

# Assessment of risk factors for coronavirus disease 2019 (COVID-19) in health workers: protocol for a case-control study

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The emergence of a new virus means that understanding transmission patterns, severity, clinical features and risk factors for infection will be limited at the start of an outbreak. To address these unknowns, WHO has provided a range of early seroepidemiological investigation protocols (rebranded as the WHO Unity Studies). One additional study protocol to evaluate environmental contamination with the COVID-19 virus has also been provided.

These protocols are designed to allow for the rapid and systematic collection and sharing of data in a format that facilitates aggregation, tabulation and analysis across different settings.

Data collected using these investigation protocols will be crucial for refining recommendations for case definitions and surveillance, characterizing the key epidemiological features of COVID-19, helping to understand the spread, severity, spectrum of disease and impact on the community, and informing guidance on the use of countermeasures such as case isolation and contact tracing.

All of the WHO protocols for COVID-19 are available on the WHO website at:

<https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/early-investigations>

COVID-19 investigation and study protocols currently available include:

- **The First Few X cases and contacts (FFX) investigation protocol for coronavirus disease 2019 (COVID-19)**
- **Household transmission investigation protocol for coronavirus disease 2019 (COVID-19)**
- **Protocol for assessment of potential risk factors for COVID-19 infection among health care workers in a health care setting**
- **Assessment of risk factors for coronavirus disease 2019 (COVID-19) in health workers: protocol for a case-control study**
- **Population-based age-stratified seroepidemiological investigation protocol for COVID-19 virus infection**
- **Surface sampling of coronavirus disease (COVID-19): A practical “how to” protocol for health care and public health professionals**

For any questions, please contact: [earlyinvestigations-2019-nCoV@who.int](mailto:earlyinvestigations-2019-nCoV@who.int) – attention: Alessandro Cassini and Isabel Bergeri.

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## Summary

The spread of an emerging novel respiratory pathogen such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is accompanied by uncertainty concerning its key epidemiological, clinical and virological characteristics, particularly its ability to spread in the human population and its virulence. Understanding SARS-CoV-2 infection among health workers and identifying the risk factors for adverse outcomes are important not only for characterizing virus transmission patterns and risk factors for infection, but also for preventing the future infection of health workers and patients, for informing and updating infection prevention and control (IPC) measures at health care facility and national levels, and for reducing secondary SARS-CoV-2 transmission within health care settings.

<b>Assessment of risk factors for coronavirus disease 2019 (COVID-19) in health workers: protocol for a case-control study</b>	
<b>Study population</b>	Health workers exposed to COVID-19 patients
<b>Study design</b>	<p>Nested case-control study of health workers exposed to confirmed COVID-19 patients</p> <p>Health workers with confirmed COVID-19 will be recruited as cases and other health workers in the same health care setting without infection will be recruited as controls (incidence density sampling).</p>
<b>Potential outputs and analysis</b>	Risk factors for COVID-19 in health workers; effectiveness of current COVID-19 IPC measures among health workers; clinical presentation of COVID-19 patients; serological response following SARS-CoV-2 infection
<b>Minimum information and specimens to be obtained from participants</b>	<p><b>Data collection</b></p> <p>Demographic and epidemiological information, along with information on risk factors related to IPC</p> <p><b>Specimens</b></p> <ul style="list-style-type: none"> <li>Paired serology samples from cases and controls for serology testing – comprising one baseline serum sample taken during week 1 and another taken 21–28 days later</li> <li>Optional – respiratory (and other) to diagnose current COVID-19 infection</li> </ul>

# 1 Background

## 1.1 Introduction

The spread of an emerging novel respiratory pathogen is accompanied by uncertainty concerning its key epidemiological, clinical and virological characteristics, particularly its ability to spread in the human population and its virulence (case severity). This is the case for the novel coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first detected in Wuhan, China as a cluster of atypical pneumonia cases in December 2019. This novel coronavirus may have been circulating for several months before the detection of sustained human-to-human transmission in December 2019, with incidence rates of infection doubling in size every 7.4 days in the early stages and an estimated basic reproductive number of 2.2 (1).

