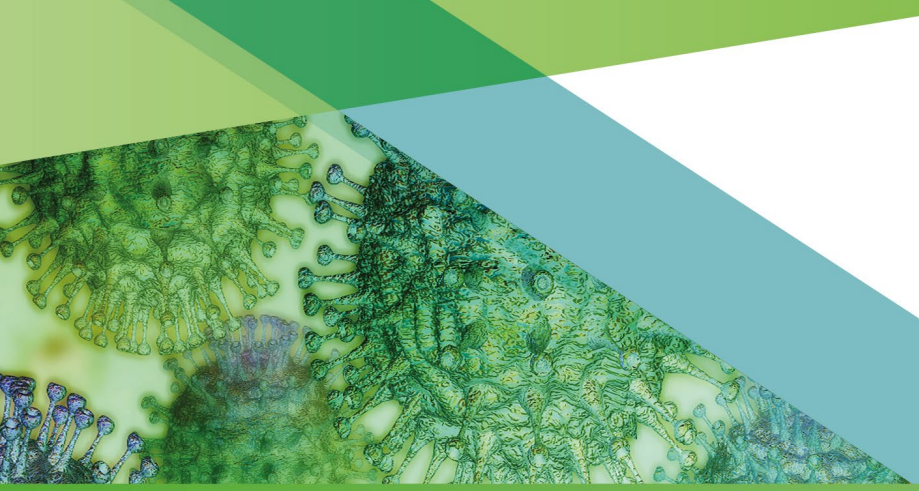

TECHNICAL REPORT

Interim analysis of COVID-19 vaccine effectiveness in healthcare workers, an ECDC multi-country study, May 2021–July 2022

November 2022

Key facts

- ECDC is building infrastructure to allow the regular monitoring of COVID-19 vaccine effectiveness (VE) over time, using a multi-country approach that involves studies implemented in different settings [1,2].
- This document reports on one of ECDC's multi-country studies in the hospital setting to measure product-specific COVID-19 VE against any laboratory-confirmed SARS-CoV-2 infection among healthcare workers (HCWs) eligible for vaccination.
- As of July 2022, 16 hospital sites (in Croatia, Estonia, Greece, Ireland, Italy, Latvia, Poland, Portugal, and Spain) have participated in the study, covering the period from 3 May 2021 to 19 July 2022. In this period, the study teams approached 2 832 HCWs, enrolled 2 629 of them, and followed up with 2 369 . Aside from 18 HCWs who remained unvaccinated during the study period, all other HCWs recruited to date have been vaccinated with one or more doses of COVID-19 vaccines at enrolment. Nearly two thirds (64%) of them have received a booster dose.
- At enrolment, over a quarter (26%) of the HCWs reported having had a COVID-19 infection, of which the majority (87%) were diagnosed 46 or more days prior to enrolment. Serological results have been reported by 11 sites, of which all reported detection of anti-spike antibodies in >90% of HCWs at enrolment.
- Genetic sequencing data for breakthrough infections have been submitted for 176 HCWs from eight sites, of which 116 were Omicron variant infections (B.1.1529) isolated since 15 December 2021. Thirty were Delta variant infections isolated between May 2021 and January 2022.
- Omicron variant BA.1 was isolated until May 2022, when it was replaced by BA.2, which was subsequently replaced in June 2022 by BA.4/5.
- Among HCWs who had received only the primary vaccination schedule, 196 SARS-CoV-2 infections were reported, representing a cumulative incidence of 2.9 per 1 000 person days, and 257 SARS-CoV-2 infections were reported among those who had a received a booster dose, representing a cumulative incidence of 2.7 per 1 000 person days.
- The adjusted rVE was 7% (95%CI: -28% to 32%) overall, while the adjusted rVE was 11% (95%CI: -48% to 47%) in the HCWs reporting a previous COVID-19 episode before enrolment and -6% (95%CI -81% to 38%) in HCWs without a previous COVID-19 episode.
- These results are in line with published evidence indicating that current COVID-19 vaccines have low effectiveness against mild Omicron infections, including after a booster dose. While this analysis does not include VE against severe disease, published literature indicates that VE against severe disease due

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to the Omicron variant is high following the administration of both the primary course and further maintained by a booster dose. Although point estimates of VE indicated some protective effects, the wide confidence intervals make the interpretation of the results difficult. The precision of the rVE estimates may improve through the continuation of the study in the participating sites (longer follow-up) or through the recruitment of new sites to increase the size of the HCW cohort.

Scope of this document

This document reports the interim pooled estimates from ECDC's study of COVID-19 vaccine effectiveness (VE), conducted through the implementation of a multi-country approach using the Core protocol for ECDC studies of COVID-19 vaccine effectiveness using healthcare worker cohorts, versions 1.0 and 2.0 (after March 2022) [1, 2].

Nearly all the 2 629 HCWs recruited between 3 May 2021 and 19 July 2022 had been vaccinated with one or more doses of COVID-19 vaccines, and nearly two thirds had also received a booster dose. Due to the low number of unvaccinated individuals in this study, the relative VE of any booster COVID-19 vaccine dose compared to primary vaccination schedules in HCWs was investigated.

The study is ongoing and interim analyses will be conducted on a regular basis, with results updated as relevant. While VE estimates are important to inform vaccine recommendations, it is also important to ensure that robust methods were used to produce these estimates. Hence, this document presents a detailed description of both the methods used and the characteristics of the cases and controls enrolled in the study. For more details regarding the methods of the study, reference should be made to the ECDC core protocol [1, 2].

Background

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.

International collaborative efforts have accelerated the development of COVID-19 vaccines. As of 22 July 2022, 169 candidate vaccines were in clinical development and 198 were in preclinical development [3]. As of week 45 2022, six vaccines (Comirnaty, Spikevax Vaxzevria, Jcovden (previously COVID-19 Vaccine Janssen), Valneva and Nuvaxovid) have been authorised by the European Commission based on the scientific opinion of the European Medicines Agency (EMA) for use in the European Union, and others are under rolling review. In addition, four adapted bivalent vaccines are authorised for use (Comirnaty Original/Omicron BA.1, Comirnaty Original/Omicron BA.4-5, Spikevax bivalent Original/Omicron BA.1, and Spikevax bivalent Original/Omicron BA.4-5 [4]. In the context of limited vaccine supplies in 2021, target groups for the prioritisation of COVID-19 vaccination were developed. Many countries included healthcare workers (HCWs) as a priority group for COVID-19 vaccination as they are considered at a higher risk of SARS-CoV-2 infection [5], can transmit the infection to susceptible patients at high risk of severe COVID-19, and are needed to maintain essential healthcare services [5-7].

Evaluating the real-world COVID-19 vaccine performance is critical for understanding the risks and benefits of vaccination programmes. Many factors affect real-world VE, including vaccine transportation and storage and how patients are vaccinated. In addition, types of populations included in vaccine clinical trials are limited, and different from those who will receive vaccines in the real world [8]. 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 various numbers of doses and their timings, and effectiveness of the vaccine against new variants of SARS-CoV-2.

Objective of the analysis presented in this document

The objective of this interim analysis is to measure, in a pooled analysis, the direct effectiveness of overall COVID-19 vaccines against laboratory-confirmed SARS-CoV-2 in HCWs who received:

- **full vaccination** with the primary series (one dose for vaccine products with a one-dose course, two doses for vaccine products with a two-dose course, as per the manufacturer's instructions); or
- **full vaccination plus a first booster dose** (full vaccination as above plus one booster dose, as per the manufacturer's instructions).

