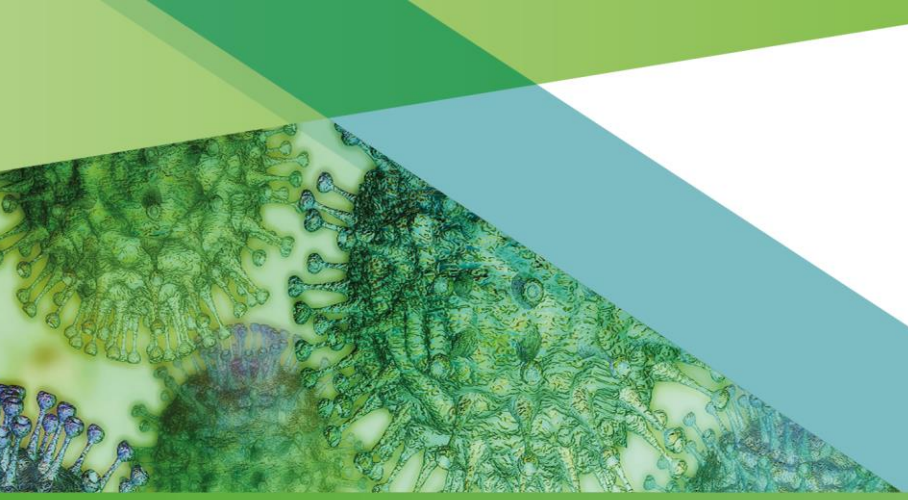


TECHNICAL REPORT

Interim analysis of COVID-19 vaccine effectiveness against Severe Acute Respiratory Infection due to laboratory-confirmed SARS-CoV-2 among individuals aged 50 years and older, ECDC multi-country study – first update

20 January 2022

Key facts

- ECDC is building infrastructure to allow regular monitoring of COVID-19 vaccine effectiveness over time, using a multi-country approach that involves studies implemented in different settings [1,2].
- This update reports on one of the ECDC multi-country studies that is centred around the hospital setting and severe disease, with the aim of assessing vaccine effectiveness against severe acute respiratory infection (SARI) due to laboratory-confirmed SARS-CoV-2.
- A total of 10 EU countries are participating in the multicentric study (Belgium, Croatia, Czechia, France, Greece, Ireland, Luxembourg, Malta, Portugal, Spain).
- As the study is ongoing, this report contains updated results following those previously published on 8 October 2021 [3].
- In this second report, results for the 50-64 years age group have been added. One of the conditions for individuals to be included in the study was their eligibility for COVID-19 vaccination. For this reason, when the study started, only older age groups could be included. As the study continues and countries extend their vaccination programmes across their entire adult populations, more individuals will be eligible to be included, which is expected to lead to an increased sample size.
- The COVID-19 vaccine effectiveness estimates presented are pooled estimates from six countries.
- Most individuals enrolled in the study received COVID-19 mRNA vaccine Comirnaty (Pfizer/BioNTech). The effectiveness of a full vaccination course (two doses) was higher than for partial vaccination (a single dose for those vaccines with a two-dose schedule) in all available age groups.
- The results presented in this report suggest a high vaccine effectiveness in preventing SARI associated with laboratory-confirmed SARS-CoV-2 for COVID-19 vaccines deployed during the first six months of the vaccination campaign across EU/EEA countries in all age groups 50 years and older, albeit with wide confidence intervals. The adjusted vaccine effectiveness against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients observed ≥14 days after full vaccination with any vaccine product was 90% (95% confidence interval (CI): 83-95%) (Figure 7). Results of the analysis by age group showed that adjusted vaccine effectiveness was higher in those aged 50-64 years than in older age groups. The adjusted vaccine effectiveness for Comirnaty observed ≥14 days after full vaccination (two doses) was 94% (95% CI: 88-97%).
- Estimated results were in the range of estimates published in other studies for similar outcomes in this population during the pre-Delta period [4-6].
- More extensive analyses are planned in future stages of the study to assess factors that may affect vaccine effectiveness, such as different variants and the length of time since vaccination.

Suggested citation: European Centre for Disease Prevention and Control. Interim analysis of COVID-19 vaccine effectiveness against Severe Acute Respiratory Infection due to laboratory-confirmed SARS-CoV-2 among individuals aged 50 years and older, ECDC multi-country study – first update. ECDC: Stockholm; 2022.

Executive summary

Evaluating the real-world performance of COVID-19 vaccines is critical to understanding the risks and benefits of COVID-19 vaccination programmes. ECDC has been building infrastructure to allow regular monitoring of COVID-19 vaccine effectiveness over time, using a multi-country approach that involves studies implemented in different settings across EU/EEA countries. The project allows for progressive inclusion of more countries over time and the same generic protocol is used across all countries.

This update reports on a multi-country study that aims to estimate vaccine effectiveness against severe COVID-19 disease, by assessing it in individuals hospitalised for SARI. This ECDC hospital vaccine effectiveness study began at the end of 2020 and, as of 25 October 2021, has recruited 10 participating countries across the EU/EEA (Belgium, Croatia, Czechia, France, Greece, Ireland, Luxembourg, Malta, Portugal and Spain), including 42 hospitals among them (ranging from 1 to 13 hospitals per country). Five countries began their vaccination campaigns at the end of December 2020 and five in early January 2021. The analysis presented in this report aims to estimate vaccine effectiveness among SARI patients aged 50 years and older, from the first vaccination campaign start date on 27 December 2020 up to and including 30 June 2021. This end date was selected to provide a study period before wide circulation of the Delta variant of concern (VOC) in the European region.

By 25 October 2021, eight countries had submitted data at least once. However, only seven countries submitted data for the study period (up to 30 June 2021) and only six reported enough cases to be included in the vaccine effectiveness estimates, as the total number of SARI patients in one country was too low (<5 patients). For the next round of analyses, taking place in January 2022, all 10 countries should have submitted their data.

Data for the descriptive analysis included 1 893 SARI patients (1 258 cases and 635 controls) from 25 hospitals in seven of the eight countries. A majority of cases and controls were male (58% and 55%, respectively; p=0.201). The median age of cases (72 years) was younger than for controls (76 years). One-third of cases (33%) and 43% of controls were aged 80 years or older (p<0.001). More controls than cases had at least one chronic condition (73% vs 53%; p<0.001) and were vaccinated (41% vs 7%; p<0.001). The median delay from first dose to onset of SARI symptoms was more than twice as long for controls than cases (57 vs 26 days; p<0.001), while the delay from second dose to onset of symptoms was not significantly longer in controls than cases (50 vs 41 days; p=0.494). Median delays between first and second doses were identical (21 days) in the two groups.

The adjusted vaccine effectiveness against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients observed ≥14 days after only one dose of any vaccine product was 72% (95% CI: 58-81%). The vaccine effectiveness observed ≥14 days after being fully vaccinated with any vaccine product (one dose for COVID-19 Vaccine Janssen and two doses for all others) was 90% (95% CI: 83-95%). Age-stratified results showed that adjusted vaccine effectiveness was higher in those aged 50-64 years than in the older age groups (for those receiving one dose only, vaccine effectiveness was 85% (95% CI: 64-93) in the youngest included age group and 73% (95% CI: 45-87) for those aged 80 years and older). Very small numbers of fully vaccinated cases in the younger age groups makes these vaccine effectiveness estimates difficult to interpret.

Among the 349 vaccinated SARI patients, most received a two-dose vaccine, the most common product being Comirnaty (Pfizer/BioNTech): 51/91 vaccinated cases (56%) and 196/258 vaccinated controls (76%). Adjusted vaccine effectiveness was estimated for this product only: 76% (95% CI: 61-86%) for a single dose and 94% (CI: 88-97%) for those receiving both doses. Age-stratified results were very similar to those for any vaccine product, as Comirnaty was the predominant product used.

Very few genetic sequencing results (n = 21, from two countries) were received. Most (18; 86%) were the Alpha variant (B.1.1.7). Provision of genetic sequencing results was one of the major challenges experienced during the study period. Going forward, addressing individual site sequencing issues is a priority with regards to the implementation of the study. The representativeness of an increasingly smaller pool of unvaccinated controls compared with those from earlier in the study period needs to be further investigated. Some sites were unable to recruit many controls, as their participating hospital(s) were overwhelmed with COVID-19 cases. The very small numbers of vaccinated cases over the study period makes interpretation of some of the estimates (particularly in subgroups) difficult, although it is a sign that vaccination is effective in preventing hospitalisation.