Other coronaviruses, such as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), have been characterized by amplification events in health care settings, occasionally resulting in large nosocomial outbreaks. Overcrowding in emergency rooms, non-adherence to IPC measures and possible environmental contamination are thought to be implicated in such amplification events during MERS-CoV outbreaks. Health workers play a critical role, not only in the clinical management of patients but also in ensuring that adequate IPC measures are implemented in health care facilities. In addition, initial surveillance often focuses primarily on patients with severe disease. As a result, the full spectrum of disease may not be clear, including the extent and proportion of mild or asymptomatic infections that do not require medical attention and the role such infections may play in secondary transmission.

SARS-CoV-2 infection is thought to spread via respiratory droplets, contact with bodily fluids and with contaminated surfaces (2) and transmission to health workers is known to have occurred (3). Individuals who are asymptomatic may be able to transmit infection, while individuals who have not reported close proximity to any known case have also been infected (4). During the SARS-CoV outbreak, health workers accounted for 21% of cases (5). Assessing the potential risk factors for SARS-CoV-2 infection among health workers will be essential for characterizing virus transmission patterns, preventing future infections of health workers and preventing the health-care-associated spread of COVID-19.

## 1.2 Objectives

The **primary objective** of this case-control study among health workers is:

- to characterize and assess the **risk factors for SARS-CoV-2 infection** in health workers exposed to COVID-19 patients.

The **secondary objectives** of the study are:

- to evaluate the **effectiveness of current COVID-19 IPC measures** among health workers;
- to describe the **range of clinical presentation** for SARS-CoV-2 infection in health workers, including disease duration and outcome; and
- to determine **serological responses** in health workers with confirmed SARS-CoV-2 infection following exposure to COVID-19 patients, and in those exposed to COVID-19 patients but without SARS-CoV-2 infection.

## 2 Methods

### 2.1 Design and duration

The current protocol for assessing COVID-19 risk factors consists of a **nested case-control study** of health workers involved in the care of any confirmed COVID-19 cases. The study is based upon the use of incidence density sampling (see section 2.3 Recruitment).

The study is to be initiated as soon as a case of SARS-CoV-2 infection is confirmed among health workers in a health care setting. Health workers with confirmed COVID-19 will be recruited as **cases**. Health workers exposed to COVID-19 patients in the same setting but without infection will be recruited as **controls** with a target of at least 2–4 controls for every case.

For countries or health care facilities willing and able to participate, WHO is proposing to conduct an **international multi-centre case-control study** in health care settings. Starting in May 2020 and running for 1 year, this proposed study will be coordinated by WHO and will be based upon the current protocol and its associated tools. Interested parties (facility or institution) are asked to send an email to: [earlyinvestigations-2019-nCoV@who.int](mailto:earlyinvestigations-2019-nCoV@who.int) for the attention of Alessandro Cassini. Please note that in order to ensure data quality and completeness all health care facilities participating in the multi-centre study will need to meet the criteria set out in section 2.2.3 below.

Countries or health care facilities that are either unwilling or unable to participate in the international multi-centre nested case-control study can still apply the same study methods to conduct a case-control study among health workers in one or several health facilities. In this case, the individual level data will not be pooled across sites and will be managed and analysed only by local investigators and according to local agreements.

### 2.2 Population

For the purpose of this study, the definition of a “health worker” should not be too restrictive so that a large number of potentially exposed personnel can be included. For this reason, a **health worker** should be defined as any member of staff in the health care facility involved in the provision of care for a COVID-19 patient, including those who have been present in the same area as the patient as well as those who may not have provided direct care to the patient but who have had contact with the patient’s body fluids, potentially contaminated items or environmental surfaces. This will include health care professionals, allied health workers and auxiliary health workers such as cleaning and laundry personnel, x-ray physicians and technicians, clerks, phlebotomists, respiratory therapists, nutritionists, social workers, physical therapists, laboratory personnel, cleaners, admission/reception clerks, patient transporters, catering staff and so on.

**Exposure to COVID-19 patients** is then defined as:

- close contact (within 1 metre and for more than 15 minutes) with a suspected/probable/confirmed COVID-19 patient(s);
- OR
- indirect contact with fomites (for example, clothes, linen, utensils, furniture and so on) or with materials, devices or equipment linked to a suspected/probable/confirmed COVID-19 patient(s).

