World Health Organization
REGIONAL OFFICE FOR Europe

Cohort study to measure COVID-19 vaccine effectiveness among health workers in the WHO European Region

Guidance Document

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Contents

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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
WHO	World Health Organization

Executive Summary

Many critical questions remain about the effectiveness of COVID-19 vaccines in real-world settings. These questions can only be answered in post-introduction vaccine effectiveness studies.

This guidance document outlines the methods of a prospective one-year cohort study of hospital-based healthcare workers (HWs) to evaluate the effectiveness of COVID-19 vaccine in preventing laboratory-confirmed SARS-CoV-2 infection. 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 survey about demographics, clinical comorbidities, and work- and community-related behaviours related to infection risk. In addition, a baseline serology and a respiratory swab should be collected from participants at enrolment.

During the course of the study, participants should be actively followed for suspected COVID-19 infection. Symptomatic participants who meet a suspected case definition should provide a respiratory sample, by self-swab (following training) or collected by trained HW, which should be tested for SARS-CoV-2 by RT-PCR.

In addition, during the course of the study, as resources permit, participants should be asked to provide a respiratory sample, weekly, regardless of their symptoms, in order to evaluate asymptomatic infection. Samples should be tested by RT-PCR for SARS-CoV-2.

Finally, during the course of the study, serology should be collected periodically from participants. At a minimum 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. In addition, if resources allow, sera can undergo additional laboratory testing for correlates of disease protection, 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 one-year period, interim analyses at different points during the study can be undertaken.

1. 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 January 9, 2020, 28,320,275 million cases and 616,465 deaths had been reported to the World Health Organization (WHO) Regional Office for Europe *(1).*

International collaborative efforts have accelerated the development of COVID-10 vaccines. As of January 9, 2020, 63 candidate vaccines were in clinical development, 173 were in preclinical development *(2)*.

Health workers (HW) 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. This recommendation was further supported by the European Technical Advisory Group on immunizations in November 2020 *(3).*

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 *(4).*

Real-world VE studies can also answer questions about effectiveness by age-group and risk factors, duration of vaccine protection, protection against transmission, relative effectiveness of different vaccines, relative effectiveness of one dose vs. two doses, and effectiveness of the vaccine against new strains of SARS-CoV-2.

This document outlines the methods of a prospective cohort study to evaluate the effectiveness of the COVID-19 vaccine in the health workers (HWs), with a focus on hospital-based HWs. This document is intended to be used as a guidance document to support countries and institutions that are interested in conducting research on COVID-19 vaccine effectiveness in health workers. It outlines an approach to post-introduction COVID-19 vaccine effectiveness evaluation in HWs that complements existing WHO Unity Studies, which focus on sero-epidemiological investigations *(5)*. Research should be conducted only after site-specific protocols are developed and approved by the relevant local ethical review committee(s).

2. Objectives

2.1. General objective

To measure product-specific COVID-19 vaccine effectiveness (VE) amongst hospital health workers eligible for vaccination against any laboratory-confirmed SARS-CoV-2 infection

2.2. Secondary objectives

Depending on sample size, to measure COVID-19 VE:

- against symptomatic laboratory-confirmed COVID-19 infection
- against asymptomatic laboratory-confirmed COVID-19 infection
- against severe laboratory-confirmed COVID-19 infection
- by time since vaccination
- by different age groups
- by different high-risk comorbidities
- previous SARS-CoV-2 infection
- by HW occupation and/or ward
- patient-facing vs. non-patient-facing HWs
- in individuals who have been partially vaccinated (one dose for most COVID-19 vaccines) compared to those who are fully vaccinated (two doses for most COVID-19 vaccines)
- against SARS-CoV-2 variant strains

Table 1. Secondary Objectives

Secondary Objective	Description/Notes
1. What is VE against symptomatic laboratory-confirmed COVID-19 infection	Outcome is symptomatic infection defined by accepted case definition for suspected COVID-19
2. What is VE against asymptomatic laboratory-confirmed COVID-19 infection	No symptoms are reported in relation to positive SARS-CoV-2 infection
3. What is the VE against severe laboratory-confirmed COVID-19 infection	Severe infection can be defined by WHO case definition. Hospitalization can also be considered as a proxy
4. What is the duration of protection conferred by the vaccine	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 comorbidities	High-risk comorbidities can be defined according to known risk factors for severe COVID-19 disease
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 rather than profession
9. What is the VE in patient-facing health workers	Patient-facing status should be determined through