The establishment of this multi-country study in the various sites has provided a powerful platform to monitor and further investigate vaccine effectiveness, as well as inform the development of key vaccine policy issues in 2022. Continuation and expansion of this vaccine effectiveness study to other countries and hospitals is vital to maintain and further enhance this important work. Pooling of data with other multi-centre studies following similar protocols is ongoing (with the I-MOVE-COVID-19 hospital vaccine effectiveness study) or being considered (with the WHO Regional Office for Europe hospital vaccine effectiveness study), as appropriate, and may allow the calculation of more precise estimates. Additional analyses and bilateral site meetings are also planned to address sequencing barriers, as well as site visits to understand the potential for heterogeneity across the different countries.

Scope of this document

This document reports the pooled estimates from the ECDC study of COVID-19 vaccine effectiveness, 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* [2].

In a report published on 8 October 2021 [3], the first interim pooled estimates of COVID-19 vaccine effectiveness against SARI due to laboratory-confirmed SARS-CoV-2 among hospitalised individuals aged 65 years and older were calculated for all COVID-19 vaccines deployed, across the participating EU/EEA countries.

As the study is ongoing, interim analyses are being conducted on a regular basis. Pooled estimates are from patients recruited across several hospital study sites in the EU/EEA. Compared to the previous interim report, the current update includes vaccine effectiveness results in the 50-64 years age group [3]. These estimates cover the pre-Delta period, adding further evidence to the existing literature on COVID-19 vaccine effectiveness during this time in age groups above 50 years old.

While vaccine effectiveness 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 [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. As of 23 October 2021, over 39 million cases and almost 5 million deaths were reported in the EU/EEA [7].

International collaborative efforts have accelerated the development of COVID-19 vaccines. As of 29 October 2021, 128 candidate vaccines were in clinical development and 194 were in preclinical development [8]. As of 20 December 2021, five COVID-19 vaccines – all of which are spike protein based – were given conditional marketing authorisation within the EU/EEA by the European Commission, based on the scientific opinion of the European Medicines Agency [9-10]: Comirnaty (BNT162b2), Spikevax (mRNA-1273), Vaxzevria (AZD1222), COVID-19 Vaccine Janssen (Ad26.COV 2.5) and Novavax's COVID-19 vaccine Nuvaxovid (NVX-CoV2373). All vaccine products authorised in the EU/EEA were initially registered for use in people aged 18 years and older, with the exception of Comirnaty (approved for those aged 16 years and older). Comirnaty and Spikevax indications were first extended to include children aged 12-15 years and 12-17 years, respectively, and subsequently Comirnaty was extended further to include children aged 5-11 years [10].

In the context of limited vaccine supplies, target groups for the prioritisation of COVID-19 vaccination have been established [11,12], with many European countries initially rolling out vaccines to vulnerable populations (e.g. older adults, those in long-term care, those with comorbid conditions leading to greater vulnerability to COVID-19, and/or healthcare workers) [13]. ECDC has been summarising this information and publishing it regularly [11].

Many factors impact real-world vaccine effectiveness, including vaccine transportation and storage, as well as how patients are vaccinated. In addition, people recruited to vaccine clinical trials are often young and healthy, and therefore may differ from those who will actually receive the vaccines [13]. Real-world vaccine effectiveness studies can also answer questions about effectiveness by age group and risk factors, duration of vaccine protection, protection against transmission, relative effectiveness of different vaccines, relative effectiveness of a full vaccination course versus partial vaccination and the timing of additional doses, and effectiveness of the vaccine against new SARS-CoV-2 variants.

Objectives of the multi-country study

As presented in the core ECDC protocol [2], the primary objective of this vaccine effectiveness study is:

- 'To measure, within each European participating 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 and over), COVID-19 vaccination prioritized target group, time since vaccination and regularly over calendar time, vaccine doses number 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, the role of long-term medications (depending on availability of these data in the participating country).'

These three secondary objectives are aimed at understanding the duration of protection of vaccines and identifying any differences in vaccine effectiveness among each of these strata, potential target groups for vaccination, and key SARS-CoV-2 virus phenotypic or genotypic changes that could affect vaccine performance.

Objectives of the analysis presented in this document

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 50 years and older who received:

- at least one dose (one or two doses of the two-dose vaccine course or one dose of the single-dose vaccine course),
- partial vaccination (one dose only, for the two-dose vaccine course), or
- full vaccination (one or two doses, as per manufacturer's recommendation).

Methods

Study design

This is a multi-centre, hospital-based, test-negative, case-control study, using pooled data from several countries.

Study population

This hospital-based vaccine effectiveness study was conducted primarily in countries with pre-existing SARI surveillance systems, to facilitate the recruitment of patients. Therefore, the study population comprised individuals of all ages who belonged to the target group for vaccination, were hospitalised with SARI symptoms in participating hospitals/services and had no contraindication for COVID-19 vaccination.

Inclusion criteria

All SARI patients who consented to participate (where this is a requirement) and were not part of the exclusion criteria were included in the study.

Exclusion criteria

Patients were not enrolled in the study if they:

- were unwilling to participate or unable to communicate and give consent (the consent could also have been provided by their legal representative or by specific consent procedures that are acceptable according to the local ethical review process);
- had a contraindication for the COVID-19 vaccine;
- could not be swabbed due to severe septum deviation, obstruction or other conditions that contraindicate; or
- had a history of hospitalisation within the 14 days immediately prior to this admission (including transfers from other hospitals).

Patients were not included in this analysis if they:

- tested negative on admission, but had a previous positive SARS-CoV-2 RT-PCR result >14 days before admission;
- were living in a long-term care facility (LTCF);
- had errors in vaccination dates (e.g. first dose date was later than second dose date) or a non-recommended delay between the doses for two-dose regimens (<21 days for Comirnaty, <28 days for Vaxzevria or Spikevax);
- had onset of SARI symptoms >3 days after their swab;
- were swabbed >10 days after onset of symptoms; or
- received the first or second vaccine dose within 14 days of onset of symptoms.

Exposure

An individual was considered vaccinated against COVID-19 with a product-specific vaccine during the current pandemic under the following categories:

- **Fully vaccinated with a two-dose vaccine:** patients were considered fully vaccinated if they **received both doses** at least 14 days before onset of symptoms.
- **Fully vaccinated with a single-dose vaccine:** patients were considered fully vaccinated if they **received one dose** at least 14 days before onset of symptoms.
- **Partially vaccinated (two-dose vaccine only):** patients were considered partially vaccinated if they **received one of two doses** at least 14 days before onset of symptoms or received a second dose on the same day as or after onset of symptoms.
- **Unvaccinated:** patients were considered unvaccinated if they did not receive a COVID-19 vaccine or if they were vaccinated on the same day as or after onset of symptoms.

Definitions of outcomes

The outcome of interest for the primary analysis was SARS-CoV-2 infection that was laboratory confirmed by RT-PCR (documented either on admission to hospital or within 14 days before admission) in patients of all ages who were hospitalised with SARI symptoms.

Secondary outcomes of interest, in the same patient group, were laboratory-confirmed infections with genetic variants of SARS-CoV-2 and confirmed SARS-CoV-2 infections in patients with severe outcomes (ICU admission, invasive ventilation, death).

