

Interim analysis of COVID-19 vaccine effectiveness against Severe Acute Respiratory Infection due to laboratory-confirmed SARS-CoV-2 among individuals aged 65 years and older, ECDC multi-country study

8 October 2021

Key facts

- Monitoring vaccine effectiveness (VE) in real-world conditions is essential for informed decision-making with regards to vaccination strategies.
- ECDC is building infrastructure to allow regular monitoring of COVID-19 VE over time, using a multi-country approach that involves studies implemented in different settings. This document describes the study, conducted in the hospital setting, and presents results from the first interim analysis of COVID-19 VE against severe acute respiratory infection due to laboratory-confirmed SARS-CoV-2 among individuals aged 65 years and older. Regular updates of these results will be provided periodically as the study continues.
- A total of 10 European Union (EU) countries have joined the study (Belgium, Croatia, Czechia, France, Greece, Ireland, Luxembourg, Malta, Portugal, Spain); this first interim analysis presents data from six of these countries for the period 27 December 2020 to 30 June 2021.
- Interim results suggest a good VE against laboratory-confirmed SARS-CoV-2 for COVID-19 vaccines deployed during the first six months of the vaccination campaign across EU and European Economic Area (EEA) countries, albeit with wide confidence intervals. The effectiveness of a complete vaccination course, with two doses of COVID-19 vaccine, was better than for a single dose (for those vaccines with a two-dose schedule).
- Estimated results were in the range of estimates published in other studies for similar outcomes in this population during the pre-Delta period.
- Real-world studies of VE estimates in the hospital setting are important to understand the extent of protection the vaccines may have against severe outcomes such as hospitalisation, intensive care unit (ICU) admission or death.
- More extensive analyses will be conducted to assess factors that may affect VE, such as different variants and length of time since vaccination.

Scope of this document

This document reports the first interim pooled estimates from the ECDC 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 against hospitalisation with Severe Acute Respiratory Infection laboratory-confirmed with SARS-CoV-2, version 1.0* [1].

Interim pooled estimates of COVID-19 VE were calculated for all COVID-19 vaccines deployed, including the COVID-19 mRNA vaccine Comirnaty (Pfizer/BioNTech), among hospitalised individuals aged 65 years and older with SARI due to laboratory-confirmed SARS-CoV-2, across EU/EEA participating countries. The study is currently ongoing and interim analyses will be conducted on a regular basis, with results updated as relevant. Pooled estimates are from patients recruited across several hospital study sites in the EU/EEA. These interim estimates mainly cover the pre-Delta period, adding further evidence to the existing literature on COVID-19 VE during this time.

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 core ECDC protocol [1].

Target audience

Target audiences for this document are the European Commission, the Health Security Committee, the EU/EEA National Immunization Technical Advisory Groups (NITAGs), national public health institutes and ministries of health in the EU/EEA, and public health experts and decision makers at national and subnational levels.

Background

Vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection plays a key role in the control of the coronavirus disease (COVID-19) pandemic and the lifting of some non-pharmaceutical interventions. All vaccines approved by the European Medicines Agency (EMA) have demonstrated good vaccine efficacy/effectiveness (VE) against severe COVID-19 [2,3].

Assessment of the real-world performance of the vaccines is important to be able to adapt vaccination strategies, as many questions that could not be assessed in the pre-authorisation phase are still to be answered (e.g. regarding specific circulating SARS-CoV-2 variants, different administration policies adapted to short vaccine supplies, heterologous vaccination schemes, long-term effectiveness and specific population groups). These results will help to inform vaccination strategies and guidance in all of these areas.

In 2020, the European Commission (EC) emphasised the importance of continuously monitoring the safety and effectiveness of vaccines in the EU/EEA and called on ECDC and EMA to develop a structured post-authorisation monitoring platform for vaccines, prioritising COVID-19 vaccines. In November 2020, the EC proposed to the European Parliament and the Council of the EU that a change be made to the mandates of EMA and ECDC in the context of its COVID-19 lessons learned package and the creation of a European Health Union, empowering the two agencies to jointly coordinate independent vaccine monitoring studies. As a result, ECDC has started building infrastructure to perform COVID-19 VE studies in a number of settings (e.g. hospitals, primary care, healthcare worker cohorts), using a multi-country approach.

Since the beginning of the vaccination rollout in the EU in late December 2020, four COVID-19 vaccines have received conditional marketing authorisation in the EU, following evaluation by the EMA [4]: Comirnaty (BNT162b2), Spikevax (mRNA-1273), Vaxzevria (AZD1222), and COVID-19 Vaccine Janssen (Ad26.COV 2.5). All vaccine products authorised in the EU were initially registered for use in people aged 18 years and older, with the exception of Comirnaty, which was approved for use in individuals aged 16 years and older [5]. Comirnaty and Spikevax indications were recently extended to include children aged 12 to 15 years and 12 to 17 years, respectively. COVID-19 Vaccine Janssen is not distributed to Liechtenstein or Sweden and is not in use in Finland (though it was distributed to Finland, it was not used). Vaxzevria is not distributed to Liechtenstein and is no longer in use in Denmark or Norway. Sputnik V is distributed to Hungary and Slovakia, and Inactivated Beijing CNBG is distributed to Hungary through bilateral negotiations with the manufacturers.

Objectives

As presented in the core ECDC protocol [1], the primary objective of this VE study is:

- “To measure, within each European participating site/country and in a pooled, multi-country analysis, the direct effect (effectiveness) of overall and product-specific COVID-19 vaccines against SARI due to laboratory-confirmed SARS-CoV-2 in hospitalised patients, in order to provide up-to-date information on the ability of COVID-19 vaccines to prevent severe disease under real conditions of use.”

The secondary objectives are:

- “To measure overall and product-specific COVID-19 VE against SARI due to laboratory-confirmed SARS-CoV-2 in hospitalised patients by participating study site/country, risk group (e.g. specific chronic conditions), sex, age group (18-49 years, 50-64 years, 65-79 years, 80+ years), COVID-19 vaccination target group, time since vaccination and regularly over calendar time, vaccine doses when applicable;
- To measure overall and product-specific COVID-19 VE among SARI patients requiring hospitalisation against specific genetic variant(s) of laboratory-confirmed SARS-CoV-2, more severe outcomes (ICU admission, invasive ventilation, in-hospital mortality); and
- To identify potential factors that may modify COVID-19 VE: prior SARS-CoV-2 infection, chronic conditions, the role of influenza vaccination, the role of settings such as long-term care facilities (LTCFs), the role of long-term medications (depending on availability of these data in the participating country).”