Description

In December 2020, ECDC initiated a project to support the development and implementation of a multicentre European study to evaluate the effectiveness of COVID-19 vaccines in hospital-based HCWs. A call for expression of interest administered by ECDC to National Focal Points in January 2021 identified interest in five countries (Croatia, Estonia, Greece, Ireland, and Portugal). In April 2021, an amended contract was signed to expand the work and allow the inclusion of sites from two further countries (Italy and Spain). To consolidate and strengthen the European multicentre network of hospital sites participating in this study, ECDC continued the project through the 'Enhanced laboratory testing' which was implemented between August 2021 – 23 February 2022.

Starting in December 2021, the HCW study set up in 2021 continued under the first specific contract of the ECDC-funded Framework Contract ECDC/2021/017 'Assessment of COVID-19 vaccine effectiveness among healthcare workers'. The HCW VE cohort study included in February 2022, 14 sites in seven countries. Among these sites, 12 agreed to continue under the new contract (except Estonia).

This report presents a summary, as of 19 July 2022, of the cumulative data collected in the HCW studies since the beginning of data collection. The report includes a descriptive and analytical part of the HCW cohort study, including vaccine effectiveness analysis, description of limitations and challenges and proposed options for the continuation of the study.

Countries participating in the study and in this analysis

As of 19 July 2022, a total of 20 hospitals/sites in nine countries (Croatia, Estonia, Greece, Latvia, Ireland, Italy, Poland, Portugal, and Spain) had participated or had been invited to participate in ECDC's multi-country vaccine effectiveness studies in healthcare workers since the beginning of the study in May 2021.

Figure 1. Participating countries and hospital sites in the ECDC multi-country HCW VE study, 19 July 2022

Methods

General study design

The full study protocol for estimating COVID-19 VE in HCWs provides greater detail of the study procedures [2]. Below is a brief overview of the study.

Study design

Prospective longitudinal multicentre cohort study among HCWs eligible for vaccination.

Study population

The study population was recruited from HCWs in participating hospitals, eligible for vaccination, with no contraindication to receive COVID-19 vaccine.

Inclusion criteria

HCWs included all categories of staff working in the hospitals and were defined as all staff involved in the provision of care for patients, including those providing direct care to patients and those who may not have provided direct care to patients but who have had contact with patients' body fluids, potentially contaminated items or environmental surfaces present, as well as those who may have been in the same area as patients.

HCWs who have already been vaccinated against COVID-19 as part of the routine COVID-19 vaccine rollout were included, as long as information could be collected about the vaccine brand(s), number of doses, and dates of vaccination.

Exclusion criteria

HCWs who were not eligible for COVID-19 vaccination, or where vaccination was contra-indicated, or who have not signed an informed consent form were not eligible to participate in the study and were excluded.

HCWs who had already been vaccinated against COVID-19 vaccine in clinical trials were excluded.

Exposure

Precise vaccination status documentation was collected for this study. Vaccine ascertainment depended on how vaccination was delivered and registered in each setting. It was recommended that self-reported vaccination status was verified and confirmed through occupational health, vaccine registry, vaccination card, or any other verifiable data source. Participants were informed in the consent form that these additional sources would be accessed, when relevant, to confirm their vaccination status.

HCWs could change status between unvaccinated, partially vaccinated, vaccinated with the primary course, or vaccinated with the first booster dose status during the course of the study. HCWs were allocated, according to the definitions below, to the following categories: vaccinated with the primary course, vaccinated with the first booster, partially vaccinated, or unvaccinated status:

- Vaccinated with first booster dose: ≥14 days after having received the first booster dose after a double-dose primary course vaccine or ≥14 days after having received the first booster dose for a single-dose primary course (i.e. COVID-19 vaccine Jcovden, previously known as COVID-19 Vaccine Janssen);
- Vaccinated with primary course: ≥14 days after having received the second dose for a double-dose vaccine or ≥14 days after having received the first dose of a single-dose vaccine (i.e. COVID-19 vaccine Jcovden, previously known as COVID-19 Vaccine Janssen);
- Partially vaccinated: For HCWs receiving a double-dose vaccine, this period ran from ≥14 days after receiving the first dose until <14 days after the second dose;
- Unvaccinated: HCWs who have not received any dose of vaccine as well as HCWs who have received the first dose of a vaccine <14 days before.

As the per protocol analysis was not possible due to low number of unvaccinated HCWs at enrolment and during the follow-up, an as-treated analysis was performed considering the HCWs who were:

- **Vaccinated with a booster dose:** have received their booster/ dose of vaccine ≥14 days previously.
- **Vaccinated with primary series only**: have received either a primary schedule with two doses for a double-dose vaccine or one dose of a single-dose vaccine or had a confirmed COVID-19 infection and received one[1] or two doses of a vaccine.

Those HCWs who were unvaccinated or partially vaccinated were excluded from the analysis. A 'wash-out' period of 0-13 days after each dose of vaccine was used (e.g. a HCW was considered vaccinated with first booster dose ≥14 days after having received the first booster dose as per definitions above).

For the analysis of time since vaccination, a stratification setting the cut-off at three months since the third/booster dose was used, according to current vaccination recommendations in place and knowledge acquired at the moment of the analysis in terms of waning of vaccination-induced immunity.

Definitions of outcomes

The primary outcome was a confirmed SARS-CoV-2 infection detected by a laboratory RT-PCR test in any participant, regardless of symptoms.

Secondary outcomes included symptomatic COVID-19, defined as participants with confirmed SARS-CoV-2 infection detected by a laboratory RT-PCR test who reported one or more of the following clinical criteria to conform with ECDC's case definition of COVID-19 [9]:

- cough;
- fever;
- shortness of breath/dyspnoea;
- anosmia;
- ageusia/dysgeusia.

Fourteen days before to seven days after the first positive RT-PCR test.

Secondary outcomes of COVID-19 related to disease severity were defined as participants who conformed to the definition of a primary outcome with the following stages:

- Asymptomatic: no reported symptoms consistent with the ECDC definition of COVID-19.
- Mild disease: reported symptoms consistent with the ECDC definition of COVID-19 requiring attendance at a medical service but requiring no further assistance for activities of daily living.
- Moderate disease: reported symptoms consistent with the ECDC definition of COVID-19 requiring either hospitalisation but not requiring oxygen treatment or not hospitalised but requiring assistance for activities of daily living.
- Severe disease: reported symptoms consistent with the ECDC definition of COVID-19 requiring hospitalisation and oxygen treatment.
- Very severe disease: reported symptoms consistent with the ECDC definition of COVID-19 requiring admittance to an intensive care unit and/or intubation or mechanical ventilation.

Secondary outcomes related to re-infection: Positive PCR or rapid antigen test (RAT) in a sample ≥60 days following:

- Previous positive PCR;
- Previous positive RAT;
- Previous positive serology (anti-spike IgG Ab), not related to vaccination.

To investigate hybrid protection, a combined variable including COVID-19 vaccination and previous COVID-19 episode with four levels of exposure was used:

- booster vaccination and previous infection (booster/previous);
- primary schedule and previous infection (primary/previous);
- booster vaccination without previous infection (booster only); and
- primary schedule without previous infection (primary only).