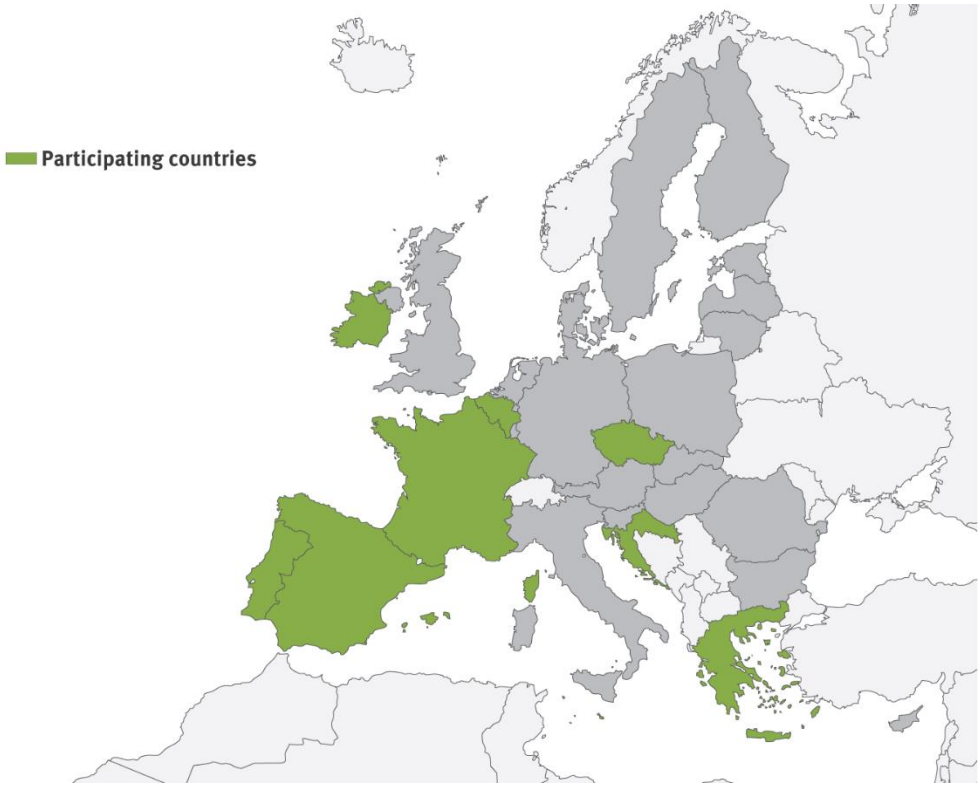
Analysis

The vaccine effectiveness estimated in this analysis was among hospitalised SARI patients aged 50 years and older, who were swabbed between the start of the vaccination campaign in their country and 30 June 2021. Vaccine effectiveness is calculated as 1 minus the odds ratio (OR), where the OR is estimated from logistic regression (OR is the ratio of the odds of being vaccinated among cases over the odds of being vaccinated among controls). Study site (country) was included in the logistic regression as a fixed effect, with date of swab modelled as swab month. Additional adjustments included sex, age group (as a categorical variable), and at least one of four commonly collected chronic conditions (diabetes, heart disease, lung disease and asthma). For the age-specific vaccine effectiveness estimates, SARI patients were stratified into three age groups: 50-64, 65-79 and ≥80 years.

Enrolment of countries in the study

As of 25 October 2021, a total of 42 hospitals across 10 countries (Belgium, Croatia, Czechia, France, Greece, Ireland, Luxembourg, Malta, Portugal and Spain; Figure 1) were participating in the study. Two countries (Ireland and Luxembourg) were unable to submit data by the deadline to be included in this report. The earliest vaccination campaign start date among the 10 countries was 27 December 2020 (for five countries; see Table 1).

Figure 1. Map of the 10 participating EU/EEA countries, ECDC multi-country COVID-19 vaccine effectiveness study among hospitalised SARI patients, as of 25 October 2021



Ethical approval has been obtained by all 10 countries. Eight countries have started to recruit SARI patients, with start dates ranging from the end of December 2020 through to the most recent in late July 2021. One of the remaining two countries started recruitment in November 2021 and the last will start in January 2022 (Table 1).

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

Country	Participating Hospitals	Vaccination campaign start date	Study start date	Start of dominance of the Delta variant
Belgium	Cliniques universitaires (UCL)	5 Jan 2021	15 Jan 2021	Week 25 2021
	Algemeen Ziekenhuis Sint-Jan Bugge-Oostende			
	Centre Hospitalier Universitaire Saint-Pierre			
	Universitair Ziekenhuis Brussel			
	Jessaziekenhuis			
	Grand Hôpital de Charleroi			
Croatia	Clinical Hospital Centre Split	27 Dec 2020	1 Feb 2021*	Week 27 2021
	Zabok General Hospital and Croatian Veterans Hospital			
	Clinical Hospital Centre Rijeka			
Czechia	University Hospital Brno	28 Dec 2020	20 Jul 2021	Week 25 2021
France	CIC Cochin Hospital	27 Dec 2020	1 Jan 2021	Week 26 2021
	CIC Montpellier University Hospital			
	CIC Rennes University Hospital			
Greece	Hippocratio General Hospital	27 Dec 2020	1 Jul 2021	Week 27 2021
Ireland	Saint Vincent's University Hospital	29 Dec 2020	Jan 2022 (expected)	Week 25 2021
Luxembourg	Centre Hospitalier de Luxembourg (CHL)	29 Dec 2020	2 Nov 2021	Week 24 2021
Malta	Mater Dei Hospital	1 Jan 2021	1 Feb 2021	Week 26 2021
Portugal	Centro Hospitalar de Setúbal (CHS)	27 Dec 2020	2 Feb 2021	Week 23 2021
	Centro Hospitalar e Universitário de Lisboa Norte (CHULN)			
	Centro Hospitalar e Universitário de Lisboa Central (CHULC)			
Spain	Hospital Universitario Virgen de las Nieves – Andalucía	27 Dec 2020	27 Dec 2020	Week 27 2021
	Hospital Universitario Miguel Servet – Aragón			
	Hospital Universitario Son Espases – Illes Balears			
	Hospital Clínico Universitario de Valladolid – Castilla y León			
	Hospital Universitario de Burgos – Castilla y León			
	Hospital Clinic de Barcelona – Catalunya			
	Hospital Sant Joan de Déu Barcelona – Catalunya			
	Hospital Clinico Universitario de Santiago – Galicia			
	Hospital Universitario La Paz – Comunidad de Madrid			
	Hospital Universitario Ramón y Cajal – Madrid			
	Hospital Universitario Gregorio Marañón – Madrid			
	Hospital San Pedro – La Rioja			
	Hospital Clínico Universitario Virgen de la Arrixaca – Murcia			

**Retrospective data collection.*

Vaccination roll-out against SARS-CoV-2

By early January 2021, all EU/EEA countries had started their vaccination campaigns. Comirnaty was the first vaccine that received authorisation for use in the EU/EEA (on 21 December 2021), 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 on 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 addition of other high-risk populations, such as people with underlying conditions and essential workers.

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 first and second dose if vaccine supplies did not cover their needs.

As of week 26 2021 (28 June to 4 July, in accordance with the study end date of 30 June 2021), about 50% of adults aged 50 years and older in the EU/EEA had received at least one dose of a COVID-19 vaccine and 70% had been fully vaccinated (Table 2).

Table 2. Vaccination uptake of at least one dose/full vaccination* in participating EU/EEA countries, as of week 26 (ending 4 July 2021)

Country	Adult population (≥18 years)	Age group			
		50-59 years	60-69 years	70-79 years	≥ 80 years
	At least one dose/ full vaccination	At least one dose/ full vaccination	At least one dose/ full vaccination	At least one dose/ full vaccination	At least one dose/ full vaccination
Belgium	80.8/45.9	87.1/8.5	81.1/70.7	85.3/77.4	85.3/86
Croatia	45.3/35.9	50/38.6	63.7/53.4	70.7/63.7	54.7/50.3
Czechia	58.7/40.5	64.8/52.7	71.5/61.3	85.2/77	81.7/76.2
France	66.2/42.8	70.3/45.1	78.4/60.5	90/78.7	80.4/71
Greece	55.9/44.6	65.1/55.1	74.1/68.1	78.8/75.2	69.8/66.9
Ireland	70.7/52.3	95.9/88.8	98.2/67.2	100/100	100/100
Luxembourg	67/48.5	76.8/73.0	81.8/79.7	84.8/83	85.3/83.4
Malta	83.6/78.8	85.1/80.3	94.4/91.1	100/100	100/100
Portugal	67.6/43.9	86.4/57.2	96.7/68.8	100/81.1	99.2/94.9
Spain	68.5/48.6	89.5/79.4	94.6/53.9	98.1/97	100/100
EU/EEA Total	**63.7/43.4 (Overall)**	**70.3/48.5 (Median)**	**81.1/61.3 (Median)**	**85.3/77.4 (Median)**	**85.3/83.4 (Median)**

Source: ECDC Vaccine Tracker [5]
** Full vaccination is defined according to the manufacturer's instructions for each vaccine product.*

Results

Descriptive analysis[1]

Hospital and SARI patient recruitment

As of 25 October 2021, data were available from 25 hospitals in eight countries: Belgium (3 hospitals), Croatia (2), Czechia (1), France (3), Greece (1), Malta (1), Portugal (3) and Spain (11). Among eight countries that submitted data, one only submitted data for patients admitted after 30 June 2021 and was therefore excluded from the current analysis.