The objectives of the interim analysis presented in this document are to measure, in a pooled analysis, the direct effectiveness of overall and product-specific COVID-19 vaccines against SARI due to laboratory-confirmed SARS-CoV-2 in hospitalised patients aged 65 years and older, by:

- at least one dose (one or two doses of the two-dose vaccine schedule or one dose of the single-dose vaccine schedule)
- partial vaccination (one dose only, for the two-dose vaccine schedule)
- complete vaccination (one or two doses, as indicated by the schedule of the vaccine received)

Methods

Enrolment of countries in the study

The monitoring of VE against SARI due to laboratory-confirmed SARS-CoV-2 is performed through an active, prospective, continuous system that collects information in agreement with the core ECDC protocol [1]. As of September 2021, a total of 32 hospitals in 10 EU countries (Belgium, Czechia, Croatia, France, Greece, Ireland, Luxembourg, Malta, Portugal, Spain) are part of this system (Figure 1, Table 1). Detailed information on SARI patients admitted to these hospitals is collected, including their demographics, the clinical course of their illness, epidemiological data, laboratory confirmation of SARS-CoV-2 and its virological characteristics. The study population comprises all SARI patients (suspected COVID-19 patients) admitted to participating hospitals with onset within 10 days of swab, from which cases and controls are enrolled. Following local requirements, each local protocol was submitted to and approved by the ethics committee of each site, as needed. Patient consent is an inclusion criterion for the study in each hospital, as described in the protocol.

Figure 1. Map of participating countries, ECDC multi-country COVID-19 vaccine effectiveness study among hospitalised SARI patients, EU/EEA countries, as of September 2021



Table 1. Number of hospitals and start dates of data collection in each participating country, ECDC multi-country COVID-19 vaccine effectiveness study among hospitalised SARI patients, EU/EEA countries, 27 December 2020–30 June 2021

Country	Number of hospitals	Start of data collection	Start of dominance of Delta variant [6]
Belgium	6	15 January 2021	Week 25 2021
Czechia	1	20 July 2021	Week 25 2021
Croatia	3	1 February 2021	Week 27 2021
France	3	January 2021*	Week 26 2021
Greece	1	31 May 2021	Week 27 2021
Ireland	1	-	Week 25 2021
Luxembourg	1	-	Week 24 2021
Malta	1	1 February 2021	Week 26 2021
Portugal	3	2 February 2021	Week 23 2021
Spain	12	27 December 2020	Week 27 2021

*: Start day not available in the current report.

-: At the time of writing, these countries had not yet started data collection.

Study design

A test-negative study design was used to provide VE estimates [7]. In the test-negative design, VE is assessed by comparing the odds of vaccination among SARI patients testing SARS-CoV-2 positive (cases) with the odds of vaccination among those testing SARS-CoV-2 negative (controls).

Individuals aged 65 years and older (belonging to the COVID-19 vaccine age-specific target groups at the time of specimen collection date) were included in the study up to the middle of week 26 2021 (up to 30 June 2021). The study period slightly differed between countries (Table 1); in two countries (Ireland and Luxembourg), data collection was about to start at the time of writing this report, following finalisation of study applications as relevant.

Primary outcome and exposure

SARI

The primary outcome was laboratory-confirmed SARS-CoV-2 infection in hospitalised SARI patients. The ECDC clinical case definition for a SARI patient (possible COVID-19 case) applied to a hospitalised patient, was used for this interim analysis. It defines a SARI case-patient as: "A hospitalised individual with **at least one** of the following symptoms: cough, fever, shortness of breath, **or** sudden onset of anosmia, ageusia or dysgeusia" [8].

A confirmed COVID-19 case was defined as a possible COVID-19 case (ECDC SARI case definition above), with a respiratory sample positive for SARS-CoV-2 by reverse transcription polymerase chain reaction (RT-PCR) either on admission to hospital or documented within 14 days prior to hospital admission [9].

Vaccination against COVID-19

By early January 2021, all EU/EEA countries had started their vaccination rollout. Comirnaty was the first vaccine that received authorisation for use in the EU/EEA (on 21 December 2020), followed by Spikevax on 6 January 2021, Vaxzevria on 29 January 2021 and COVID-19 Vaccine Janssen on 11 March 2021. Countries started vaccination programmes at different dates, prioritising specific risk groups. In general, most EU/EEA countries prioritised individuals living in closed settings, healthcare workers, vulnerable individuals and older adults, albeit with different age groups across countries. Eligibility criteria expanded over time, with an age-staggered approach and additions of other high-risk populations, such as people with underlying conditions, essential workers, etc.

In terms of dosing schedule, while priority groups most likely received the recommended schedule during the initial phase of the campaign, some countries may have extended the time between the first and second dose if vaccine supplies did not cover their needs during the campaign. As of 30 June 2021 (end of the study period for this interim report), about 64% of adults aged 60 years and older in the EU/EEA had received at least one dose of a COVID-19 vaccine and 43% had been fully vaccinated (Table 2).

Table 2. Vaccination uptake of at least one dose/complete vaccination, by age group, EU/EEA participating countries, as of week 26 (ending 4 July 2021)

Country	Vaccination uptake (one dose/complete vaccination)			
	≥18 years	60–69 years	70–79 years	≥80 years
Belgium	80.8/45.9	81.1/70.7	85.3/77.4	85.3/86
Croatia	45.3/35.9	63.7/53.4	70.7/63.7	54.7/50.3
Czechia	58.7/40.5	71.5/61.3	85.2/77	81.7/76.2
France	66.2/42.8	78.4/60.5	90/78.7	80.4/71
Greece	55.9/44.6	74.1/68.1	78.8/75.2	69.8/66.9
Ireland	70.7/52.3	98.2/67.2	100/100	100/100
Luxembourg	67/48.5	81.8/79.7	84.8/83	85.3/83.4
Malta	83.6/78.8	94.4/91.1	100/100	100/100
Portugal	67.6/43.9	96.7/68.8	100/81.1	99.2/94.9
Spain	68.5/48.6	94.6/53.9	98.1/97	100/100
Total EU/EEA	63.7/43.4	81.1/61.3	85.3/77.4	85.3/83.4

Source: COVID-19 Vaccine Tracker [10]

In the interim analysis presented in this document, vaccination status was defined as follows:

- **At least one dose:** any individual who received at least one dose of vaccine ≥14 days before onset of symptoms
- **Partially vaccinated (one dose only):** any individual who received only the first dose of a two-dose vaccine course ≥14 days before onset of symptoms
- **Completely vaccinated:** any individual who received the second dose of a two-dose vaccine course or one dose of COVID-19 Vaccine Janssen ≥14 days before onset of symptoms
- **Unvaccinated:** any individual who had not received any vaccine or who was vaccinated on the day that symptoms started or after symptom onset

Exclusion criteria

Individuals were not enrolled in the study if:

- they were unwilling to participate or unable to communicate and give consent (the consent may also be given by their legal representative or by specific consent procedures that are considered acceptable according to the local ethical review process),
- they had a contraindication for the COVID-19 vaccine,
- no specimen could be tested due to severe septum deviation, obstruction or other condition that contraindicated swabbing, or
- they had a history of hospitalisation within the 14 days immediately prior to this admission (including transfers from another hospital).