[1] In some countries, people with confirmed previous SARS-CoV-2 infection were only given one dose of two-dose vaccine and were considered fully vaccinated with primary course.

Data analysis

Considering the very high COVID-19 vaccine coverage rates, with nearly all HCWs having received at least one dose of vaccine before enrolment (see Table 1 below), comparing the incidence of SARS-CoV-2 infection or COVID-19 disease in vaccinated and unvaccinated groups was not possible. Therefore, the rates in HCWs who had received any booster dose with those of the HCWs who had received a primary course of vaccination more than three months since the last dose of primary course vaccination were compared.

Due to the specific features of the Omicron variant, the analysis was also restricted to HCWs who were followed up before or after 15 December 2022, when the first cases of the Omicron variant were identified in the study, defining the waves dominated by Delta (3 May 2021 to 14 December 2021) and Omicron (15 December 2021 to 19 July 2022). Using Cox regression, the rVE as (1-hazard ratio (HR))*100 and adjusting for age, sex, underlying condition, site, and month of follow-up was calculated.

To investigate the effects of hybrid immunity, SARS-CoV-2 incidence in the four categories defined above were compared. The rVE of booster vaccination with/without previous episodes compared to primary schedule and no booster (primary only reference) was calculated as (1-HR)*100, adjusted for age, sex, underlying condition, site, and month of follow-up.

Study procedures

Enrolment: questionnaire, respiratory sample, and serology sample

All participants provided informed consent prior to their enrolment into the study.

Once informed consent had been obtained, HCWs were enrolled regardless of their individual vaccination and:

- Provided a nasal, naso- or oropharyngeal swab or saliva specimen for RT-PCR;
- Provided a blood sample for serology;
- Completed an enrolment questionnaire that includes demographic, clinical, and epidemiological information, information about vaccination history, and occupation- and community-related behaviour.

Active follow-up

The objective of the follow-up was to identify new SARS-CoV-2 infections, changes in vaccination status (e.g. unvaccinated who received the vaccine, those vaccinated with one dose who received the second dose, those with a primary dose completed that received a booster dose) among the cohort of participating HCWs.

Study participant were regularly and actively followed up to perform:

- **Molecular (RT-PCR and genomic sequencing) testing:** Samples were collected from participants once every one or two weeks, irrespective of symptoms, and tested by RT-PCR. Samples could be either nasal, naso- or oropharyngeal swabs which could be taken by a trained study monitor or by the HCWs themselves after suitable training. As alternatives to improve acceptability and feasibility of the weekly follow-up, HCWs could provide self-taken saliva samples as an alternative to swabbing; these have been shown to perform well in comparison to naso- or oropharyngeal swabs, particularly in the early stages of infection [10-13]. Participants were followed-up with weekly questionnaires and weekly/biweekly samples. Biweekly collection included only naso- or oropharyngeal swabs (and not saliva or nasal samples), for RT-PCR testing an interval which remained within acceptable bounds of test sensitivity [14].
- Participants diagnosed with SARS-CoV-2 infection were followed-up for outcomes including disease severity. Site investigators selected all or a proportion of SARS-CoV-2 confirmed infections in participants for genetic sequencing.
- **Serology:** Blood samples were taken regularly during the follow-up of 4–12 weeks, to identify asymptomatic cases that could have been infected during the study period and to assess antibody levels over time.
- **Monitoring:** Participants were followed up with a weekly survey questionnaire to report changes in health or vaccination status as well as likely professional and personal exposures. Sites were provided with an online platform for the weekly survey questionnaire which was also mobile phone enabled. The questionnaire was completed directly by the HCWs or by a study site monitor as part of regular weekly contacts.

Table 1. Timing of questionnaires and specimen collection, ECDC multi-country vaccine effectiveness studies

Timing in the study	Questionnaire	Molecular testing	Serology
Enrolment			
	Enrolment questionnaire	Nasal, naso- or oropharyngeal swab Saliva specimen	Serum
Follow-up			
Weekly/biweekly	Weekly update	Nasal, naso- or oral-pharyngeal swab or saliva specimen	-
Every 4-12 weeks	-	-	Serum
Onset of symptoms	Update on symptoms	Nasal, naso- or oral-pharyngeal swab	-
Confirmed SARS-CoV-2 infection	Update on symptoms and outcomes	Genetic sequencing of all or a sample of confirmed cases	-

Descriptive analysis[2]

Description of cohort at enrolment

Since the start of the HCW VE study, and as of 19 July 2022, data were available from 16 hospitals from nine countries: Croatia (2), Estonia (2), Greece (1), Ireland (2), Italy (3), Latvia (1), Poland (1), Portugal (2), and Spain (2).

In total, 2 832 HCWs were approached and 2 629 HCWs were enrolled, ranging from 68 HCWs in Poland to 689 in Italy. A total of 203 (7.1%) HCWs were not enrolled and seven (2.4%) HCWs presented contraindications for COVID-19 vaccination; recruitment is ongoing in Ireland (Galway University Hospital) and Poland.

Of the 2 629 HCWs with an enrolment questionnaire available, 23 HCWs positive at the time of enrolment and two HCWs with missing enrolment date were excluded, leaving 2 604 enrolled HCWs. Among these, 2 369 HCWs had at least one follow-up test/questionnaire. The description below concerns data available at enrolment for the cohort (N=2 604).

The enrolled HCWs were predominantly female (1 983, 77.2%), with the highest proportion in the 18-34 years age group (24.2%) followed by those aged ≥55 years (21.2%). Most HCWs (71.3%) recruited were in clinical roles, either nurses (49.0%) or medical doctors (22.3%). The other half was made up of a variety of roles of which the most commonly reported were administration/reception roles (9.4%).

Of the 2 604 HCWs that provided the information on underlying conditions, 717 (28.2%) reported one or more chronic health conditions of whom 363 (50.6%) reported more than one. The three most commonly reported chronic conditions were hypertension (388; 54.1%), asthma (317; 44.2%) and rheumatic disease (273; 38.1%), while 328 (29.6%) of enrolled HCWs reported obesity. Regarding behaviours, 579 (23.1%) HCWs self-reported as currently smoking and 41 (2.2%) drinking daily. Of 2 552 HCWs with information available, 1 053 (41.3%) reported taking regular medication of which the three most common classes of medication were statins, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. Of the 2 604 HCWs enrolled in the cohort, 2 487 (95.5%) received at least one dose of COVID-19 vaccines and 1 672 (64.2%) had received three doses of COVID-19 vaccines. Eighteen HCWs reported being unvaccinated at enrolment remained unvaccinated during the follow-up (18/2604; 0.7%). The vaccination status of the first COVID-19 vaccine dose was documented for 65.1% (48% in vaccine registries and 16% by vaccine cards), while a third (32.3%) were self-reported. The proportions of the vaccination ascertainment for the second and third dose were similar (data not shown). Nearly all HCWs were vaccinated with Comirnaty (>80%) or Spikevax (10% for first and second dose, 20% for the third dose) and less than 5% were vaccinated with other vaccines (Jcovden, previously known as COVID-19 Vaccine Janssen and Vaxzevria). Fewer than 10% of the participating HCWs reported different brands between the first and second dose or between the booster and primary course of vaccination (Table 2).

At enrolment, 1 367 (54.1%) HCWs reported having been vaccinated against influenza for the most recent season and 172 (7.6%) against pneumococcus. (Table 2)

[2] All data presented in this section are provisional and remain open to correction and further revision by study sites.