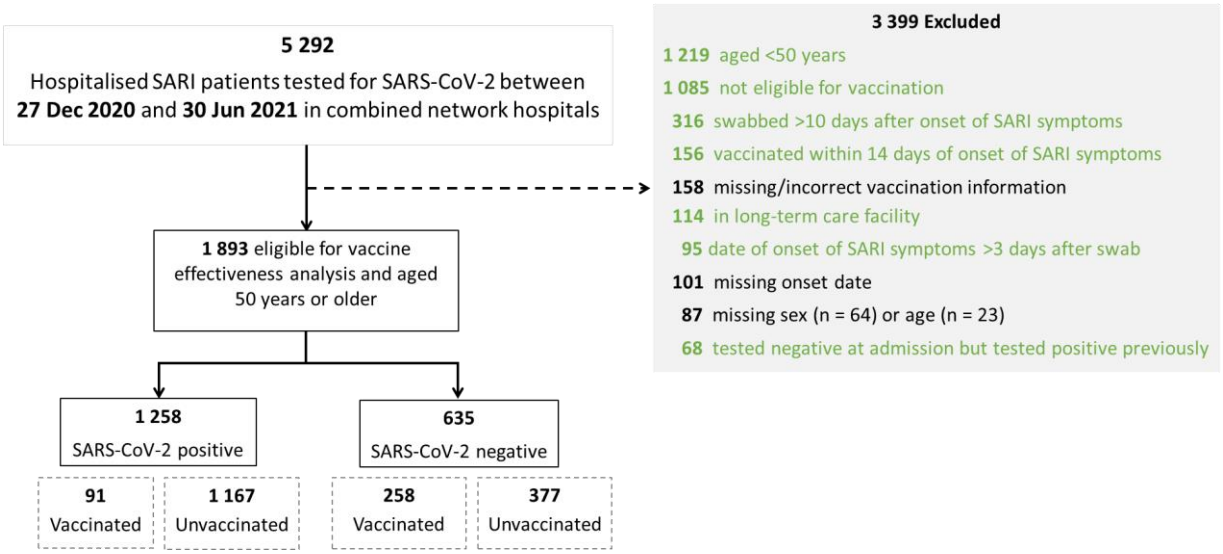
[1] It should be noted that all data presented in this section are provisional and remain open to correction and further revision by study sites.

By 25 October 2021, there were 12 900 records submitted from 8 of the 10 countries. This analysis estimates vaccine effectiveness among SARI patients aged 50 years and older, from the first vaccination campaign start date (27 December 2020; Table 1) up to 30 June 2021. The end date was selected to provide a study period before wide circulation of the Delta VOC in the European region [15]. A separate analysis is being undertaken for the Delta period, for SARI patients swabbed between July and October 2021. After excluding 7 608 records for patients that did not have an RT-PCR test or had a missing RT-PCR test result (4 009), were recruited outside of the study period (2 520), or were not SARI patients (1 078), as well as a duplicate record (1), there were 5 292 records from SARI patients within the study period. Of these, a further 3 399 were excluded from this analysis (1 219 were <50 years, 1 085 were not part of a vaccine target group at the time of their swab (and were therefore ineligible for inclusion in the study), 336 were missing key variable information (age, sex, swab date, and vaccine dates), 316 were swabbed >10 days after onset of symptoms, 156 had onset within 14 days of their first or second vaccine dose, 114 lived in long-term care facilities, 95 had onset >3 days after their swab, 68 were controls with a prior positive result, and 10 had errors in vaccination date or a non-recommended delay between their two vaccine doses). This left 1 893 eligible to be included in the vaccine effectiveness estimation (Table 3 and Figure 2; see Table A1 in the Annex for details of exclusions by country).

Table 3. Number of submitted records, exclusions and inclusions for vaccine effectiveness estimates among SARI patients aged 50 years and older, from the start of the vaccination campaign in each country to 30 June 2021, by participating EU/EEA country

Country	Number of submitted records	Number of exclusions	Total number of included records in vaccine effectiveness analysis	Number of cases	Number of controls
Belgium	1 234	985	249	130	119
Croatia	1 648	1 063	585	517	68
Czechia	14	13	1	1	0
France	704	400	304	153	151
Greece	21	21	0	0	0
Ireland	0	0	0	0	0
Luxembourg	0	0	0	0	0
Malta	710	543	167	77	90
Portugal	77	42	35	19	16
Spain	8 492	7 940	552	361	191
Total	**12 900**	**11 007**	**1 893**	**1 258**	**635**

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



Analysis exclusions are indicated in green text.

Hospitalised SARI patient characteristics

The 1 893 eligible hospitalised SARI patients were from 7 of the 10 participating countries (one country that submitted data had no SARI patients eligible for the study, as all fell outside of the study period). A little over one-third (691; 37%) of the hospitalised SARI patients from participating countries were aged 80 years and older. Nearly one in four cases (305; 24%) and one in five controls (117; 18%) were <65 years of age. More than half were male (727 cases; 58% and 347 controls; 55%). More controls than cases (464 controls; 73% vs 660 cases; 53%) had at least one of four commonly collected chronic conditions (diabetes, heart disease, lung disease or asthma), and more controls were vaccinated (258 controls; 41% vs 91 cases; 7%) (Table 4).

The median time between receiving the first and second vaccine doses was 21 days for both cases and controls, as per vaccine administration recommendations (Table 4). The longest delays between doses were 42 days for cases and 70 days for controls (Figure 3). The median number of days from the administration of the first vaccine dose to the onset of SARI symptoms was greater in controls (57 days) than cases (26 days; $p<0.001$) (Table 4). Over half of cases (53; 58%) and almost one in five controls (46; 18%) had between 14 and 30 days delay between the first dose and onset of symptoms. A similar proportion of cases (11; 58%) vs 64 controls (44%) had a delay of between 14 and 45 days between the second dose and onset of symptoms (Figures 4 and 5).

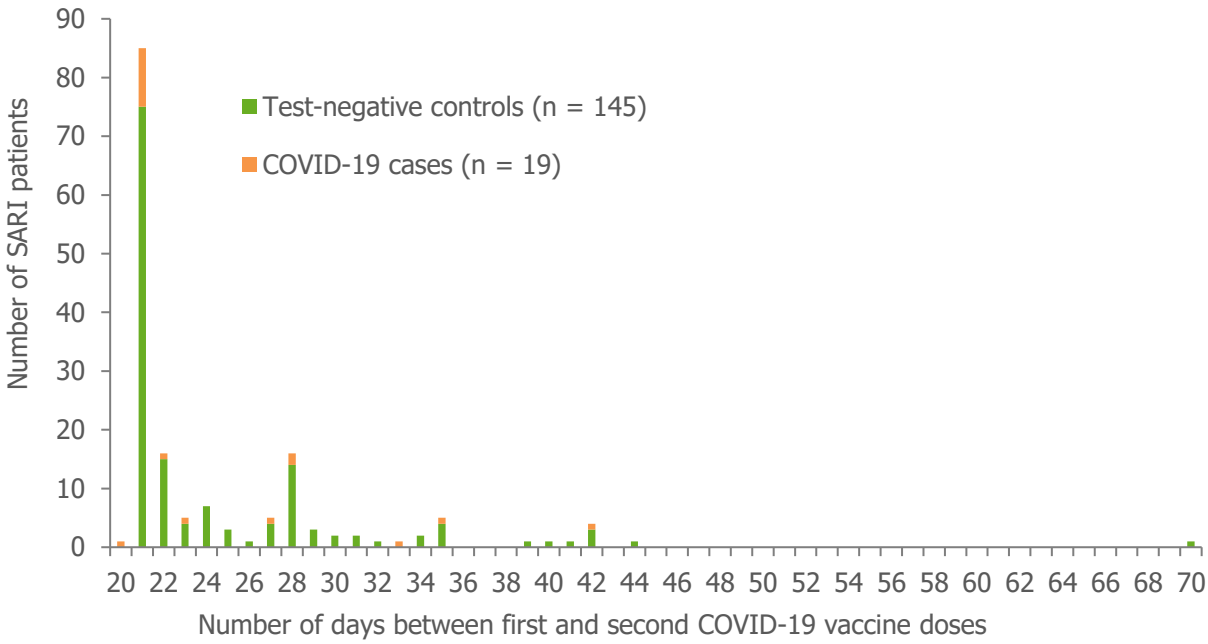
The number of eligible cases recruited into the study between week 53 2020 and week 27 2021 peaked in week 14, at 141 cases. The number of recruited controls fluctuated by week, with a low of <10 swabbed per week between the end of 2020 and week 3 2021, and a high of 39 in week 23 2021. Most vaccinated SARI patients received their vaccine between weeks 6 and 16 (Figure 6).

