the time □ Occasionally □ Rarely □ Never
67. Do you use alcohol-based hand rub or soap and water after touching a patient?	□ Always, as recommended □ Most of the time □ Occasionally □ Rarely □ Never

68. Do you use alcohol-based hand rub or soap and water after touching a patient's surroundings?	□ Always, as recommended □ Most of the time □ Occasionally □ Rarely
69. Do you follow Infection Prevention Control (IPC) standard precautions when in contact with any patient? (define for setting)	□ Always, as recommended □ Most of the time □ Occasionally □ Rarely □ Never □ I don't know what IPC standard precautions are
70. Do you wear the recommended Personal Protective Equipment (PPE) when indicated? (PPE includes: medical/surgical mask, face shield, gloves, goggles/glasses, gown, coverall, head cover, respirator (e.g. N95 or equivalent) and shoe covers)	□ Always, according to the risk assessment □ Most of the time, according to the risk assessment □ Occasionally □ Rarely □ Never

Part 4. Symptoms and clinical course of disease in the last 14 days before enrolment	
71. In the last 14 days, have you had any of the following symptoms?	□ Yes □ No
a) Acute onset	□ Yes □ No □ Unknown
b) Fever (≥ 38 °C) or history of fever	□ Yes □ No □ Unknown If yes, specify maximum temperature:_____
c) Cough	□ Yes □ No □ Unknown
d) General weakness/fatigue[25]	□ Yes □ No □ Unknown
e) Headache	□ Yes □ No □ Unknown
f) Myalgia	□ Yes □ No □ Unknown
g) Sore throat	□ Yes □ No □ Unknown
h) Coryza	□ Yes □ No □ Unknown
i) Dyspnoea	□ Yes □ No □ Unknown
j) Anorexia/ Nausea / Vomiting1	□ Yes □ No □ Unknown
k) Diarrhoea	□ Yes □ No □ Unknown
l) Altered mental status	□ Yes □ No □ Unknown
m) Loss of smell	□ Yes □ No □ Unknown
n) Loss of taste	□ Yes □ No □ Unknown
o) Altered taste	□ Yes □ No □ Unknown
72. Have you had radiological evidence of lesions compatible to COVID-19 (e.g. by chest X-ray or computed tomography scan)?	□ Yes □ No □ Unknown
73. If you had any of the above symptoms, on what day did the first symptom start	___/___/___ (dd/mm/yyyy)

[25] Signs separated with slash(/) are to be counted as one sign.

74. Did you see a doctor for your symptoms?	□ Yes □ No □ Unknown
75. Did you go to an emergency room?	□ Yes □ No □ Unknown
76. Did you get hospitalized for your symptoms?	□ Yes □ No □ Unknown
77. Did you get tested for SARS-CoV-2 outside the hospital?	□ Yes □ No □ Unknown
a) If yes, what test was done?	□ PCR □ Rapid Antigen Test □ Serology Test □ I don't remember
b) What was the test(s) result(s)?	□ PCR positive □ PCR negative □ Serology positive □ serology Negative □ Rapid antigen positive □ Rapid antigen negative

Part 5: Hospitalisation for COVID-19	
If yes to Q76 (hospitalized), the study team should collect the information below:	
a) Date of hospitalisation	__/___/___
b) Date of discharge	__/___/___
c) Admission to ICU or high-dependency unity	□ Yes □ No □ Unknown
d) Admission date to ICU/HDU	__/___/___
e) Discharge date ICU/HDU	__/___/___
f) What was respiratory rate at time of admission or enrolement (if available)	…… breaths/minute
g) What was SpO2 at time of admission or enrolment (if available)	……. % SpO2
h) Required supplementary oxygen therapy	□ Yes □ No □ Unknown
i) Intubated	□ Yes □ No □ Unknown
j) Required mechanical ventilation	□ Yes □ No □ Unknown
k) Severe respiratory distress (when known)	□ Yes □ No □ Unknown
l) Acute Respiratory distress syndrome (ARDS) (when known)	□ Yes □ No □ Unknown
m) Sepsis (when known)	□ Yes □ No □ Unknown
n) Septic shock (when known)	□ Yes □ No □ Unknown
o) In-hospital death	□ Yes □ No □ Unknown
p) Death date	__/___/___