Table 2. Vaccination history of HCWs enrolled in the ECDC multi-country vaccine effectiveness studies, 3 May 2021 to 19 July 2022 (N=2 604)

Characteristic	Number	Denominator**	%
COVID-19 vaccination			
Unvaccinated	18	2 604	0.7
1 dose only*	80	2 604	3.1
2 doses only	734	2 604	28.2
3 doses only	1 672	2 604	64.2
4 doses	3	2 604	0.1
Ascertainment 1st vaccine dose			
Self-report	793	2 406	33.0
Vaccination registry	1 225	2 406	50.9
Vaccination card	342	2 406	14.2
Not documented	0	2 406	0.0
Other	46	2 426	1.9
COVID-19 brand of 1st dose			
Comirnaty	2 092	2 488	84.1
Spikevax	261	2 488	10.5
Vaxzevria	122	2 488	4.9
Jcovden	11	2 488	0.4
Other	2	2 488	0.1
COVID-19 brand of 2nd dose			
Comirnaty	2 046	2 405	85.1
Vaxzevria	99	2 405	4.1
Spikevax	258	2 405	10.7
COVID-19 brand of 3rd dose			
Comirnaty	1 366	1 703	80.2
Vaxzevria	4	1 703	0.2
Spikevax	331	1 703	19.4
Heterogenous vaccination			
Different brand 1st & 2nd dose	35	2 371	1.5
Different brand of primary course versus booster	233	2 407	9.7
Influenza vaccination			
Vaccination in most recent influenza season at enrolment	1 367	2 527	54.1
Pneumococcal vaccination			
Pneumococcal vaccination	172	2 267	7.6

**Includes 11 vaccinated with 1 dose of Jcovden, previously known as COVID-19 Vaccine Janssen.*
***The denominator includes the total number of HCWs with information available at enrolment.*

Prior to enrolment, 662 HCWs (26.1%) reported one or more previous episodes of COVID-19, of whom 587 (88.7%) reported a laboratory-confirmed diagnosis. The most commonly reported symptoms were other non-specific symptoms, as well as fever, anosmia, and ageusia. The majority of HCWs who reported a previous COVID-19 episode (465; 72.3%) reported an onset day of their previous COVID-19 infection of >90 days prior to their enrolment (Table 3).

Table 3. History of previous COVID-19 in HCWs prior to enrolment into the ECDC multi-country vaccine effectiveness studies, 3 May 2021 to 19 July 2022 (N=2 604)

Characteristic	Number	Denominator*	%
Previous episode of COVID-19			
Any previous diagnosis of SARS-CoV-2 infection	662	2 538	26.1
Reported ≥1 episode	637	662	96.2
Laboratory confirmed diagnosis	587	662	88.7
Self-reported diagnosis	68	662	10.3
Specific symptoms of last COVID-19 episode			
Reported ≥1 symptom	511	532	96.1
Fever	204	488	41.8
Cough	301	506	59.5
Dyspnoea	155	497	31.2
Ageusia	202	501	40.3
Anosmia	223	501	44.5
Other symptoms	393	529	74.3
Interval between last episode and enrolment			
≤45 days	87	643	13.5
46-90 days	91	643	14.2
>90 days	465	643	72.3

The denominator includes the total number of HCWs with the information available at enrolment.

Outcomes identified in cohort during follow-up

Of the 16 sites reporting follow-up data, 2 604 HCWs were enrolled and follow-up data were reported for 2 369 (91.0%) HCWs. The number of median days of follow-up per HCWs per site ranged from 10 days (Galway, Ireland) to 230 (Zaragoza, Spain).

In total, 711 confirmed SARS-CoV-2 infections have been reported which includes 482 SARS-CoV-2 infections identified by PCR testing as part of the study, and a further 229 identified by HCWs testing outside of the study. Of these SARS-CoV-2 infections, 479 were symptomatic (Table 4). The first peak of cases was recorded in January-February 2022 while in July 2022, a second peak was recorded (Figure 1). A description of 682 (95.9%) cases included in the person time VE analyses (after dropping 29 cases with no proper follow-up) is included in Table 4.

One re-infection was reported among the HCWs during the study: a male HCW, aged 57 years with underlying conditions (hypertension, immune disease cortico-dependent, renal disease), working in the administration of one participating hospital who was infected with the Delta variant in November 2021 and the Omicron variant in May 2022. He was vaccinated with the primary series of Comirnaty vaccine in February–March 2021, with the third dose in October 2021, and with the fourth dose in March 2022.

Two HCWs were hospitalised for the COVID-19 episode during the follow-up, one with oxygen therapy (mask or nasal prongs) and one with no oxygen therapy.

Figure 1. Symptomatic and asymptomatic SARS-CoV-2 infections in the ECDC multi-country healthcare worker vaccine effectiveness studies by month of sample collection, 3 May 2021 to 19 July 2022 (n=711)

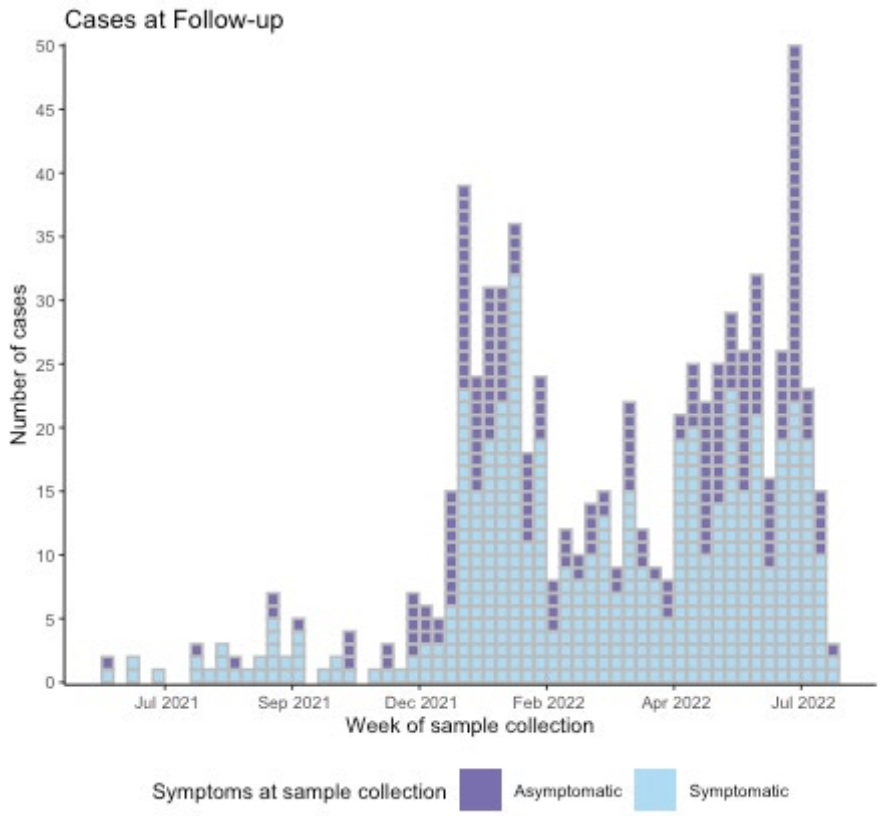


Table 4. Characteristics of outcomes included in the ECDC multi-country healthcare worker vaccine effectiveness study, 1 June 2021 to 19 July 2022