Statistical analysis

Characteristics of included SARI patients (test-positive cases and test-negative controls) were described.

Using logistic regression, crude and adjusted odds ratios (ORs) were estimated, comparing the odds of vaccination between test-positive cases and test-negative controls. The unadjusted model included the study site as a fixed effect and month of swab. The adjusted model included the main covariates of the crude model, plus age group and presence of at least one of the seven underlying chronic conditions relevant to COVID-19 and collected by all participating hospitals/countries (diabetes, heart disease, chronic lung disease, immunodeficiencies, asthma, hypertension and obesity).

The VE was computed as 1 minus the OR (expressed as a percentage), using a one-stage analysis of pooled individuals from all participating EU/EEA countries reporting at least five cases and controls.

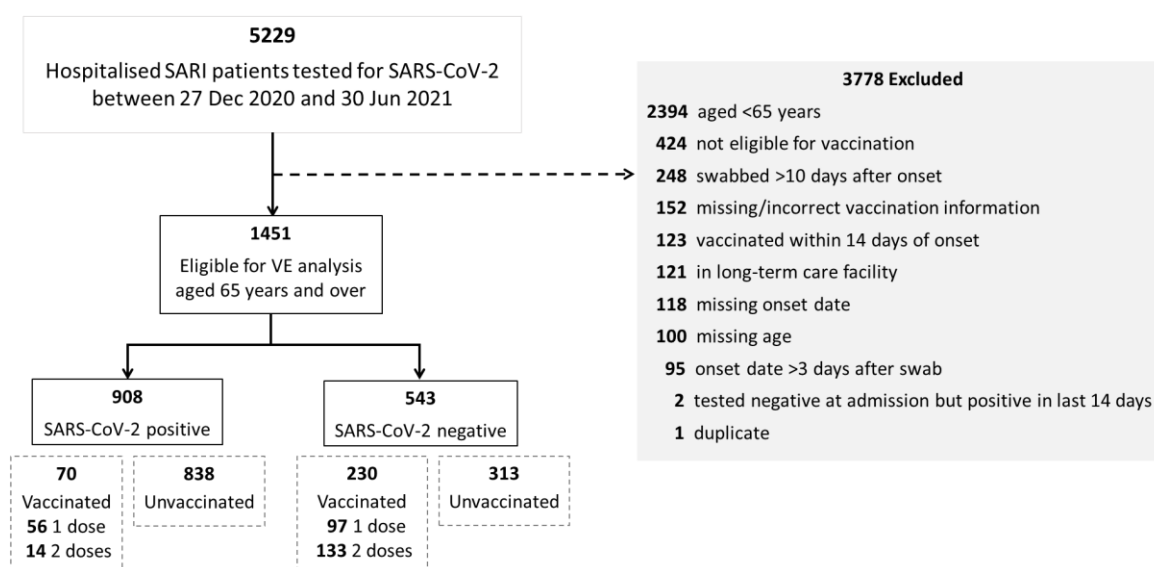
For this first interim analysis, overall VE was estimated ≥ 14 days after at least one dose of any vaccine, including Comirnaty vaccine. Analyses were repeated, with estimates calculated 14 days after completion of the full vaccination course. VE was expressed as a percentage for those aged 65 years and older, overall and by age group (65–79 years, ≥ 80 years).

Results

Descriptive analysis

The study population included in this interim analysis encompassed 1 451 individuals who met the inclusion criteria. Those under 65 years old or who were not eligible for vaccination at the time of their sample being taken, those swabbed >10 days after onset of symptoms or who only developed symptoms >3 days after their swab date, those missing key variables (age, symptom onset date, vaccination status), and those resident in a long-term care facility were excluded. Among the 1 456 included individuals, 909 tested positive for SARS-CoV-2 (cases) and 547 tested negative (controls) (Figure 2). 8% of cases (71/909) and 43% of controls (234/547) were vaccinated. Seven countries (Belgium, Croatia, Czechia, France, Malta, Portugal, Spain) contributed data to the interim descriptive analysis presented in this report (Figure 2 and Table 3), while six countries contributed data to VE estimation (Czechia was excluded for having <5 eligible cases).

Figure 2. Flowchart of inclusion, pooled data of countries providing interim data, ECDC multi-country COVID-19 vaccine effectiveness study among hospitalised SARI patients, EU/EEA countries, 27 December 2020–30 June 2021 (n = 5 229)



Characteristics of the study population

Of the 1 451 SARI patients aged 65 years and older included in the interim VE analysis, 908 (62%) tested positive for SARS-CoV-2 (cases), of whom 505 (56%) were male, about half (56%) reported an underlying condition, 70 (8%) had received at least one dose of COVID-19 vaccine, and 15 (2%) were fully vaccinated (Table 3). Comirnaty was the most commonly administered vaccine, both as a first and second dose. Only one included individual had received the single-dose COVID-19 Vaccine Janssen. Recruitment of cases peaked in week 14 of 2021, while controls were recruited steadily up to week 26 (Figure 3).

Table 3. Characteristics of eligible SARI patients, ECDC multi-country COVID-19 vaccine effectiveness study among hospitalised SARI patients, EU/EEA countries, 27 December 2020–30 June 2021 (n = 1 451)