Form B: Laboratory form

The following part is to be filled out for each test by the main investigator after interviewing laboratory staff to obtain the laboratory data

Laboratory: Serology testing methods and results							
Complete a new line for each specimen collected and each type of test done							
Laboratory identification number	**Date sample collected (dd/mm/yyyy)**	**Date sample received (dd/mm/yyyy)**	**Type of sample**	**Type of test**	**Result**	**Result date (dd/mm/yyyy)**	**Specimens shipped to other laboratory for confirmation?**
	___/___/___ Timing of the testing: □ Enrolment □ Follow-up at month #	___/___/___	□ Serum □ Blood □ Dried Blood Sport (DBS) □ Other, specify:	Specify type: (e.g. ELISA/IFA neutralization assay, RDT etc.)	□ POSITIVE If positive, COVID-19 antibody titre: (IgM, IgG, total Ab) _____ □ NEGATIVE □ INCONCLUSIVE	___/___/___	□ Yes If yes, specify date shipped: ___/___/___ If yes, name of the laboratory: □ No

	Laboratory: Virology testing methods and results								
	Complete a new line for each specimen collected and each type of test done								
Laboratory identification number	**Date sample collected (dd/mm/yyyy)**	**Date sample received (dd/mm/yyyy)**	**Type of sample (check all that apply)**	**Result PCR**	**CT value**	**Result sequencing**	**Results other pathogens**	**Result date (dd/mm/yyyy)**	**Specimens shipped to other laboratory for confirmation ?**
	__/___/___ Timing of the testing: □ Enrolment □ Follow-up at week # □ End Follow-up	__/___/___	□ Nasal swab □ Throat swab □ Naso-pharyngeal swab □ Other, specify:	□ POSITIVE for COVID-19 □ NEGATIVE for COVID-19 □ INCONCLUSIVE		Variant	□ POSITIVE for other pathogens Please specify which pathogens (LIST TO BE ADDED DEPENDING ON TESTS PEFORMED)	___/___/___	□ Yes If yes, specify date shipped: ___/___/___ If yes, name of the laboratory: □ No

Form C: Follow up questionnaire

***Instruction 1**: This questionnaire should be filled in weekly OR any time the HW develop symptoms compatible with* SARS-CoV-2 *infection*

Administration	
Unique health worker ID	
If HW does not accept to continue the study, reasons	
Form completion date (dd/mm/yyyy)	___/___/___

Part A. Health worker symptoms	
1. In the last 7 days, have you felt ill at any time?	□ Yes □ No (if yes, continue with the questionnaire symptoms)
a) Acute onset	□ Yes □ No □ Unknown
b) Fever (≥ 38 °C) or history of fever	□ Yes □ No □ Unknown If yes, specify maximum temperature:_____
c) Cough	□ Yes □ No □ Unknown
d) General weakness/fatigue[26]	□ Yes □ No □ Unknown
e) Headache	□ Yes □ No □ Unknown
f) Myalgia	□ Yes □ No □ Unknown
g) Sore throat	□ Yes □ No □ Unknown
h) Coryza	□ Yes □ No □ Unknown
i) Dyspnoea	□ Yes □ No □ Unknown
j) Anorexia/ Nausea / Vomiting1	□ Yes □ No □ Unknown
k) Diarrhoea	□ Yes □ No □ Unknown
l) Altered mental status	□ Yes □ No □ Unknown
m) Loss of smell	□ Yes □ No □ Unknown
n) Loss of taste	□ Yes □ No □ Unknown
o) Altered taste	□ Yes □ No □ Unknown
p) Have you had radiological evidence of lesions compatible to COVID-19 (e.g. by chest X-ray or computed tomography scan)?	□ Yes □ No □ Unknown
2. If you had any of the above symptoms, on what day did the first symptom start (dd/mm/yyyy)	___/___/___
3. Did you see a doctor for your symptoms?	□ Yes □ No □ Unknown
4. Did you go to an emergency room?	□ Yes □ No □ Unknown

[26] Signs separated with slash(/) are to be counted as one sign.