	All cases (n=682)		Symptomatic (n=479)	
Characteristic	**Number**	**%**	**Number**	**%**
Age (median, range)	44	(21-74)	44	(21-68)
Sex (female)	552	80.9	396	82.7
Reported chronic condition	201	29.8	144	30.5
Professional role				
Medical doctor	123	18.2	81	17.1
Nurse/nurse assistants	328	48.5	228	48.1
Administration/reception	73	10.8	52	11
Other	61	9	51	10.8
Contact COVID-19 case				
At home	35	5.1	24	5
At work	129	18.9	79	16.5
Applied AGP	61/404	8.9	43/297	9
Vaccination				
Primary course vaccination	268	39.3	206	43.0
Vaccination with booster dose	147	21.6	96	20.0
Median time since booster (days)	195 (155,268.5)		194 (149,288)	

Variants of concern

As of 19 July 2022, eight of the 16 sites had reported the sequencing data. Of the 482 cases detected in the study, 184 samples in 176 HCWs have been sequenced. The following strains were identified (see Figure 2):

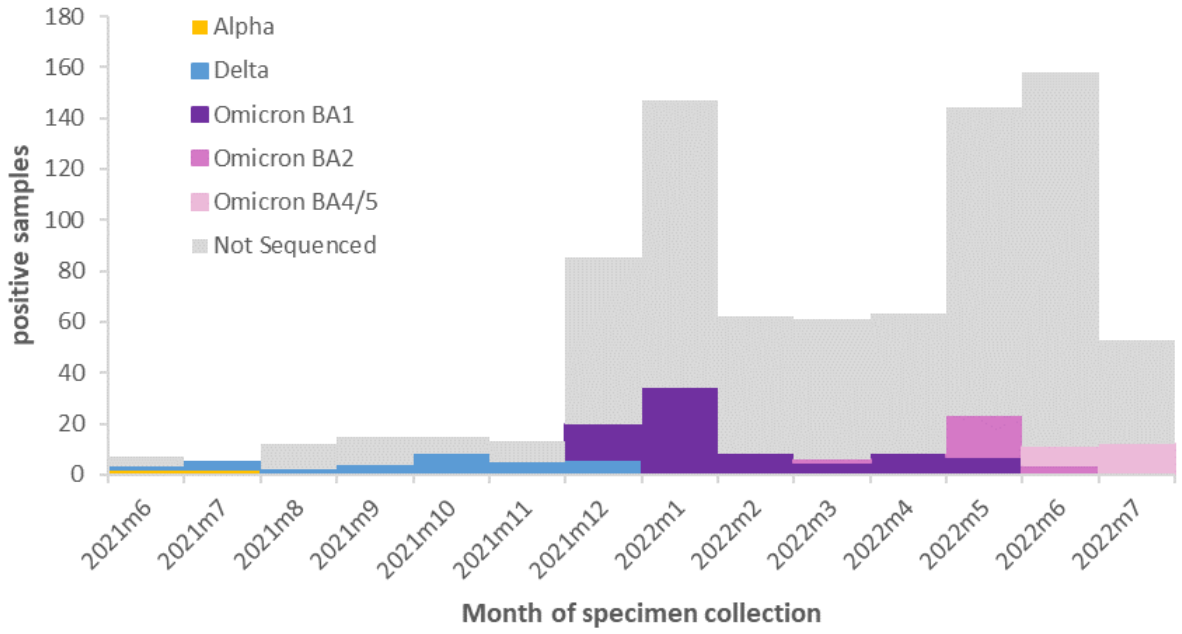
- 116 Omicron infections (B.1.1529) isolated starting from 20 December 2021, lineage BA.1 until May 2022 when it was replaced by BA.2, which was replaced in June 2022 by BA.4/5.
- 30 Delta infections (B.1.617) isolated between July 2021 and January 2022.
- 4 Alpha infections (B1.1.7) isolated in June and early July 2021.
- 1 n/a infection genetically sequenced as B.1.1.318 in June 2021.

For eight HCWs, two positive samples were tested for variant characterisation:

- For five HCWs, both samples had a cycle threshold (Ct) value<30;
- For one HCW, one sample was characterised by PCR and another with Ct value<30 was sequenced;
- For two HCWs, the first sample of the two sequenced had a Ct value near 30 (31 and 33 respectively), and the second had a lower Ct value.

All these samples had concordant results.

Figure 2. Genetic sequences identified in HCWs recruited for ECDC's multi-country healthcare worker vaccine effectiveness studies by month of specimen collection (n=476), 1 June 2021 to 19 July 2022



COVID-19 vaccine effectiveness estimates: Omicron period (15 December 2021 to 19 July 2022)

Due to the changing epidemiology of SARS-CoV-2 variants, we restricted the analysis to the period of circulation of the Omicron variant that was predominant during the study period from 15 December 2021 (the date of the first detection of the Omicron variant infection in the study).

Included in this analysis are 1 728 (66.3%) HCWs who completed the primary vaccination course, of whom 1 129 were vaccinated with any booster dose during the study period. A description of the main characteristics of these HCWs is included in Table 5.

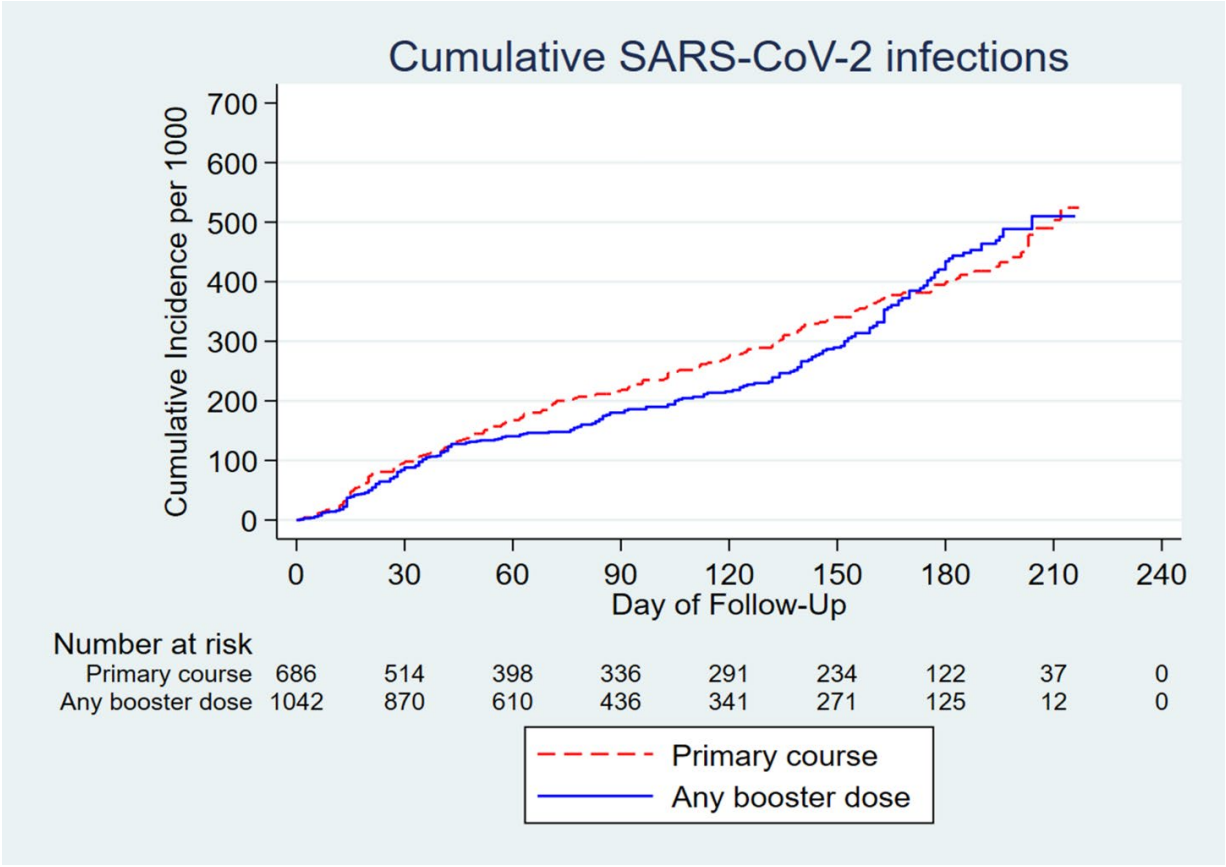
Table 5. Main characteristics of the HCWs included in the analysis restricted to the HCWs who completed the primary vaccination course only and those that received any booster vaccination, 15 December 2021 to 19 July 2022