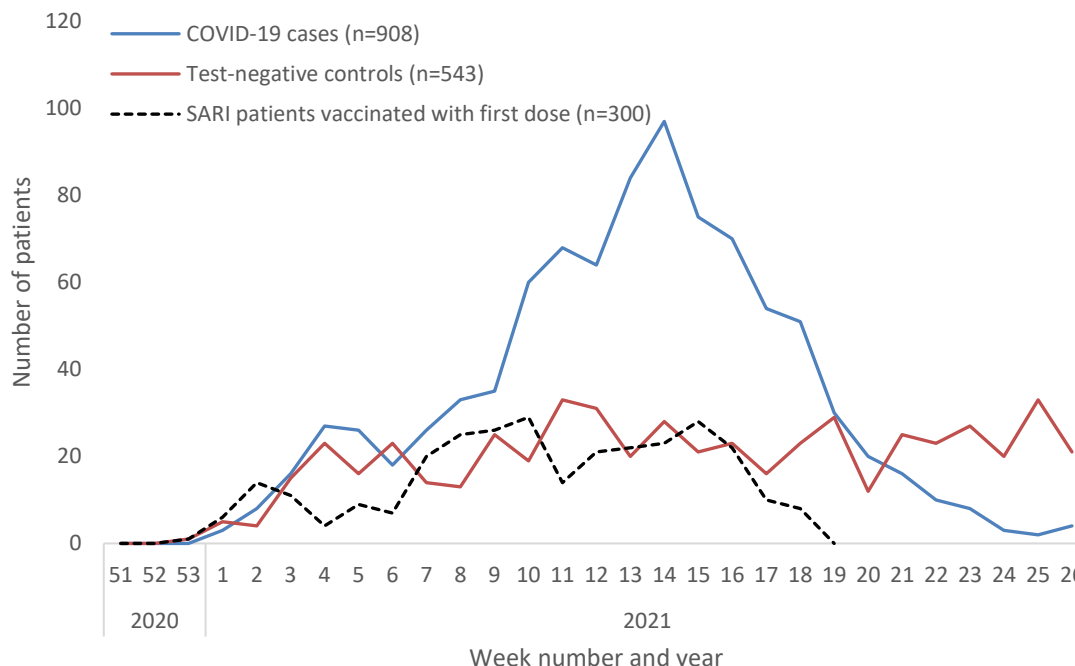
Characteristics		Cases (n = 908)	Controls (n = 543)	p value
Sex	Male	505 (56)	310 (57)	0.58
	Female	396 (44)	228 (42)	
	Missing	7 (<0.5)	5 (1)	
Age groups (years)	65-69	197 (22)	88 (16)	0.003*
	70-74	193 (21)	104 (19)	
	75-79	139 (15)	73 (13)	
	80-84	194 (21)	125 (23)	
	85+	185 (20)	153 (28)	
Any one of seven* chronic conditions	Yes	509 (56)	401 (74)	<0.001
	No	399 (44)	142 (26)	
	Missing	0	0	
COVID-19 vaccination status	Not vaccinated	838 (92)	313 (58)	
	Vaccinated with at least one dose	70 (8)	230 (42)	
	Partially vaccinated (one dose only)	56	97	
	Completely vaccinated	14	134 [§]	
Number of dose(s) of COVID-19 vaccine administered	None	838 (92)	314 (58)	
	One	56 (6)	97 [§] (18)	
	Two	14 (2)	133 (25)	
Number of individuals administered with first dose	Comirnaty	36 (51)	156 (68)	
	Vaxzevria	16 (23)	23 (10)	
	Spikevax	5 (7)	12 (5)	
	COVID-19 Vaccine Janssen	0	1 (<1)	
	Curevac	0	2 (1)	
	Unknown	3 (4)	8 (3)	
	Missing	10	28	
Number of individuals administered with second dose	Comirnaty	12 (86)	121 (91)	
	Vaxzevria	0	1 (<1)	
	Spikevax	1 (7)	6 (5)	
	Curevac	0	1 (<1)	
	Unknown product	1 (7)	2 (1)	
Median time delay in days (range)	From first dose to onset of disease	0	2	<0.005 [†]
	From second dose to onset of disease	28 (14-109)	56 (14-175)	

* Fisher's exact

† Wilcoxon rank-sum (Mann-Whitney)

§ Including one control that received a single dose of COVID-19 Vaccine Janssen.

Figure 3. Number of cases and controls by ISO week of specimen collection and number of patients vaccinated by ISO week of vaccination, pooled data of countries providing interim data, ECDC multi-country COVID-19 vaccine effectiveness study among hospitalised SARI patients, EU/EEA countries, 27 December 2020–30 June 2021 (n = 1 451)



Characteristics of vaccinated individuals

Almost all vaccinated individuals received a two-dose vaccine: Comirnaty, Spikevax, Vaxzevria or Curevac. One received the COVID-19 Vaccine Janssen. The median time between the first and second dose was 21 days for both cases and controls, as per vaccine administration recommendations (Figure 4). Maximum delays between doses were 42 days for cases and 44 days for controls (Figures 5 and 6).

The median number of days from the administration of the second vaccine dose to the onset of SARI symptoms was significantly greater in controls (50 days) than cases (39 days; $p < 0.16$) (Table 3).

Figure 4. Number of days between first and second COVID-19 vaccine doses among cases and controls, pooled data for countries providing interim data, ECDC multi-country COVID-19 vaccine effectiveness study among hospitalised SARI patients, EU/EEA countries, 27 December 2020–30 June 2021 (n = 147)

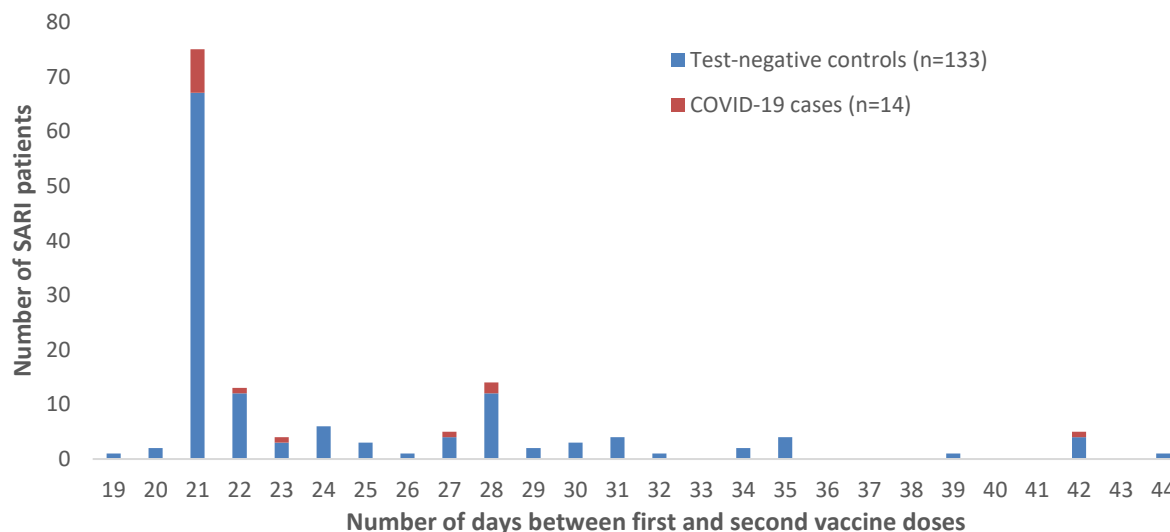


Figure 5. Number of days between first COVID-19 vaccine dose and onset of symptoms among cases and controls, pooled data for countries providing interim data, ECDC multi-country COVID-19 vaccine effectiveness study among hospitalised SARI patients, EU/EEA countries, 27 December 2020–30 June 2021 (n = 300)