Table 4. Characteristics of eligible SARI patients in EU/EEA participating countries[a], ECDC multi-country COVID-19 vaccine effectiveness study among hospitalised SARI patients, 27 December 2020–30 June 2021 (n = 1 893)

Characteristics		Cases n (%)	Controls n (%)	p-value
Sex	Male	727 (57.8)	347 (54.6)	0.201
	Female	531 (42.2)	288 (45.4)	
Age (years)	Median	72	76	–
	50–64	305 (24.2)	117 (18.4)	<0.001[b]
	65–79	553 (42.4)	247 (38.9)	
	≥80	420 (33.4)	271 (42.7)	
Any of the four chronic conditions[c]	Yes	660 (52.5)	464 (73.1)	<0.001[b]
	No	598 (47.5)	171 (26.9)	
COVID-19 vaccination status[e]	Unvaccinated	1 167 (92.8)	377 (59.4)	–
	Partially vaccinated	72 (5.7)	112 (17.6)	0.0189
	Fully vaccinated	19 (1.5)	146 (23.0)	0.0291
Number of COVID-19 vaccine doses administered	None	1 167 (92.8)	377 (59.4)	–
	At least one dose	72 (5.7)	113 (17.8)	
	Two doses	19 (1.5)	145 (22.8)	
Median time delay in days (IQR)	From first dose to onset of symptoms	26 (20–52)	57 (35–82)	<0.001[d]
	From second dose to onset of symptoms	41 (36–57)	50 (30–80)	0.494[d]
	From first to second dose	21 (21–28)	21 (21–27)	0.838[d]

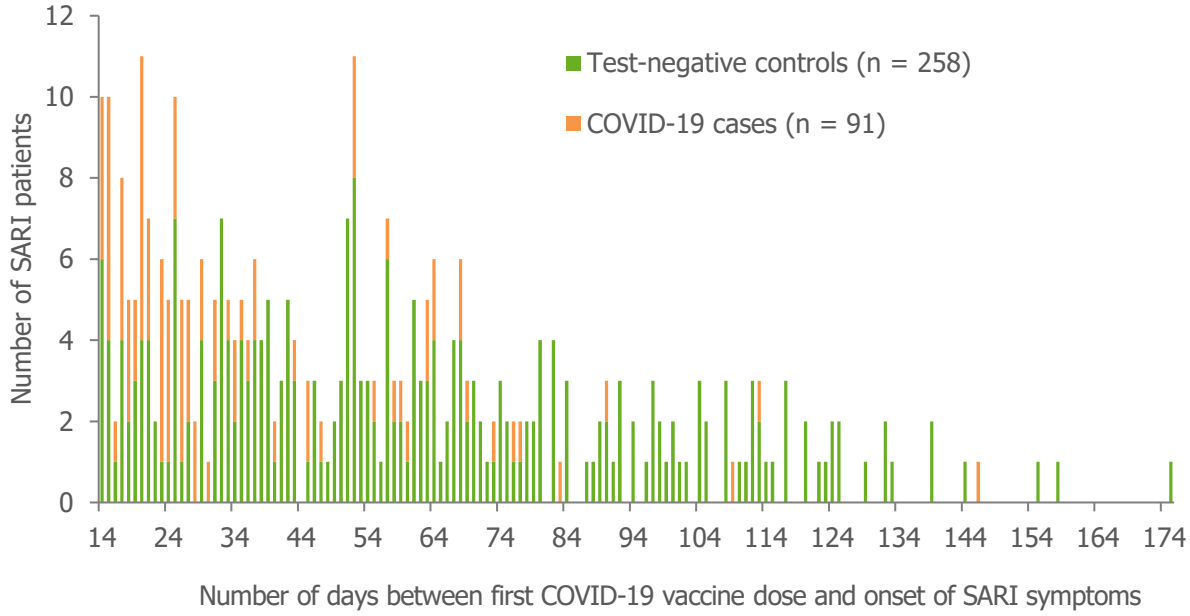
[a] Seven participating countries submitted eligible data by 25 October 2021: Belgium, Croatia, Czechia, France, Malta, Portugal and Spain.
[b] Fisher's exact.
[c] The four chronic conditions are: diabetes, heart disease, lung disease and asthma.
[d] Wilcoxon rank-sum (Mann-Whitney).
[e] Patients were considered fully vaccinated if they received both doses of a vaccine with a two-dose course or one dose of a vaccine with a one-dose course at least 14 days before onset of symptoms. Patients were considered partially vaccinated if they had received only one dose of a vaccine with a two-dose course at least 14 days before onset of symptoms.

Figure 3. Number of days between first and second COVID-19 vaccine doses among cases and controls, pooled data for ECDC multi-country COVID-19 vaccine effectiveness study among hospitalised SARI patients, seven EU/EEA countries*, 27 December 2020–30 June 2021 (n = 164)



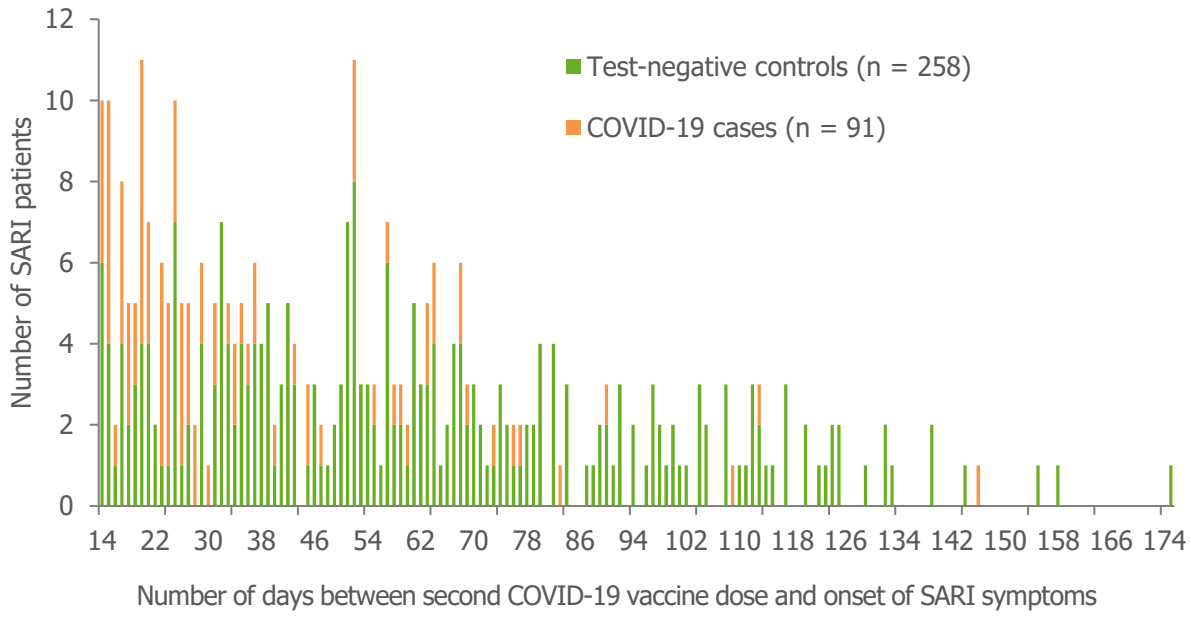
** Data from one participating EU/EEA country were excluded from this vaccine effectiveness analysis because the sample size was too small (<5 cases and controls).*

Figure 4. Number of days between first COVID-19 vaccine dose and onset of symptoms among cases and controls, pooled data for ECDC multi-country COVID-19 vaccine effectiveness study among hospitalised SARI patients, seven EU/EEA countries*, 27 December 2020–30 June 2021 (n = 349)