	Completed primary vaccination course only (N=1728)		Received any booster dose (N=1129)	
Characteristic	**N**	**%**	**N**	**%**
Sex				
Female	1 387	80.3%	928	82.3%
Age group (years)				
18-34	362	20.9%	242	21.4%
35-39	228	13.2%	149	13.2%
40-44	248	14.4%	170	15.1%
45-49	283	16.4%	187	16.6%
50-54	239	13.8%	145	12.8%
55 and older	368	21.3%	236	20.9%
Role				
Medical doctor	306	18.1%	197	17.9%
Nurse	876	51.7%	606	55.0%
Administration/reception	55	3.2%	38	3.5%
Ancillary	95	5.6%	54	4.9%
Allied	175	10.3%	120	10.9%
Laboratory	41	2.4%	7	0.6%
Other	147	8.7%	79	7.2%
Smoking				
Never smoked	971	57.2%	668	59.7%
Ex-smoker	376	22.1%	241	21.6%
Current smoker	351	20.7%	209	18.7%
Chronic condition				
Reporting chronic conditions	495	28.9%	336	30.1%
Reporting >1 condition	236	47.7%	101	30.1%
Regular medication				
Reporting taking medication	742	43.1%	517	46.0%
Taking >1 medication	294	39.6%	117	22.6%
Previous COVID-19 episode				
Yes	519	30.2%	392	35.0%
Median time since last previous COVID-19 episode (range)	226	(4 - 821)	273	(4 - 821)
No	1 197	69.8%	728	65.0%
Missing/Unknown	12	0.7%	9	0.8%
Time since last dose vaccination				
Median time (range)	183	(0 - 519)	83	(0 - 519)
<90 days	592	34.3%	579	51.3%
90+ days	1 136	65.7%	550	48.7%

A total of 453 SARS-CoV-2 infection events (Figure 2a) were reported, of which:

- 196 SARS-CoV-2 infections in the completed primary vaccination group representing a cumulative incidence of 2.9 per 1 000 person days of observation; and
- 257 SARS-CoV-2 infections were identified in HCWs who received a booster dose representing a cumulative incidence of 2.7 per 1 000 person days of observation.

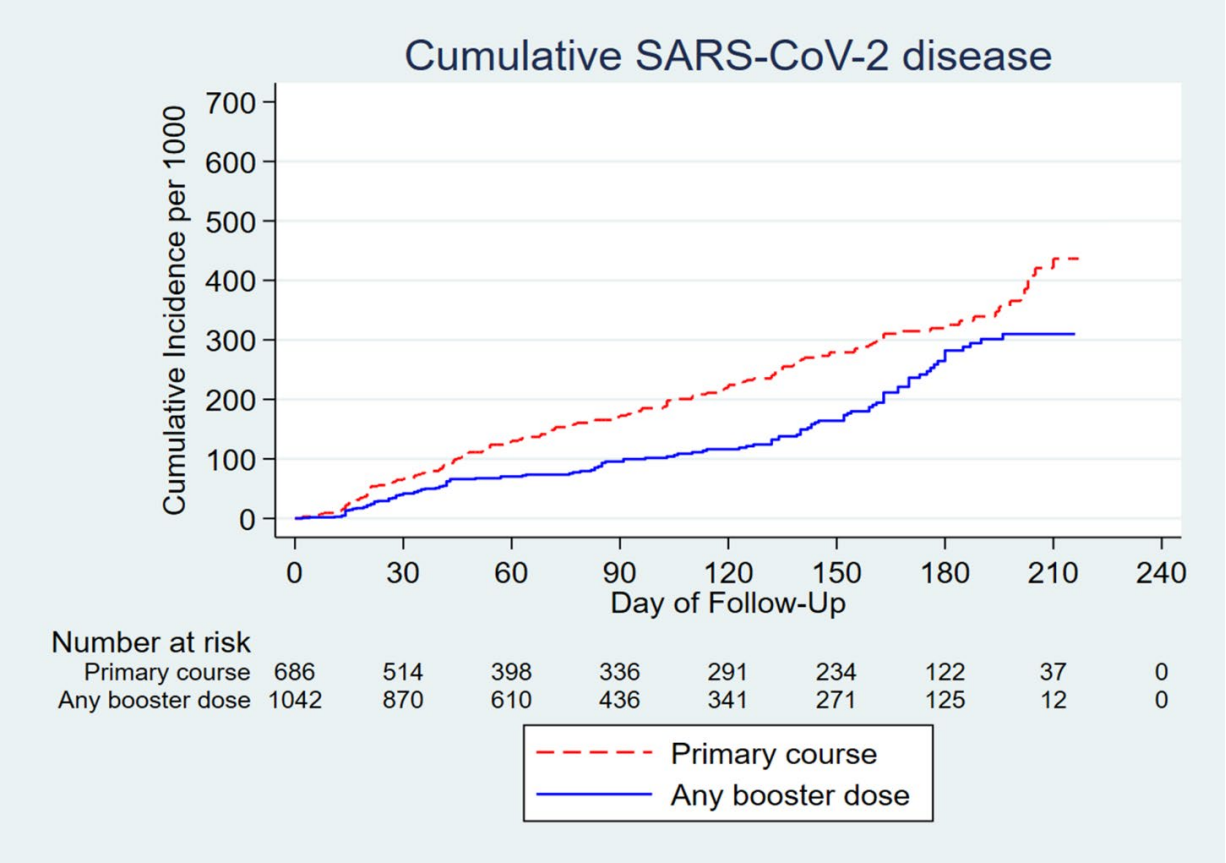
Figure 2a. Kaplan-Meier plots of time from enrolment to SARS-CoV-2 infection in screened healthcare workers recruited for ECDC's multi-country healthcare worker vaccine effectiveness studies by any booster dose versus completed primary vaccination, 15 December 2021 to 19 July 2022



A total of 285 cases of symptomatic SARS-CoV-2 infection (i.e. COVID-19 disease) were reported (Figure 2b), of which:

- 151 symptomatic SARS-CoV-2 infections were identified in the group that only completed the primary vaccination schedule, with a cumulative incidence of 2.3 per 1 000 person days of observation;
- 134 symptomatic SARS-CoV-2 infections were identified among the HCWs who received a booster dose, representing a cumulative incidence of 1.4 per 1 000 person days of observation.