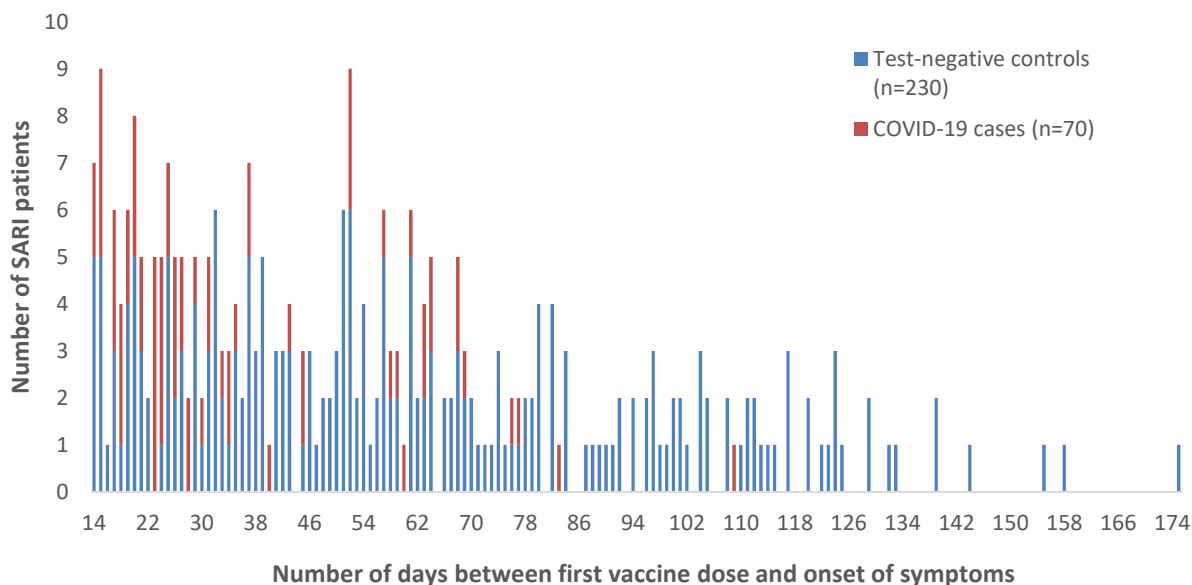
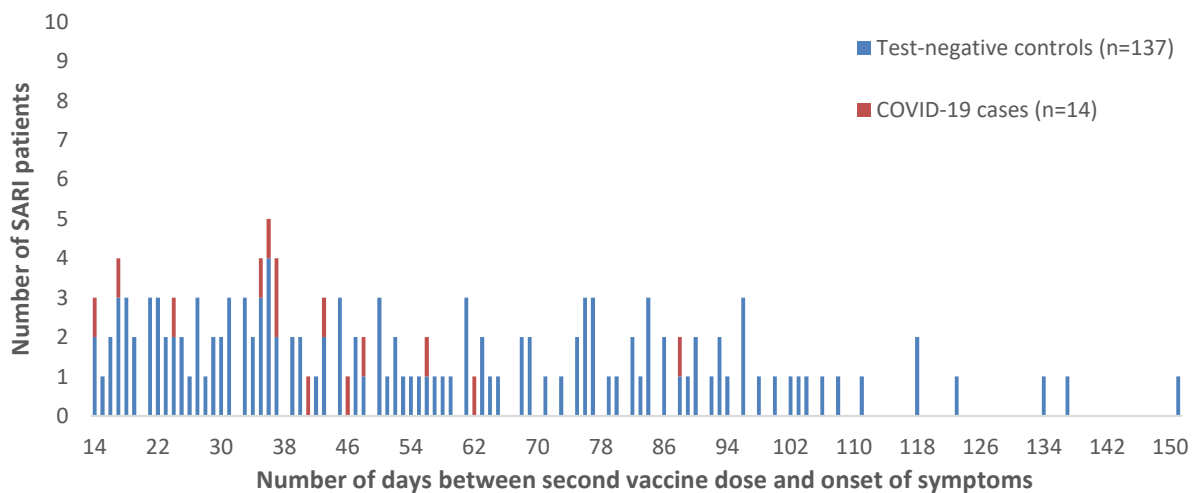


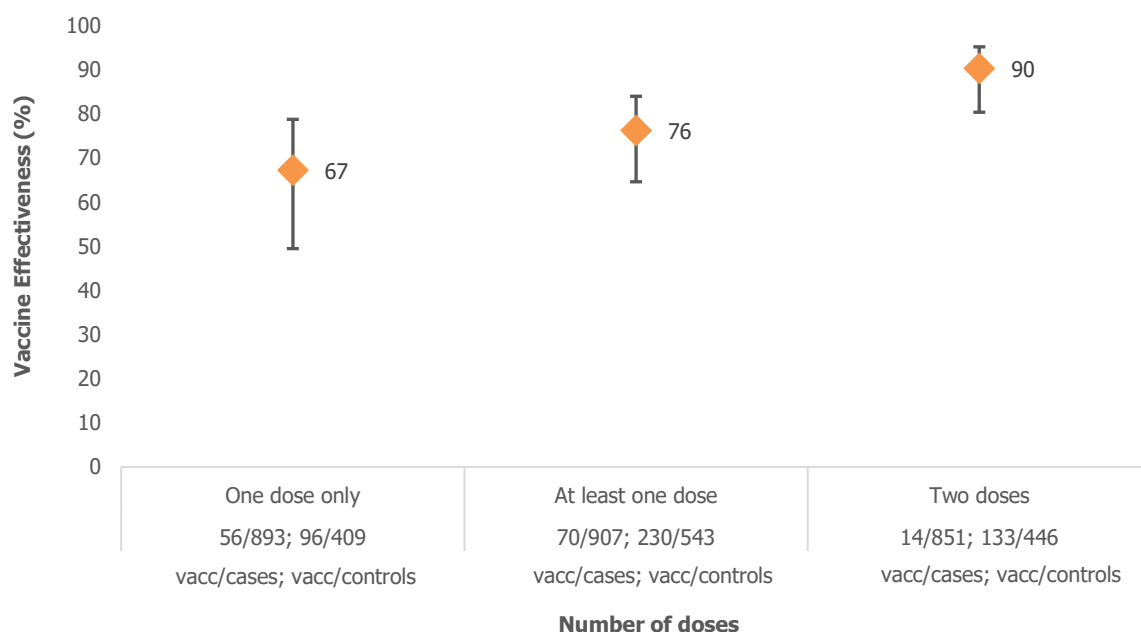
Figure 6. Number of days between second COVID-19 vaccine dose and onset of symptoms among cases and controls, pooled data for countries providing interim data, ECDC multi-country COVID-19 vaccine effectiveness study among hospitalised SARI patients, EU/EEA countries, 27 December 2020–30 June 2021 (n = 151)