5. Did you get hospitalized for your symptoms?	□ Yes □ No □ Unknown
6. If you have had COVID-19 symptoms, have you taken any COVID-19 treatment since last testing?	□ Yes □ No □ Unknown
a) If yes, date started treatment (dd/mm/yyyy)	___/___/___
b) If yes which treatment did you take?	

Hospitalisation for COVID-19	
If yes to Q5, the study team should collect the information below (when information available)	
a) Date of hospitalisation	__/___/___
b) Date of discharge	__/___/___
c) Admission to ICU or high-dependency unity	□ Yes □ No □ Unknown
d) Admission date to ICU/HDU	__/___/___
e) Discharge date ICU/HDU	__/___/___
f) What was respiratory rate at time of admission or enrolment (if available)	…… breaths/minute
g) What was SpO2 at time of admission or enrolement (if available)	……. % SpO2
h) Required supplementary oxygen therapy	□ Yes □ No □ Unknown
i) Intubated	□ Yes □ No □ Unknown
j) Required mechanical ventilation	□ Yes □ No □ Unknown
k) Severe respiratory distress (when known)	□ Yes □ No □ Unknown
l) Acute Respiratory distress syndrome (ARDS) (when known)	□ Yes □ No □ Unknown
m) Sepsis (when known)	□ Yes □ No □ Unknown
n) Septic shock (when known)	□ Yes □ No □ Unknown
o) In-hospital death	□ Yes □ No □ Unknown
p) Death date	__/___/___

Part B. COVID-19 vaccines	
7. Have you received a dose (first or second) of COVID-19 vaccine since the last testing/questionnaire?	□ Yes □ No □ Unknown (If yes, continue with the questions below)
a) Number of the dose	□ = First dose □ = Second dose

b) If yes, what was the date of the dose? (dd/mm/yyyy)	___/___/___
c) Which COVID-19 vaccine did you receive? (product name: provide list according to products available in country with "other" as an option)	List
d) Mode of COVID-19 vaccine ascertainment (to be the verified by study staff)	□ = vaccination card □ = vaccination registry □ = patient self-report □= other (specify_____) □ = not documented
e) What was the Batch of the COVID-19 vaccine received?	Please provide the batch number from the above documents or state □ Unknown
Other vaccines	
8. Have you received any other vaccine in the last 7 days?	□ Yes □ No □ Unknown (If yes, continue with the questions below)
If yes, which vaccine:	□ Influenza □ Other, Specify_____ (If yes for influenza vaccine, continue with the questions below)
Date of the influenza vaccine(dd/mm/yyyy)	___/___/___
Name of influenza vaccine received (product name)	

Part C: Exposures in the last 7 days	
C1: Work-related exposures in last 7 days	
9. Have you had any change in the working condition since last testing?	□ Yes □ No □ Unknown
10. Working ward(s) in the last 7 days	□ Intensive Care Unit □ Surgery □ Medicine □ Emergency Department □ Pediatrics and/or Pediatric Specialties □ Gynecology and/or Obstetrics □ Oncology and/or Hematology □ Dentistry □ Radiology □ Outpatient clinic □ Pharmacy □ Laboratory □ Nutrition □ Social Assistance