Figure 2b. Kaplan-Meier plots of time from enrolment to COVID-19 disease in healthcare workers recruited for ECDC's multi-country healthcare worker vaccine effectiveness studies by any booster versus primary course vaccination, 15 December 2021 to 19 July 2022



Rate ratios were also calculated for different characteristics presented in Tables 6 and 7.

Table 6. Comparison of incidence of SARS-CoV-2 infection in HCWs enrolled in the ECDC multi-country healthcare worker vaccine effectiveness studies by any booster dose/primary schedule vaccinations status, 15 December 2021 to 19 July 2022

	N events/person time		Rate Ratio (95%CI)
	Booster vaccination	Completed primary course vaccination only	
Overall			
	257/94 568	196/66 537	0.92 (0.76 – 1.12)
Previous infection			
Reported	72/28 123	23 /13 022	1.45 (0.90 – 2.43)
Not reported	185 /66 445	173/53515	0.86 (0.70 – 1.07)
Vaccine type			
Spikevax	70/18 477	28 /6 218	0.84 (0.54 – 1.35)
Comirnaty	168/69 820	165/58 788	0.86 (0.69 – 1.07)
Vaxzevria	19/5 948	3/1 344	1.43 (0.42 – 7.55)
Sex			
Male	48/17 486	51/17 418	0.94 (0.62 – 1.42)
Female	257/94 554	196/66 537	0.92 (0.76 – 1.12)
Age group			
<50	175/58 507	128/38 970	0.91 (0.72 – 1.15)
50+	82/36 061	68/27 567	0.92 (0.66 – 1.29)
Chronic conditions			
	182/64 388	147/46 862	0.90 (0.72 – 1.13)

Table 7. Comparison of incidence of symptomatic SARS-CoV-2 infection (COVID-19 disease) in HCWs enrolled in the ECDC multi-country healthcare worker vaccine effectiveness studies by any booster dose / primary schedule vaccinations status, 15 December 2021 to 19 July 2022

	N events/person time		Rate Ratio (95%CI)
	Booster vaccination	Completed primary course vaccination only	
Overall	134/96 934	151/66 537	0.61 (0.48 - 0.77)
Previous infection			
Reported	39/28 361	15/13 022	1.19 (0.64 - 2.33)
Not reported	95/68 573	136/53 515	0.55 (0.41 - 0.71)
Vaccine type			
Spikevax	53/19 947	22/6 218	0.75 (0.45 - 1.30)
Comirnaty	76/70 520	126/58 788	0.50 (0.37 - 0.67)
Vaxzevria	5/6 144	3/1 344	0.36 (0.07 - 2.35)
Sex			
Male	21/17 780	37/17 418	0.56 (0.31 - 0.98)
Female	113/79 140	114/49 119	0.62 (0.47 - 0.81)
Age group			
<50	97/60 215	94/38 970	0.67 (0.50 - 0.90)
50+	37/36 719	57/27 567	0.49 (0.31 - 0.75)
Chronic conditions			
	98/66 180	109/46 862	0.64 (0.48 - 0.84)

The adjusted relative vaccine effectiveness (rVE) of the booster vaccination compared to completed primary vaccination by site, age, sex, month of follow-up, and underlying condition was 7% (-28 to 32) overall. The adjusted rVE was 11% (-48 to 47) in the HCWs without previous COVID-19 episode before enrolment and -6% (-81 to 38) in HCWs with a previous COVID-19 episode. The results of a sensitivity analysis using the categorical variable to measure the hybrid protection of vaccination with a booster dose and a previous COVID-19 episode was 27% (-5 to 50). The adjusted rVE of previous COVID-19 episode and vaccination with primary course only was 40% (4-62) (Table 8).

Table 8. Crude and adjusted relative Hazard Ratios of A) stratified analysis according to previous COVID-19 infection before enrolment B) additional effect of the previous COVID-19 infection and vaccination with additional/booster dose, 15 December 2021 to 19 July 2022

Analysis	Crude rHR	Adjusted by site rHR	Fully adjusted* rHR
A) Overall effect	0.95 (0.78 - 1.15)	0.94 (0.69 - 1.28)	0.93 (0.68 - 1.28)
B) Stratified analysis according to previous COVID-19 infection before enrolment	1.45 (0.90 - 2.33)		
HCWs with previous COVID-19 infection	1.45 (0.90 - 2.33)	1.07 (0.63 - 1.82)	1.06 (0.62 - 1.81)
HCWs with no previous COVID-19 infection	0.87 (0.70 - 1.08)	0.88 (0.53 - 1.47)	0.89 (0.53 - 1.48)
C) Additive effect of any booster dose vaccination and previous COVID-19 infection (hybrid protection)			
No previous COVID-19 infection & primary course vaccination	Ref	Ref	Ref
No previous COVID-19 infection & booster vaccination	0.86 (0.70 - 1.07)	0.99 (0.67 - 1.47)	0.99 (0.66 - 1.47)
Previous COVID-19 infection & Primary course vaccination	0.53 (0.34 - 0.83)	0.62 (0.40 - 0.97)	0.60 (0.38 - 0.96)
Previous COVID-19 infection & booster vaccination	0.80 (0.60 - 1.08)	0.74 (0.51 - 1.07)	0.73 (0.50 - 1.05)
D) **Time since booster dose compared to primary course >3 months since second dose**			
Vaccinated with booster dose >14 days < 90 days	0.74 (0.57 - 0.96)	0.66 (0.45 - 0.98)	0.68 (0.45 - 1.02)
Vaccinated with booster dose ≥ 90 days	1.10 (0.88 - 1.37)	1.02 (0.74 - 1.39)	1.02 (0.74 - 1.40)

**Adjusted by age sex, month of follow-up, site, at least one underlying condition*

Challenges and limitations

The very high COVID-19 vaccine coverage rates, in which most recruited HCWs have received the primary course of vaccination, mean that very few unvaccinated HCWs have been recruited, compromising the possibility of estimating VE of COVID-19 vaccines and reducing the power of the study. The calculation of a relative VE (rVE) is used to mitigate the impact of the high vaccine coverage in the calculation of the VE. Although the high vaccine coverage may indicate a possible selection bias as the recruited cohorts may not be representative of HCWs in general, official data from EU countries indicate similarly high levels of vaccination [15].

The acceptability among HCWs of weekly nasopharyngeal swabbing to detect SARS-CoV-2 infections varied by site leading to a variation in practice by sites. Some sites have managed to perform weekly nasopharyngeal or oropharyngeal swabbing in HCWs, but many sites have employed other approaches to regular screening of HCWs, including biweekly, rather than weekly, nasopharyngeal swabbing or the collection of weekly saliva sample. Feedback from sites using weekly saliva samples has highlighted the greater acceptability of this approach among HCWs and increased recruitment and retention. Although a meta-analysis reported the lower sensitivity of ~85% of saliva and nasal samples when compared to nasopharyngeal swabs, both offered good diagnostic performance and were considered clinically acceptable alternatives [16]. Nonetheless, there remains the possibility of a misclassification bias due to differing test performance. The revised version of the study protocol has emphasised that sites employing alternative screening approaches should undertake validation of their methods. Even if all sites used the same approach, there remains a need to standardise site assays through common international, national or research standards to address possible variation in test performance.