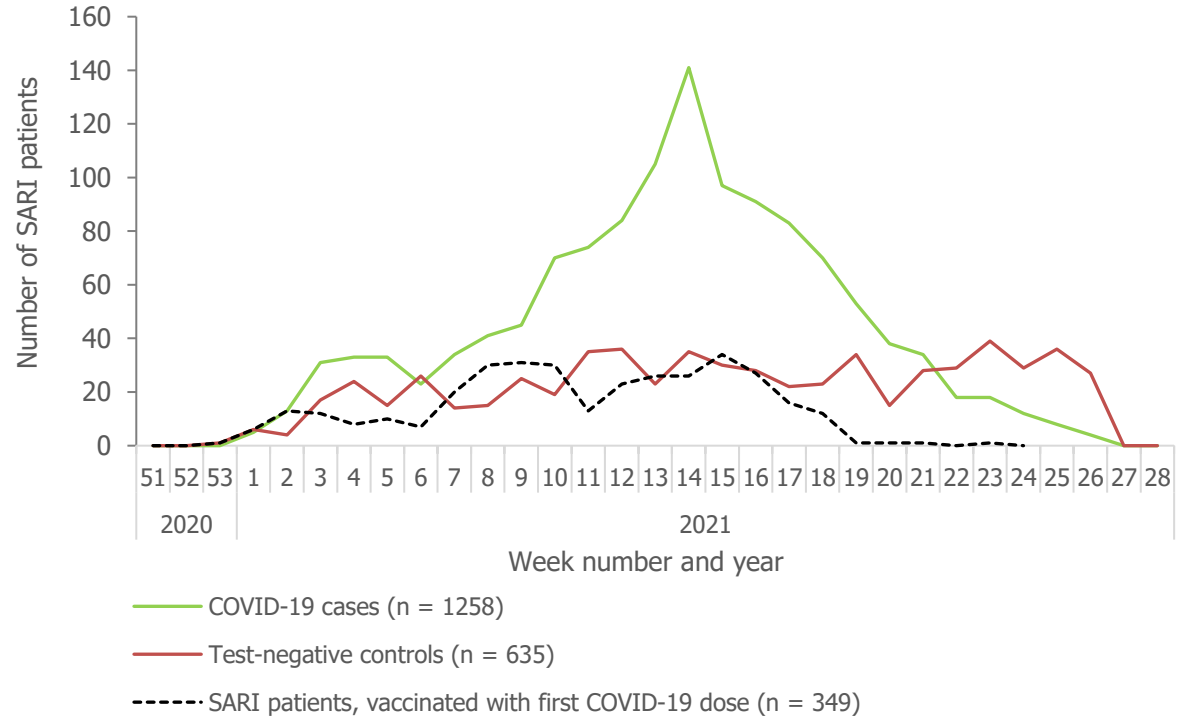
** Data from one participating EU/EEA country were excluded from this vaccine effectiveness analysis because the sample size was too small (<5 cases and controls).*

Figure 5. Number of days between second COVID-19 vaccine dose and onset of symptoms among cases and controls, pooled data for ECDC multi-country COVID-19 vaccine effectiveness study among hospitalised SARI patients, seven EU/EEA countries*, 27 December 2020–30 June 2021 (n = 164)



** Data from one participating EU/EEA country were excluded from this vaccine effectiveness analysis because the sample size was too small (<5 cases and controls).*

Figure 6. Number of cases and controls by ISO week of specimen collection and number of patients vaccinated by ISO week of vaccination, ECDC multi-country COVID-19 vaccine effectiveness study among hospitalised SARI patients, seven EU/EEA countries*, 27 December 2020–30 June2021 (n = 1 893)



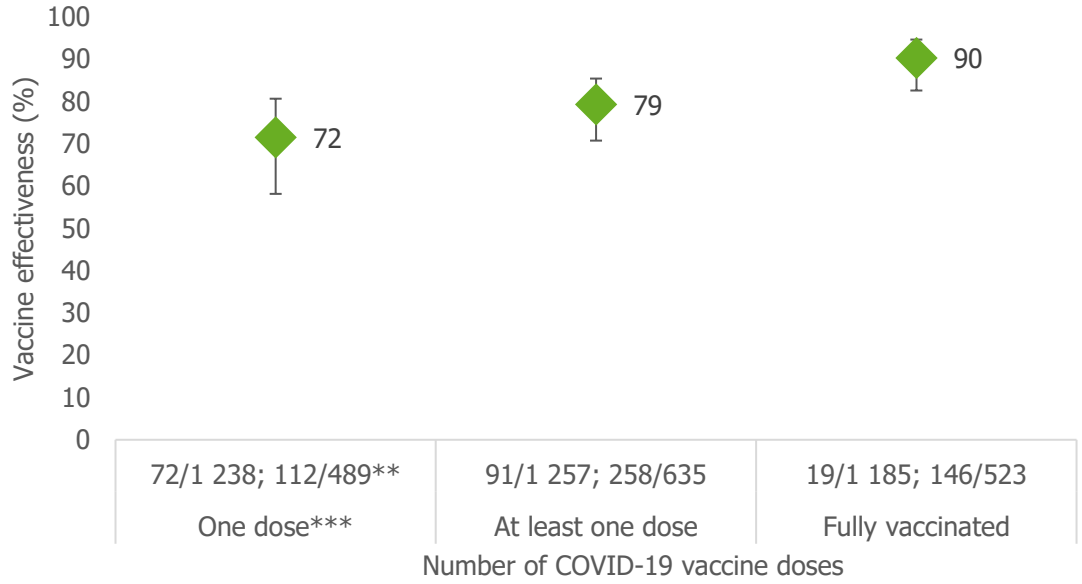
** Data from one participating EU/EEA country were excluded from this vaccine effectiveness analysis because the sample size was too small (<5 cases and controls).*

COVID-19 vaccine effectiveness estimates (any vaccine product)

The adjusted vaccine effectiveness against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients observed ≥14 days after only one dose of any vaccine product was 72% (95% CI: 58-81%). The vaccine effectiveness observed ≥14 days after full vaccination with any vaccine product was 90% (95% CI: 83-95%) (Figure 7).

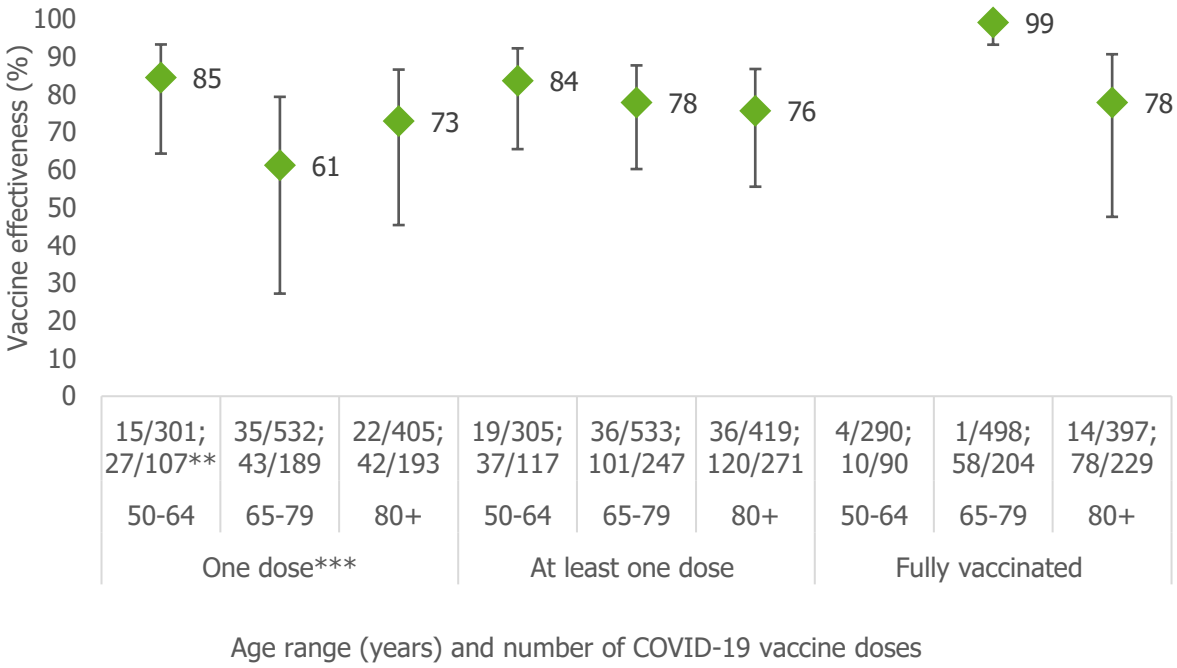
Results of the analysis by age groups showed that adjusted vaccine effectiveness was higher in those aged 50-64 years than in the older age groups (Figure 8). Very small numbers of completely vaccinated cases in the younger age groups makes these vaccine effectiveness estimates difficult to interpret.