	□ Physiotherapy □ Occupational therapy □ Other (specify) _____
11. In the past 7 days, which of those aerosol generating procedures have you performed?	□ Tracheal intubation □ Laryngeal mask airway (LMA) □ Non-invasive ventilation using mask or similar device □ Tracheotomy □ Cardiopulmonary resuscitation □ Manual ventilation □ Bronchoscopy □ Sputum induction with nebulized saline □ Autopsy procedures □ Other If other, specify _____ Number of each procedure
12. How many COVID-19 patients have you been exposed to during your occupational duties in the last 7 days? (provide an appropriate scale according to size of facility i.e. 0, 1-10, 11-100, 100+ etc.)	scale
13. Have you had close contact (within 1 metre) with the patient(s) since their admission?	□ Yes □ No □ Unknown
14. Have you been involved in nebulizer treatment in the last 7 days?	□ Yes □ No □ Unknown
15. Have you been involved in providing respiratory support in the last 7 days?	□ Yes □ No □ Unknown If yes, please specify: ☐ O2 high flow ☐ O2 low flow ☐ High flow nasal cannula ☐ High pressure O2 ☐ Metered-dose inhaler ☐ not specified
C2: Exposures in the community in the last 7 days	
16. Outside of the healthcare setting, have you been in close contact with a confirmed COVID-19 patient or a person with COVID-19 symptoms in the last 7 days?	□ Yes □ No □ Unknown

17. How many times have you used public transportation besides a family car (public bus, shared van, train, subway/metro) in the last 7 days?	□ 0 □ 1-2 □ 3-5 □ 6-8 □ 9 or more
18. How many times have you attended a social indoor social event or gathering with MORE than 10 people in the last 7 days? (This includes activities such as attending church, parties, weddings, and sporting events, or visiting a bar or restaurant).	□ 0 □ 1-2 □ 3-5 □ 6-8 □ 9 or more
19. How often have you worn a mask when in an indoor setting outside of your home?	□ always □ often □ sometimes □ rarely □ never □ did not go to indoor locations outside home
20. How often have you stayed at least 2 metres from other people in indoor spaces outside your home?	□ always □ often □ sometimes □ rarely □ never □ did not go to indoor locations outside home
21. How many times have people who do not live in your household visited your home in the last 7 days? (a household is defined as a group of people (two or more) living in the same residence.)	□ 0 □ 1-2 □ 3-5 □ 6-8 □ 9 or more
22. How many times have you visited other people in their homes in the last 7 days?	□ 0 □ 1-2 □ 3-5 □ 6-8 □ 9 or more

Annex 4: Example of variables, definitions and coding of study data

Table variables baseline questionnaire (T1). Optional variables are highlighted in grey.

Variable name	Type	Values and coding	Definition
participate	Numeric (binary)	0 = No 1 = Yes	Agrees to participate
refuse	Text		Reasons for refusal to participate
id	Type of variable at discretion of site	[needs to be unique]	Unique and persistent identifier for each record
health care facility code	Type of variable at discretion of site	[needs to be unique]	Unique identifier for each health care facility
Socio-demographics			
age	Numeric (continuous)	Integer	Age of each participant in years
sex	Numeric (binary)	0 = female 1 = male	Sex of study participant
res	Text		Place of residence
educ			Education level (optional)
ethn	Numeric (categorical)		Ethnicity: collection to be determined according to country-specific guidelines
Height	Numeric (continuous)	Integer	Height in cm

weight	Numeric (continuous)	Integer	Weight in kg
blood	Numeric (categorical)	1 = A 2 = B 3 = O 4 = Do not know	Blood group (Optional)
Work related			
hw_type	Numeric (categorical)	1 = medical doctor 2 = Registered nurse (or equivalent) 3 = Assistant nurse, nurse technician (or equivalent) 4 = Radiology/x-ray technician 5= Phlebotomist 6 = Physical therapist 7 = Nutritionist/dieticians 8 = Biologist 9 = Laboratory personnel 10 = Admission/reception clerk 11 = Patient transporter 12= Catering staff 13 = Cleaner 13= Other	Occupation in health care facility *(to be adapted as needed)*
hw_ward	Numeric (categorical)	1 = ICU 2 = surgery 3 = medicine 4 = obstetrics 5 = other, specify (text)	Working ward
hw_nwards		0 = No 1 = Yes If yes, specify	Work in several wards