Vaccine effectiveness estimates

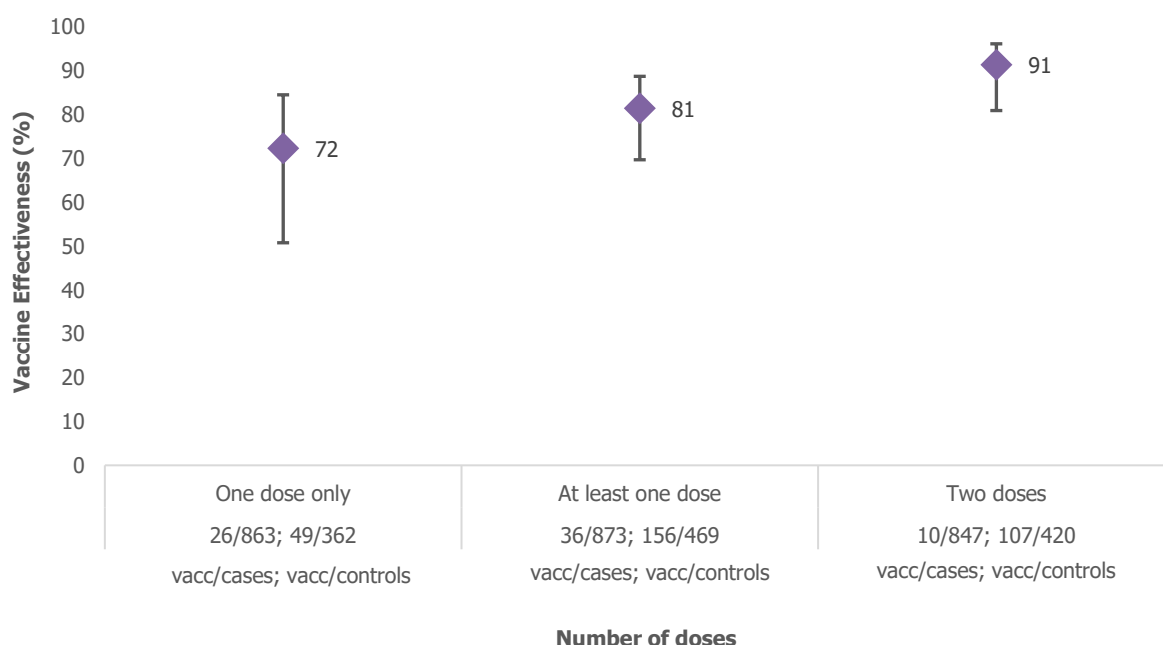
The adjusted VE against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients observed ≥ 14 days after only one dose of any vaccine product was 67% (95% confidence interval (CI): 50-79%). VE observed ≥ 14 days after two doses of any vaccine product was 90% (CI: 80-95%) (Figure 7). Looking specifically at the VE for the Comirnaty vaccine, the adjusted VE observed ≥ 14 days after only one dose was 72% (95% CI: 51-84%). The VE observed ≥ 14 days after two doses of any vaccine was 91% (CI: 80-96%) (Figure 8). Looking at the results of the analysis by subgroups, adjusted VE did not differ across the age groups 65 to 79 years and 80 years and older (Figure 9). As most patients were vaccinated with the Comirnaty vaccine, results for this vaccine alone were consistent with results for any vaccine when looking at VE by age group and sex (Figures 9 and 10).

Figure 7. Overall vaccine effectiveness of any vaccine product against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients aged 65 years and older at specimen collection date, by dose, six EU/EEA countries, 27 December 2020–30 June 2021 (n = 1 450)



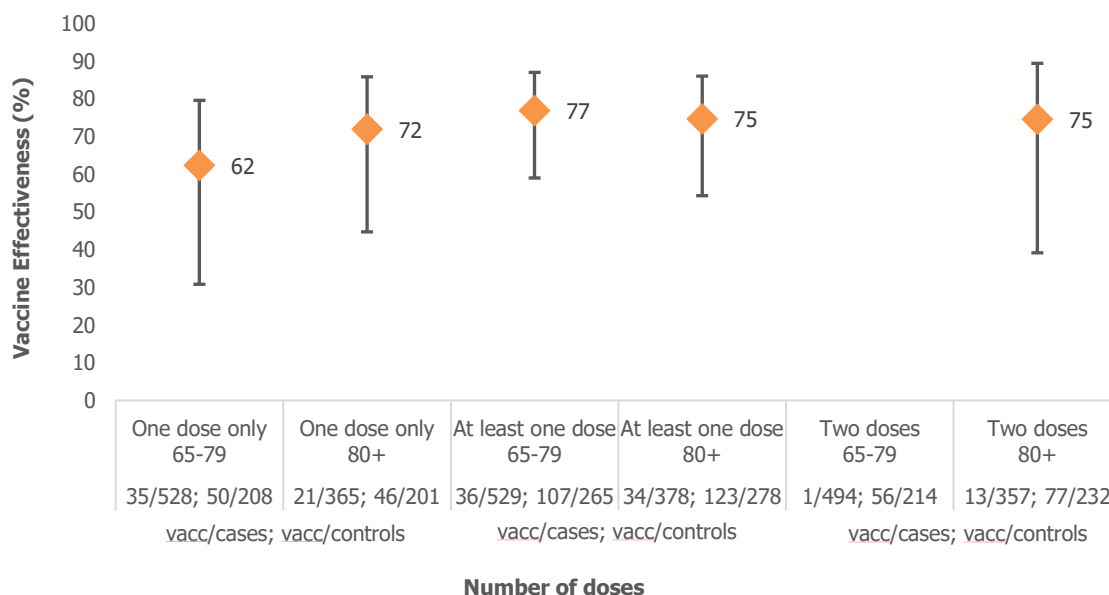
Source countries: Belgium, Spain, France, Croatia, Malta, Portugal
 vacc: Number of cases or controls that had received the specified number of vaccine doses (i.e. one dose only, at least one dose, two doses).
 VE estimates were adjusted by site, age group, month of sample, and seven common chronic conditions (diabetes, heart disease, chronic lung disease, immunodeficiencies, asthma, hypertension, obesity). One country with just one eligible case was excluded from the VE analysis (Czechia).