Figure 7. Overall vaccine effectiveness of any COVID-19 vaccine product against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients aged 50 years and older at specimen collection date, by dose, six EU/EEA countries*, 27 December 2020–30 June 2021 (n = 1 892)



** Data from one participating EU/EEA country were excluded from this vaccine effectiveness analysis because the sample size was too small (<5 cases and controls).*
*** Data are given as vaccinated cases/all cases; vaccinated controls/all controls.*
**** One dose indicates patients who received one dose of a vaccine with a two-dose course (partially vaccinated).*

Figure 8. Overall vaccine effectiveness of any COVID-19 vaccine product against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients aged 50 years and older at specimen collection date, by dose and age group, six EU/EEA countries*, 27 December 2020–30 June 2021 (n = 1 892)



** Data from one participating EU/EEA country were excluded from this vaccine effectiveness analysis because the sample size was too small (<5 cases and controls).*
*** Data are given as vaccinated cases/all cases; vaccinated controls/all controls.*
**** One dose indicates patients who received one dose of a vaccine with a two-dose course (partially vaccinated).*

Vaccinated SARI patients

Among the 349 vaccinated SARI patients, most received a two-dose vaccine: Comirnaty, Spikevax, Vaxzevria or Curevac, with only one receiving the COVID-19 Vaccine Janssen (Table 5). The predominant vaccine product among vaccinated cases (51/91; 56%) and controls (196/258; 76%) was Comirnaty.

Table 5. Characteristics of hospitalised, vaccinated SARI patients in six EU/EEA countries*, 27 December 2020–30 June 2021 (n = 349)

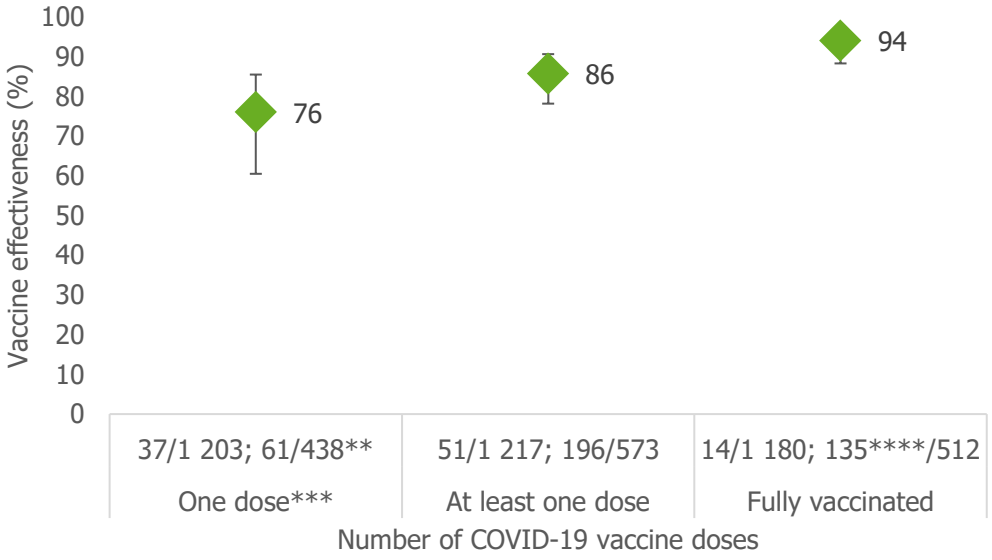
Characteristics		Cases n (%)	Controls n (%)	p-value
Sex	Male	58 (63.7)	143 (55.4)	0.177
	Female	33 (36.3)	115 (44.6)	
Age (years)	Median	76	78	0.283†
	50–64	19 (20.9)	37 (14.3)	
	65–79	36 (39.6)	101 (39.1)	
	≥80	36 (39.6)	120 (46.5)	
Any of the four chronic conditions[b]	Yes	55 (60.4)	190 (73.6)	0.018†
	No	36 (39.6)	68 (26.4)	
Number of individuals administered with first dose only (partially vaccinated)	Comirnaty	37 (51.4)	61 (54.0)	–
	Vaxzevria	26 (36.1)	35 (31.0)	
	Spikevax	5 (6.9)	11 (9.7)	
	Janssen	0 (0.0)	1 (0.4)	
	Unknown	4 (5.6)	5 (4.4)	
Number of individuals administered with second dose[d] (fully vaccinated)	Comirnaty	14 (73.7)	133 (91.7)	–
	Vaxzevria	0 (0)	1 (0.7)	
	Spikevax	3 (15.8)	6 (4.1)	
	Janssen	0 (0)	1 (0.4)	
	Curevac	0 (0)	1 (0.7)[e]	
	Unknown	2 (10.5)	4 (2.8)	

[a] Six participating countries submitted eligible data for vaccinated cases and controls by 25 October 2021: Belgium, Croatia, France, Malta, Portugal and Spain.
[b] Fisher's exact.
[c] The four chronic conditions are: diabetes, heart disease, lung disease and asthma.
[d] Or one dose of COVID-19 Vaccine Janssen.
[e] This case was kept, as they received an EU-authorised vaccine for the first dose.

COVID-19 vaccine effectiveness estimates by vaccine product

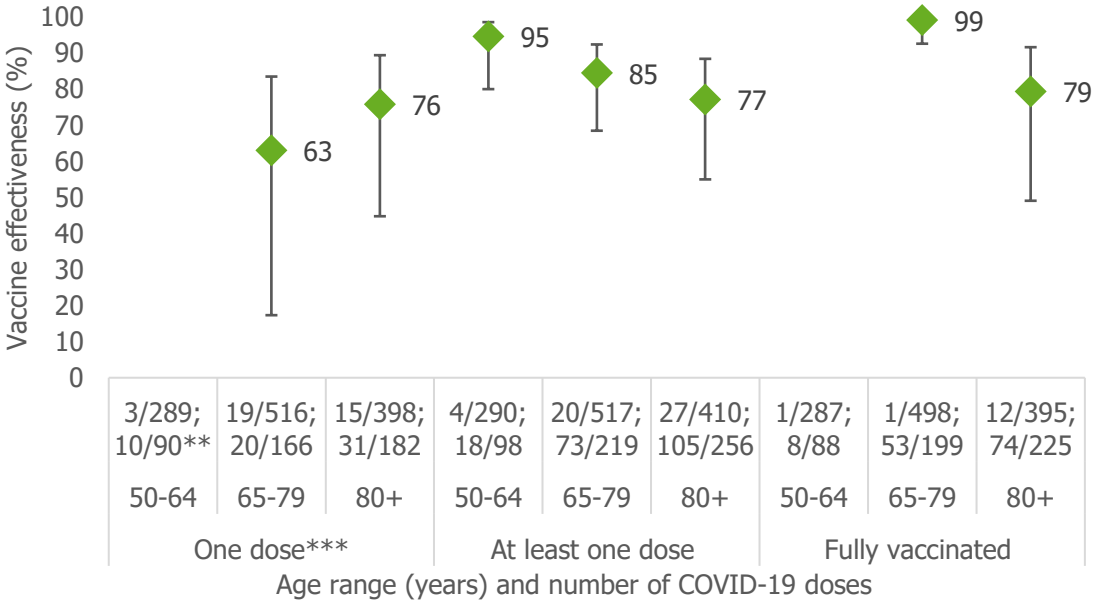
Table 5 illustrates that the only vaccine product able to be used in adjusted vaccine effectiveness estimates by individual product was Comirnaty. The adjusted vaccine effectiveness for the Comirnaty vaccine observed ≥14 days after only one dose was 76% (95% CI: 61-86%). The vaccine effectiveness observed ≥14 days after being fully vaccinated (two doses) with Comirnaty vaccine was 94% (CI: 88-97%) (Figure 9). As most patients were vaccinated with the Comirnaty vaccine, results for this vaccine alone were very similar to results for any vaccine, whether overall or when looking at vaccine effectiveness by age group (Figures 9 and 10).

Figure 9. Vaccine effectiveness of Comirnaty against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients aged 50 years and older at specimen collection date, by dose, six EU/EEA countries*, 27 December 2020–30 June 2021 (n = 1 790)



**Data from one participating EU/EEA country were excluded from this vaccine effectiveness analysis because the sample size was too small (<5 cases and controls).*
*** Data are given as vaccinated cases/all cases; vaccinated controls/all controls.*
**** One dose indicates patients who received one dose of a vaccine with a two-dose course (partially vaccinated).*
***** Although there are 135 fully vaccinated controls, only 133 received two doses of Comirnaty (two controls received Comirnaty for the first dose and another vaccine for the second dose).*

Figure 10. Vaccine effectiveness of Comirnaty against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients aged 50 years and older at specimen collection date, by dose and age group, six EU/EEA countries*, 27 December 2020–30 June 2021 (n = 1,893)



**Data from one participating EU/EEA country were excluded from this vaccine effectiveness analysis because the sample size was too small (<5 cases and controls).*
*** Data are given as vaccinated cases/all cases; vaccinated controls/all controls.*
**** One dose indicates patients who received one dose of a vaccine with a two-dose course (partially vaccinated).*

SARS-CoV-2 genetic sequencing

Twenty-one strains were sequenced from two countries (Croatia and Spain). Eighteen of these (86%) were B.1.1.7 (the Alpha VOC), with two listed only as 'Clade 20I/501Y.V1'. Two sequences were described as 'Brazilian/South African variant' (potentially Beta or Gamma) and one was the Delta VOC (B.1.617.2). A third country (Portugal) did genetic sequencing of samples, but only one of these cases was included in the final dataset for this analysis and the genetic group was not provided.