hw_covid	Numeric (binary)	0 = No 1 = Yes 2 = No COVID-19 dedicated staff	health worker specifically dedicated to caring for COVID-19 patients
hw_exp	Numeric (categorical)	1 = tracheal intubation 2 = non-invasive ventilation 3 = tracheotomy 4 = cardiopulmonary resuscitation 5 = manual ventilation before intubation 6 = bronchoscopy 7 = sputum induction induced by using nebulized saline 8 = autopsy procedures 9 = other, specify (text)	Routine performed tasks
Signs and symptoms (this section is an example of coding that could be used in the follow up questionnaires for HW reporting symptoms) *at a minimum the relevant symptoms required to meet the case definition should be recorded			
nosympt	Numeric (categorical)	0 = No 1 = Yes	No symptoms.
onset	Date	dd/mm/yyyy	Date of onset of fist symptoms
fever	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Fever or feverishness
temp	Numeric (up to one decimal)		Measured temperature
malaise	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Malaise

myalgia	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Myalgia
cough	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Cough
sorethroat	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Sore throat
suddenonset	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Sudden onset
headache	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Headache
shortbreath	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Shortness of breath
anosmia	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Anosmia (Loss of sense of smell)
ageusia	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Ageusia
dysgeusia	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Dysgeusia
fatigue	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Fatigue
coryza	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Coryza or rhinitis
nausea	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Nausea
vomiting	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Vomiting

diarrhoea	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Diarrhoea
chills	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Chills/feverishness
chestpain	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Chest pain
lossappet	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Loss of appetite
stomache	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Stomach ache
conjunc	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Conjunctivitis
dizziness	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Dizziness
cyanosis	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Cyanosis
rash	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Rash or other dermatological manifestation
palpitations	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Palpitations
radio	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Radiological evidence of pneumonia (e.g. by chest X-ray or computed tomography scan
Swabbing and testing information			
serodate_t1	Date	dd/mm/yyyy	Sample date
serobtype_t1	Numeric (categorical)	1 = Serum 2 = Other, specify	Type of sample

serotest_t1	Numeric (categorical)	1 = ELISA 2 = IFA 3 = Neutralization 4 = Rapid test 5 = Other, specify	Serology type
serores_t1	Numeric (categorical)	0 = Negative 1 = IgM Positive 2 = IgG positive 3 = total Ab positive 8 = Do not know	Serology result
seropos_t1	Text		Antibody titer
swabdate_t1	Date	dd/mm/yyyy	Swabbing date
swabtype_t1	Numeric (categorical)	1 = Nose 2 = Throat 3 = Both nose and throat 4 = Other (specify) 8 = Do not know	Type of swab taken
pcrres_t1	Numeric (categorical)	0 = Negative 1 = Positive 2 = Inconclusive 8 = Do not know	PCR result for SARS-CoV-2 (positive/negative)
clade_t1	Text		Genetic variant of SARS-CoV-2 virus (can be collected separately at different date)
Results for other respiratory pathogens			
lab-flu_t1	Numeric (categorical)	0 = Negative 1 = Positive 2 = Not done 8 = Do not know	Laboratory result for influenza (positive/negative)
lab_rsv_t1	Numeric (categorical)	0 = Negative 1 = Positive 2 = Not done 8 = Do not know	Laboratory result for RSV (positive/negative)
lab_metapneum_t1	Numeric (categorical)	0 = Negative 1 = Positive 2 = Not done 8 = Do not know	Laboratory result for human metapneumovirus (positive/negative)