Figure 8. Overall vaccine effectiveness of the Comirnaty COVID-19 vaccine against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients aged 65 years and older at specimen collection date, by dose, six EU/EEA countries, 27 December 2020–30 June 2021 (n = 1 342)



Source countries: Belgium, Spain, France, Croatia, Malta, Portugal
 vacc: Number of cases or controls that had received the specified number of vaccine doses (i.e. one dose only, at least one dose, two doses).
 VE estimates are adjusted by site, age group, month of sample, and seven common chronic conditions (diabetes, heart disease, chronic lung disease, immunodeficiencies, asthma, hypertension, obesity). One country with just one eligible case was excluded from the VE analysis (Czechia).

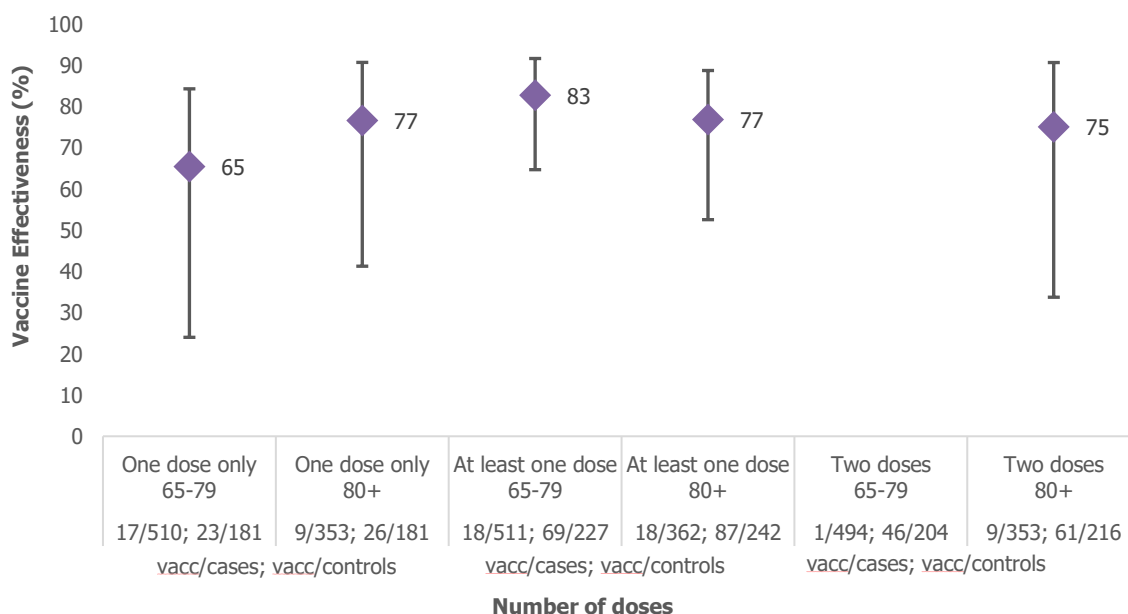
Figure 9. Vaccine effectiveness (any vaccine type) against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients aged 65 years and older at specimen collection date, by age group, six EU/EEA countries, 27 December 2020–30 June 2021 (n = 1 450)



Source countries: Belgium, Spain, France, Croatia, Malta, Portugal

vacc: Number of cases or controls that had received the specified number of vaccine doses (i.e. one dose only, at least one dose, two doses). VE estimates adjusted by site, age group, month of swab, seven common chronic conditions (diabetes, heart disease, chronic lung disease, immunodeficiencies, asthma, hypertension, obesity). One country with just one eligible case was excluded from the VE analysis (Czechia). Estimate not shown for two doses in the age group 65 to 79 years, as there was only one case in this group.

Figure 10. Vaccine effectiveness of Comirnaty vaccine against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients aged 65 years and older at specimen collection date, by age group, six EU/EEA countries, 27 December 2020–30 June 2021 (n = 1 342)



Source countries: Belgium, Spain, France, Croatia, Malta, Portugal

vacc: Number of cases or controls that had received the specified number of vaccine doses (i.e. one dose only, at least one dose, two doses). VE estimates adjusted by site, age group, month of swab, seven common chronic conditions (diabetes, heart disease, chronic lung disease, immunodeficiencies, asthma, hypertension, obesity). One country with just one eligible case was excluded from the VE analysis (Czechia). Estimate not shown for two doses in the age group 65 to 79 years, as there was only one case in this group.

Discussion and next steps

In this multi-country, test-negative study among hospitalised SARI patients aged 65 years and older (and eligible to receive the COVID-19 vaccine at the time of sample collection), interim results suggest a good VE against laboratory-confirmed SARS-CoV-2 for the COVID-19 vaccines deployed during the first six months of the vaccination campaign across EU/EEA countries. Effectiveness of complete vaccination (a full course with two doses of COVID-19 vaccine) was better than for a single dose, for those vaccines with a two-dose schedule.

As most of the population received the Comirnaty vaccine, the VE estimates presented mostly reflect the use of this vaccine. Stratified results by age groups indicated similar point estimates of VE in those aged 65 to 79 years and those aged 80 years and older, albeit with wide confidence intervals. The presented overall VE estimates for individuals aged 65 years and older are valid for the pre-Delta period. There have been a few peer-reviewed and preprint studies published with VE estimates in older adults and the results presented herein are within the range of these published data for mRNA vaccines [11,12].

Looking specifically at the VE estimates against severe COVID-19 infection in those aged 80 years and older, the presented estimates are slightly better than those previously published for this age group, albeit with wide confidence intervals. These must be interpreted with caution, as the sample size is low.

Additional analyses are expected to provide VE for hospitalised COVID-19 patients with different comorbidities, by different pandemic periods and at times of circulation of different variants (e.g. earlier variant versus Alpha variant of concern (VOC) versus Beta VOC or Gamma VOC), as well as by different delays from vaccination to symptom onset.

While this study included the ECDC clinical case definition for a SARI patient (possible COVID-19 case), further analysis and sensitivity analyses should be performed using the WHO SARI case definition, as included in the core ECDC protocol [1]. In addition, further assessment and considerations related to the test-negative study design and other study designs in a situation of high vaccination coverage is imperative, as the study and evaluation of VE progresses over time.

This ECDC multi-country study complements other international efforts to respond to COVID-19 VE questions, both globally and in Europe [12,13]. Similar approaches to data collection and study design can contribute to more comprehensive discussion on COVID-19 VE in real world conditions.