### 2.2.1 Case definition

A **case** is defined as a health worker:

- exposed in a health care setting to a COVID-19 patient in the 14 days prior to the health worker's confirmation test;
- AND
- who is a confirmed COVID-19 case.\*

#### **Exclusion criterion\*\***

- having a confirmed COVID-19 case among their close contacts, including in their household, within the previous 14 days (with the exception of the COVID-19 patient(s) to which they were exposed).\*\*

\* For the latest COVID-19 suspected, probable and confirmed case definitions refer to: Global surveillance for COVID-19 caused by human infection with COVID-19 virus. Interim guidance. Geneva: World Health Organization; 2020. Available at: [https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-\(2019-ncov\)](https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-(2019-ncov)). Depending upon the feasibility of practice, local case definitions may be applied. If local case definitions are not available, the WHO definitions should be used.

\*\* Please note that the above exclusion criterion is only applicable to the analysis of risk factors and not to the general descriptive analysis. Where a COVID-19 case answers yes to having been in close contact with confirmed cases outside their professional duties (in the community, household and so on), the record of this case will not be deleted and will be used for the descriptive analysis on exposure risks leading to infection (see section 3.2 below).

### 2.2.2 Control definition

A control is defined as a health worker:

- exposed in a health care setting to a COVID-19 patient in the 14 days prior to recruitment;
- AND
- who is not being classified as a suspected\* OR probable\* OR confirmed \*COVID-19 case.

#### **Exclusion criterion**

- having a positive serology test to SARS-CoV-2.

\* For the latest COVID-19 suspected, probable and confirmed case definitions refer to: Global surveillance for COVID-19 caused by human infection with COVID-19 virus. Interim guidance. Geneva: World Health Organization; 2020. Available at: [https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-\(2019-ncov\)](https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-(2019-ncov)). Depending upon the feasibility of practice, local case definitions may be applied. If local case definitions are not available the WHO definitions should be used.

### 2.2.3 Eligibility criteria for participation in the global multi-centre study

The criteria for participation in the international multi-centre case-control study to be coordinated by WHO are based upon the need to ensure acceptable data quality and completeness. The criteria to consider include:

- the capacity to perform follow-up of individuals (including collecting data with a standardized questionnaire), to perform data entry into a database coordinated by local investigators and to keep personal data confidential, noting that:
  - a member of staff will be needed who can dedicate time to study implementation and data-quality management,
  - previous experience in implementing a case-control study would be an advantage, and
  - leadership willingness to participate will be required;
- Capacity to perform testing for COVID-19 and to perform appropriate blood-collection procedures, specimen packaging, transport (for example, cold chain logistics) and storage, requiring:
  - access to a laboratory with adequate infrastructure for performing serological testing for SARS-CoV-2 infection (for example, using enzyme-linked immunosorbent assay),
  - blood culture diagnostics with internal quality control demonstrating quality results and laboratory accreditation, and
  - informatics capacity, including the use of data-collection tools, standardized patient records (for example, electronic medical records) and patient identifiers for linking.

## 2.3 Recruitment

### Case enrolment

Once a health worker has been identified as a case of COVID-19 in a health care setting (regardless of the type, location and size of the health care facility) the research team will approach the administrator of the facility and invite them to participate in this study.

### Control enrolment

This will be determined by considering the facility as a whole attending to COVID-19 patients then determining those health workers that have been exposed to COVID-19 patients based on the start and end dates of exposure according to the duty roster. Enrolling controls in parallel with cases in this way is known as “incidence density sampling” (see Fig. 1) and is a recommended approach for nested case-control studies. Incidence density sampling aims to produce a set of controls for epidemiological case-control studies which mimics the underlying pool of eligible cohort members. This approach can be distinguished from “traditional” case-control designs in which individuals are selected based on the criterion of remaining at risk at the end of the study.

A list of all health workers in the same health care setting with any exposure to COVID-19 patients will need to be drawn up. This will be done in consultation with infection-control nurses in the health care settings. Duty rosters will be examined to ensure all exposed health workers can be

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