lab_rhinovirus_t1	Numeric (categorical)	0 = Negative 1 = Positive 2 = Not done 8 = Do not know	Laboratory result for rhinovirus (positive/negative)
lab_adenovirus_t1	Numeric (categorical)	0 = Negative 1 = Positive 2 = Not done 8 = Do not know	Laboratory result for adenovirus (positive/negative)
lab_bocavirus_t1	Numeric (categorical)	0 = Negative 1 = Positive 2 = Not done 8 = Do not know	Laboratory result for bocavirus (positive/negative)
lab_seascorona_t1	Numeric (categorical)	0 = Negative 1 = Positive 2 = Not done 8 = Do not know	Laboratory result for seasonal coronavirus (positive/negative)
lab_enterovirus_t1	Numeric (categorical)	0 = Negative 1 = Positive 2 = Not done 8 = Do not know	Laboratory result for enterovirus (positive/negative)
COVID-19 Vaccination variables ***(this section should be completed during the follow up, each time there is a change in the COVID-19 vaccination status)***			
covidvaccany_v1	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Received COVID vaccination first dose
covidvaccdate_v1	Date	dd/mm/yyyy	COVID vaccination date first dose
covidvacctype_v1	Text		Type of vaccine (brand name) first dose
covidvaccbatch_v1	Text		Batch vaccine first dose
covidvaccdoc_v1	Numeric (categorical)	0 = not documented 1 = patient self-report 2 = vaccination card 3 = vaccination registry 4 = other (specify	Vaccination status ascertainment first dose

covidvaccany_v2	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Received COVID vaccination second dose
covidvaccdate_v2	Date	dd/mm/yyyy	COVID vaccination date second dose
covidvacctype_v2	Text		Type of vaccine (brand name second dose)
covidvaccbatch_v2	Text		Batch vaccine (second dose)
covidvaccdoc_v2	Numeric (categorical)	0 = not documented 1 = patient self-report 2 = vaccination card 3 = vaccination registry 4 = other (specify	Vaccination status ascertainment second dose
Other vaccinations ***(this section should be completed at enrolment and any time there is a change in the vaccination status)***			
fluvaccany_t1	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Received flu vaccination in current season
fluvaccdate_t1	Date	dd/mm/yyyy	Influenza vaccination date
fluvacctype_t1	Text		Type of vaccine (brand name)
pneumovacc_t1	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Received pneumococcal vaccination
pneumotype_t1	Numeric (categorical)	1 = PPSV23 2 = PCV13 3 = Other (pls specify) 8 = Do not know	Type of pneumococcal vaccine
pneumoyear_t1	Number		Year of receipt of pneumococcal vaccination

Underlying conditions			
diabetes	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Diabetes and endocrine disease
heart_dis	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Heart disease (excluding hypertension)
hyperten	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Hypertension
immuno	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Immunodeficiency and organ transplant
lungdis	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Lung disease
asthma	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Asthma
cancer	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Cancer
obese	Numeric (categorical)	0 = No 1 = BMI ≥30-39 2 = BMI ≥40 8 = Do not know	Obesity.
renal_dis	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Renal disease
liver_dis	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Liver disease
rheum_dis	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Rheumatological disease
preg	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Pregnancy

preg_trim	Numeric (categorical)	1 = first 2 = second 3 = third 8 = don´t know	Trimester pregnancy
Severity of underlying conditions	Numeric (count)	integer	Number of hospitalisations previous 12 months for the chronic disease
smoking	Numeric (count)	0 = Never 1 = Former 2 = Current 8 = Do not know	Never, former (stopped smoking at least 1 year before inclusion in the study), current smoker (Any smoking can be included: cigarettes, cigars, vaping, etc.)
Medication taken at least 14 days before enrolment: (Optional)			
statin	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Patient took statins
ace	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Patient took angiotensin-converting enzyme inhibitors
arb	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Patient took angiotensin II receptor blockers
nsaids	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Patient took non-steroidal anti-inflammatory drugs
corticosteroids	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Patient took corticosteroids
dmards	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Patient took biological disease-modifying anti-rheumatic drugs

antithrom	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	antithrombotic/ platelet aggregation inhibitors
metformin	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	metformin
Possible exclusion/sensitivity analysis criteria			
antivir	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Administration of antivirals prior to swabbing
antivirdate	Date	dd/mm/yyyy	Date administration antiviral
antivirtype	Text		Type of antiviral (brand name)
contra	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Contra-indication for COVID vaccination
Previous infection			
prevtest	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Has the patient had a positive SARS-CoV-2 test previously?
type_prev_test	Numeric (categorical)	0 = No 1 = Antigenic 2 = PCR 3 =Serology 8 = Do not know	
date_prev_test	Date	dd/mm/yyyy	Date of positive SARS-CoV-2 test?
prevcovid	Numeric (categorical)	0 = No 1 = Yes, confirmed by a clinician 2 = Yes, self-diagnosed 8 = Do not know	Has the HW ever being diagnosed (or self-diagnosed) as having COVID-19?
prev_covid_date	Date	dd/mm/yyyy	Date of symptom onset previous covid