It should be noted that all data presented in this report are provisional and may be corrected and revised. The study is still ongoing in many sites and has just started in others. The initiation of cohorts in new sites and the continued follow-up of HCWs, especially during the winter and intense circulation of the Omicron variant, has resulted in an increased cohort size and number of events being recorded. However, the skewed distribution of cases due to the circulation of the Omicron variant has resulted in restricting the VE analysis by calendar time (i.e. 15 December 2021 to 19 July 2022), which reduced the sample size. There is also the emergence of new lineages of the Omicron variant with a different epidemiology to the original strain. Therefore, although point estimates of rVE indicated some protective effects, the wide confidence intervals make the interpretation of the results difficult. In addition, the follow-up time was insufficient for more advanced analysis of time since vaccination and waning protection, although this was attempted. However, the cases identified during the follow-up had a median time since last dose >180 days, indicating that the waning vaccination protection played an important role during our study. The reduced power of the study may be addressed by the continuation of the study and including a longer follow-up period and the recruitment of new sites, some with larger target cohort sizes.

Discussion and conclusions

Aside from 18 unvaccinated HCWs, all HCWs recruited to date have been vaccinated with one or more doses of COVID-19 vaccine. In this report, the estimation of relative VE is restricted to the population of HCWs who had completed a primary vaccination schedule and compared the incidence of laboratory-confirmed SARS-CoV-2 infections among those HCWs who had received any booster dose to those with primary course vaccination. The estimation of relative VE is further restricted to the period of 15 December 2021 to 19 July 2022, a period of intense circulation of the Omicron variant, to account for the skewed distribution over time of the number of cases, the known epidemic differences between the Delta and Omicron waves [17-18] and the expected infection in vaccinated individuals [19].

In this study, the overall relative VE against infection of a booster dose compared to primary course vaccination, adjusted for key variables, suggested no significant protection offered by the booster dose compared to a completed primary series of vaccination, although the confidence intervals were wide. Available evidence from the literature indicates that current COVID-19 vaccines have low effectiveness against mild and asymptomatic Omicron infections. The protection against infection due to the Omicron variant starts waning two to three months after completing the primary series and is largely lost after six months. It was found that protection against infection also wanes rapidly after the first booster dose.

The literature also shows that a second booster improves VE against infection, but this also seems to wane rapidly, as has been seen within the short follow-up period available so far after the second booster dose. In summary, the benefit of booster doses to protect against SARS-CoV-2 infection is seemingly limited [20].

Available evidence shows that the vaccine-induced protection is stronger and more durable against severe disease, although the balance of the evidence indicates gradual waning three to six months after the primary series. Studies of VE against severe disease due to the Omicron variant by time since first booster suggest that relative vaccine effectiveness against severe outcomes is high following the administration of a booster dose, and for up to two to three months after receiving the booster. Only a few studies with a follow-up time longer than six months are available, but the available limited evidence indicates that the vaccines provide protection against severe outcomes also more than six months after the first booster dose. The first booster dose, usually administered four to six months after completion of the primary series, serves to improve the immune response after it has waned over time, as does the second booster. However, the incremental benefit of a second booster dose is likely lower compared to the primary series and first booster doses, including for severe disease [20].

Evidence from studies looking at the combined effect of naturally-acquired immunity and vaccine-induced immunity clearly point to an extra layer of protection for those with hybrid immunity. However, the scale of naturally-acquired immunity in populations is difficult to quantify due to issues such as the under-ascertainment of COVID-19 cases and reinfections, the lack of unbiased, longitudinal seroprevalence data, and the waning profiles of protection. In addition, few vaccine effectiveness studies disaggregate results by prior infection status. For those that do, direct comparison between studies is challenging, owing to heterogeneity (type of study, study population, type of vaccine, follow-up time, sequence of infection/vaccination) [20].

The findings from this study indicate that both vaccination with the primary series only and with booster doses appeared to offer more protection to HCWs reporting a COVID-19 episode prior to enrolment than those HCWs without a previous COVID-19 episode, in agreement with other studies [21].

Continuation of the study will increase the precision of the estimates and contribute to providing data to inform public health decisions in the anticipated SARS-CoV-2 waves in 2022 and 2023.

Contributing ECDC experts (in alphabetical order)

Sabrina Bacci, Kim Brolin

Contributing external experts (in alphabetical order)

Report prepared by Epiconcept: Camelia Savulescu, Albert Prats Uribe, Cristina Lopez, Ranya Mulchandani, and Anthony Nardone on behalf of the HCW VE cohort study group.

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For more information related to the content of this report or the ongoing multi-country study, please contact: vpd.vpd@ecdc.europa.eu.

ECDC HCW VE cohort study group

Croatia: Croatian Institute of Public Health: Zvjezdana Lovrić Makarić, Goranka Petrović, Gordan Sarajlić
Estonia: University of Tartu: Anneli Uusküla, Viljandi Hospital: Liis Lohur
Greece: National Public Health Organization (EODY), Athens: Marina Amerali, Kyriaki Tryfinopoulou, Georgios Panagiotakopoulos
Ireland: Health Protection Surveillance Centre: Suzanne Cotter, Lisa Domegan
Ireland: St James's Hospital, Dublin: Colm Bergin, Laura O'Doherty, Jonathan McGrath, Anne Moriarty, Yunzhu Chen, Shane Walsh
Ireland: Galway University Hospital: Catherine Fleming, Claire Kelly, Maeve Kernan, Laura Ferguson
Ireland: Beaumont Hospital, Dublin: Blanaid Hayes
Italy: Hospital San Gerardo-University of Milano-Bicocca, Monza: Paolo Bonfanti, Marianna Rossi, Valentina Orsini, Marta Iannace, Anna Spolti
Italy: Policlinico Gemelli University Hospital, Rome: Kathleen De Gaetano Donati, Rita Murri, Silvia Lamonica, Alice Tondinelli
Italy: AOUP 'G. Rodolico-San Marco', Catania: Antonella Agodi, Martina Barchitta, Venerando Rapisarda
Latvia: Centre for Disease Prevention and Control of Latvia: Renate Putnina, Larisa Savrasova
Latvia: Pauls Stradiņš Clinical University Hospital: Ilze Abolina, Viesturs Zvirbulis, Zanda Zeberga
Latvia: Children's Clinical University Hospital: Dace Zavadska, Dagne Gravele, Justs Dimants

Latvia: Riga East Clinical University Hospital: Indra Zeltina
Poland: University Clinical Centre of Warsaw Medical University – Central Clinical Hospital, Warsaw: Konstanty Szułdrzyński, Alecksandra Kulesza
Portugal: Centro Hospitalar de Lisboa Ocidental, Centro Hospitalar de Tondela Viseu: Ausenda Machado, Ana Joao Santos, Irina Kislaya, Vania da Silva Gaio, Raquel Guiomar
Spain: Hospital Sant Joan de Deu, Barcelona: Carmen Muñoz-Almagro, Lucia Sanchis, Iolanda Jordan, Pilar Subirats
Spain: Hospital Miguel Servet, Zaragoza: Miriam Latorre, Laura Clusa, Anna Milagro, Antonio Rezusta

Disclaimer

All data published in this report are correct to the best of our knowledge at the time of submission of the report to ECDC (28 July 2022).

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