Contributing ECDC experts (in alphabetical order)

Sabrina Bacci, Nathalie Nicolay

Contributing external experts (in alphabetical order)

Epiconcept: Esther Kissling, Anthony Nardone, Angie Rose, Marta Valenciano

Acknowledgements

ECDC COVID-19 VE hospital study:

- **Belgium, Universitair Ziekenhuis Brussel:** L Seyler, T Demuyser
- **Belgium, Sciensano:** N Bossuyt, I Thomas, B Lissoir, K Magerman, M Bourgeois, N Fischer, N Dauby, M Reynders, S Denayer
- **France, Innovative Clinical Research Network In Vaccinology (REIVAC):** O Launay, F Laine, F Galtier, P Vanhems, Z Lesieur, N Lenzi, LB Luong, Y Saidi, S Amour, LB Luong
- **France, Santé publique France:** D Levy-Bruhl, A Pini, A Maisa, S Bernard-Stoecklin
- **Greece, National Public Health Organization:** S Michelaki, M Amerali
- **Croatia, National Institute of Public Health:** G Petrović, Z Lovrić Makarić, I Pem Novosel, P Smoljo
- **Czechia, Public Health Institute:** H Orliková
- **Czechia, University Hospital Brno:** P Husa, L Součková
- **Ireland, Health Protection Surveillance Centre:** L Domegan, A Cotter, N Petty Saphon, M Brady
- **Luxembourg, Ministry of Health:** N Aouali, G Fagherazzi, A Al Kerwi, F Berthet, M Alexandre
- **Malta, Health Promotion and Disease Prevention Directorate:** J Baruch, JP Cauchi, M-L Borg, A Dziugyte, T Melillo
- **Portugal, Instituto Nacional de Saúde Dr Ricardo Jorge:** B Nunes, A Machado, R Guiomar, A Rodrigues, V Gomez, I Kislaya, V Gaio
- **Spain, National Centre for Epidemiology (CNE), Carlos III Health Institute (ISCIII):** A Larrauri, C Mazagatos Ateca
- **Spain, National Centre of Microbiology (CNM), Carlos III Health Institute (ISCIII):** F Pozo, V Sandonis, I Casas

Disclaimer

All data published in this report are correct to the best of our knowledge at the time of publication.

References

1. European Centre for Disease Prevention and Control. Core protocol for ECDC studies of COVID-19 vaccine effectiveness against hospitalisation with Severe Acute Respiratory Infection laboratory-confirmed with SARS-CoV-2, version 1.0. Stockholm: ECDC; 2021. Available at: <https://www.ecdc.europa.eu/en/publications-data/core-protocol-ecdc-studies-covid-19-vaccine-effectiveness-against-hospitalisation>
2. Harder T, Koch J, Vygen-Bonnet S, Külper-Schiek W, Pilic A, Reda S, et al. Efficacy and effectiveness of COVID-19 vaccines against SARS-CoV-2 infection: interim results of a living systematic review, 1 January to 14 May 2021. *Euro Surveill.* 2021;26(28):2100563. Available at: <https://doi.org/10.2807/1560-7917.ES.2021.26.28.2100563>
3. European Centre for Disease Prevention and Control. Interim public health considerations for the provision of additional COVID-19 vaccine doses, 1 September 2021. Stockholm: ECDC; 2021. <https://www.ecdc.europa.eu/en/publications-data/covid-19-public-health-considerations-additional-vaccine-doses>
4. Pan American Health Organization, World Health Organization, Regional Office for the Americas. REVELAC-COVID-19 Generic protocol: Evaluation of the effectiveness of COVID-19 vaccines in Latin America and the Caribbean (DRAFT). Washington: WHO Regional Office for Americas; 2021. Available at: <https://www.paho.org/en/documents/revelac-covid-19-generic-protocol-draft>
5. European Centre for Disease Prevention and Control. Overview of the implementation of COVID-19 vaccination strategies and vaccine deployment plans in the EU/EEA – 29 March 2021. Stockholm: ECDC; 2021. <https://www.ecdc.europa.eu/sites/default/files/documents/Overview-implementation-COVID-19-vaccination-strategies-vaccine-deployment-plans.pdf>
6. European Centre for Disease Prevention and Control. Data on SARS-CoV-2 variants in the EU/EEA. Stockholm: ECDC; 2021. Available at: <https://www.ecdc.europa.eu/en/publications-data/data-virus-variants-covid-19-ueee>
7. Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. *Vaccine.* 2013;31(17):2165-8. Available at: <https://doi.org/10.1016/j.vaccine.2013.02.053>
8. European Centre for Disease Prevention and Control. ECDC possible COVID-19 case definition. Stockholm: ECDC; 2020. Available at: <https://www.ecdc.europa.eu/en/covid-19/surveillance/case-definition>
9. World Health Organization. Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases: Interim guidance. Geneva: WHO; 2020. Available at: <https://www.who.int/publications-detail/laboratory-testing-for-2019-novel-coronavirus-in-suspected-human-cases-20200117>
10. European Centre for Disease Prevention and Control. COVID-19 Vaccine Tracker. Stockholm: ECDC; 2021. Available at: <https://qap.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#uptake-tab>
11. Tenforde MW, Olson SM, Self WH, Talbot HK, Lindsell CJ, Steingrub JS, et al, IVY Network; HAIVEN Investigators. Effectiveness of Pfizer-BioNTech and Moderna Vaccines Against COVID-19 Among Hospitalized Adults Aged ≥65 Years - United States, January-March 2021. *MMWR Morb Mortal Wkly Rep.* 2021 May 7;70(18):674-679. Available at: https://www.cdc.gov/mmwr/volumes/70/wr/mm7018e1.htm?s_cid=mm7018e1_x
12. International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health and World Health Organization (WHO). Results of COVID-19 Vaccine Effectiveness Studies: An Ongoing Systematic Review - Weekly Summary Tables 2021. IVAC/WHO; 2021. Available at: <https://view-hub.org/covid-19/effectiveness-studies/>
13. WHO Regional Office for Africa. COVID-19 vaccine effectiveness against severe acute respiratory infections (SARI) hospitalisations associated with laboratory-confirmed SARS-CoV-2, WHO-AFRO Guidance Document based on the Draft WHO/EURO Guidance Document (version January 2021). Brazzaville: WHO Regional Office for Africa; 2021. Available at: https://www.afro.who.int/sites/default/files/2021-09/210428_AFRO_COVID19_VE_SARI_v1_clean_acknowl_final.pdf
14. World Health Organization Regional Office for Europe. Estimating COVID-19 vaccine effectiveness against severe acute respiratory infections (SARI) hospitalisations associated with laboratory-confirmed SARS-CoV-2: an evaluation using the test-negative design: guidance document. Copenhagen: WHO/Euro; 2021. Available at: <https://apps.who.int/iris/handle/10665/341111>