Adherence to infection prevention and control measures			
handhygien	Numeric (categorical)	1= always as recommended 2 = most of the time 3 = occasionally 4 = rarely 5 = never	Follow recommended hand hygiene practices
wash_btouch	Numeric (categorical)	1= always as recommended 2 = most of the time 3 = occasionally 4 = rarely 5 = never	Use alcohol-based hand rub or soap and water before touching a patient?
wash_asep	Numeric (categorical)	1= always as recommended 2 = most of the time 3 = occasionally 4 = rarely 5 = never	Use alcohol-based hand rub or soap and water before cleaning/aseptic procedures?
wash_fluid	Numeric (categorical)	1= always as recommended 2 = most of the time 3 = occasionally 4 = rarely 5 = never	Use alcohol-based hand rub or soap and water after (risk of) body fluid exposure
wash_atouch	Numeric (categorical)	1= always as recommended 2 = most of the time 3 = occasionally 4 = rarely 5 = never	Use alcohol-based hand rub or soap and water after touching a patient's surroundings
ipc	Numeric (categorical)	1= always as recommended 2 = most of the time 3 = occasionally 4 = rarely 5 = never	follow IPC standard precautions when in contact with any patient

ppe	Numeric (categorical)	1= always as recommended 2 = most of the time 3 = Occasionally 4 = rarely 5 = never	wear PPE when indicated PPE includes: medical/surgical mask, face shield, gloves, goggles/glasses, gown, coverall, head cover, respirator (e.g. N95 or equivalent) and shoe covers)
Contact with COVID-19 patient in the hospital 14 days before (T1 questionnaire) or 7 days before (Follow up questionnaire)			
cont_pat	Numeric	Integer	Number of contacts with COVID-19 patients last 14 days
cont_close	Numeric (categorical	0 = No 1 = Yes 8 = Do not know	Contact within one meter
nebu	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Involvement in nebulizer treatment last 14 days
olowflow	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Involvement in respiratory support with O2 low flow last 14 days
ohighflow	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Involvement in respiratory support with O2 high flow last 14 days
hfnc	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Involvement in respiratory support with high flow nasal cannula last 14 days
mdi	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Involvement in respiratory support with metered-dose inhaler last 14 days

intub	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Involvement in intubation last 14 days (need to specify first pass, video laryngoscopy, bag-mask device, supraglottic airway intubation?)
cpr	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Involvement in cardiopulmonary resuscitation last 14 days
Exposures in the community 14 days before (T1 questionnaire) or 7 days before (Follow up questionnaire)			
contcom	Numeric	0 = No 1 = Yes 8 = Do not know	Close contact with probable or confirmed case
hhnum	Numeric	Integer	Number of individuals in the household
transp	Numeric Categorical	1 = 0 2 = 1-2 3 = 3-5 4 =6-8 5 = 9 or more	Use of public transport
gather	Numeric Categorical	1 = 0 2 = 1-2 3 = 3-5 4 =6-8 5 = 9 or more	Participation in indoor gathering event
maskcom	Numeric Categorical	1 = always 2 = often 3 = sometimes 4 = rarely 5 = never 6 = did not go to indoor locations outside home	Use of mask
distcom	Numeric Categorical	1 = always 2 = often 3 = sometimes 4 = rarely	stay at least 2 meters from other people in indoor spaces outside your home

		5 = never 6 = did not go to indoor locations outside home	
visit	Numeric Categorical	1 = 0 2 = 1-2 3 = 3-5 4 = 6-8 5 = 9 or more	people who do not live in household visit
visitother	Numeric Categorical	1 = 0 2 = 1-2 3 = 3-5 4 = 6-8 5 = 9 or more	or visit other people in their homes