Descriptive analysis of sequenced variants of concern (VOCs)

Table 6 provides a brief description of the 21 hospitalised COVID-19 patients with sequenced samples. The numbers are too small to draw any firm conclusions. This descriptive analysis will be repeated once additional sample results are received and vaccine effectiveness estimates will be calculated once sample size allows.

Table 6. Characteristics of hospitalised COVID-19 cases infected with variants of concern in two EU/EEA countries*, 27 December 2020–30 June 2021 (n = 21)

Characteristics		Alpha (n = 18)	Non-Alpha (n = 3)
Sex	Male	8 (63.7)	3
	Female	10 (36.3)	0
Age (years)	Median	70	67
	50–64	7 (38.9)	1 (33.3)
	65–79	7 (38.8)	2 (66.6)
	≥80	4 (22.2)	0
Any one of four chronic conditions‡	Yes	6 (33.3)	3
	No	12 (66.6)	0
Vaccination status**	Unvaccinated	17 (94.4)	3 (100.0)
	Partially vaccinated	1 (5.6)	0
	Fully vaccinated	0	0

** Two participating countries submitted eligible data on sequenced samples by 25 October 2021: Croatia and Spain.*
*** Patients were considered fully vaccinated if they received both doses of a vaccine with a two-dose course or one dose of a vaccine with a one-dose course at least 14 days before onset of symptoms. Patients were considered partially vaccinated if they had received only one dose of a vaccine with a two-dose course at least 14 days before onset of symptoms.*

Challenges and limitations

Initial challenges at the site (country) level included delays achieving ethics and data protection/governance documentation, particularly in countries where national vaccine effectiveness estimation with sharing of data with another EU/EEA country had not previously been done. Concomitant implementation of SARI surveillance in some participating countries, where vaccine effectiveness estimation was already being considered as part of SARI surveillance datasets, made this process smoother. One participating country had the unusual added burden of a major cyberattack, which delayed their participation by several months.

As the vaccines were rolled out across the 10 participating countries, the vaccination coverage among target groups increased. As a result, there has been an increasingly smaller group of unvaccinated controls, and in future unvaccinated controls may not be representative of those from earlier in the study period. This needs to be further investigated. Some countries had difficulty recruiting controls for the study (whether vaccinated or unvaccinated), as hospitals were overwhelmed with COVID-19 case admissions during the peak times of the pandemic in the study period.

There was a very small number of vaccinated cases over this entire six-month period, which is a positive development and indicates the effectiveness of the vaccines in reducing serious (hospitalised) events, but also makes interpreting the vaccine effectiveness estimates for some stratified groups difficult. For example, in the age-stratified vaccine effectiveness estimates in this report, for those receiving full vaccination of any vaccine, there were only four cases in the 50-64 years age group and just one in the 65-79 years age group. For those receiving Comirnaty in the youngest age group (50-64 years), there were fewer than five cases in each vaccine dose category (and only one in the 65-79 years age group, fully vaccinated category). These vaccine effectiveness estimates were therefore based on sparse data and care should be taken in their interpretation.

One of the major challenges in many countries was in providing genetic sequencing results for cases. Laboratories were overwhelmed with testing for suspected cases in communities, contact tracing, and screening, as well as hospitalised patients, leading to delays in results. As a result of this, there were difficulties in matching sequenced samples to epidemiological study results. Hence, there have been very few sequences provided to date, and these have been from only two study sites. Going forward, addressing individual site sequencing issues will be a priority.

In any multi-country study such as this, heterogeneity between sites could be a limitation. This is caused not only by differences in data collection processes and vaccination roll-out strategies, or different mixes of vaccines being provided at different times, but also from the circulation of different SARS-CoV-2 variants in each country over time. To help circumvent the differences in processes, all hospital study sites follow the same protocol. Adjustment by time and site as fixed effect in analyses should minimise some of the remaining heterogeneity, as well as stratifying vaccine effectiveness estimates by vaccine product and age group. In addition, in this analysis we selected SARI patients from only the first six months of the study (pre-Delta VOC), while the next analysis will consider the Delta period. When sample size permits, a two-stage analysis – measuring vaccine effectiveness by each study site individually and performing a meta-analysis – will allow estimation of heterogeneity.

Progress to date

Despite the challenges faced, all participating sites have implemented the generic protocol after adaptation to their local context.

Several analyses have been completed on either individual ECDC vaccine effectiveness data or on combined ECDC and I-MOVE-COVID-19 vaccine effectiveness data with SARS-CoV-2 infection with SARI as an outcome, among these an oral presentation at the ESCAIDE conference 2021.

Next steps

The next interim analysis will be conducted at the end of January, based on data reported as of 14 January 2022. Additional analyses will estimate vaccine effectiveness against SARS-CoV-2 among hospitalised SARI patients as follows (sample size permitting):

- by different pandemic periods, as a proxy for circulation of different variants (e.g. SARI patients swabbed in January to June 2021 vs those swabbed in July to October 2021);
- with age groups widened from 50 years and older to 30 years and older;
- for those with different individual comorbidities;
- by different delays from vaccination to onset of symptoms (e.g. 0-59 days vs ≥60 days);
- using the WHO SARI case definition, as included in the core ECDC protocol [16];
- including controls with previous positive RT-PCR or serology results 14-28 days and 28-59 days vs ≥60 days prior; and
- via a two-stage analysis (once individual site sample sizes permit), to assess heterogeneity.

Site visits will also be planned to understand potential qualitative heterogeneity (different vaccination roll-out strategies, different mixes of vaccines at different times, circulation of different variants at different times).

Planning of additional meetings is ongoing to identify and address barriers to timely submission, sequencing and reporting of variant results, including permitting better linkage between laboratory data and epidemiological data.

Discussion and conclusions

Ten countries participated in this multi-country, test-negative, case-control study, with eight countries submitting data at least twice (four sites submitting from July, three from August, and one from September 2021). One country, which was unable to submit data by the deadline for this report, has since submitted data and another will submit in January 2022.

Among 1 893 hospitalised SARI patients aged 50 years and older who were eligible to receive the COVID-19 vaccine at the time of sample collection, results suggest good vaccine effectiveness 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. The adjusted vaccine effectiveness for full vaccination (both doses of any two-dose course or one dose of COVID-19 Vaccine Janssen) was better than vaccine effectiveness for a single dose of a two-dose vaccine. The vaccine effectiveness was higher among those in the youngest age group (50-64 years) than in the other two age groups, for any product and for Comirnaty.

Our vaccine effectiveness estimates for older adults are similar to those already published in other studies, and our results fall within the range of results already published for mRNA vaccines [4-6].

This ECDC multi-country study complements other international efforts to respond to COVID-19 vaccine effectiveness questions, both globally and in Europe [5, 17]. Use of the same approach to study design and data collection can contribute to a more comprehensive discussion on COVID-19 vaccine effectiveness under real-word conditions; pooling

of these results with other multi-centre studies following similar protocols is ongoing (with the I-MOVE-COVID-19 hospital vaccine effectiveness study) or being considered (with the WHO/EURO hospital COVID-19 vaccine effectiveness study), as appropriate, and may allow the calculation of more precise estimates.

The establishment of the study in the various sites has provided a powerful platform to monitor and further investigate vaccine effectiveness and inform the development of key vaccine policy issues in 2022. Continuation and expansion of this vaccine effectiveness study is vital to maintain this important work.

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Disclaimer

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

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Annex

Table A1. Number of exclusions for vaccine effectiveness estimates, ECDC multi-country COVID-19 vaccine effectiveness study among hospitalised SARI patients, by country and category, as of 25 October 2021

Country	No lab results or test not RT-PCR	Outside study period	<50 years of age or not in vaccine target group	Not SARI	Missing key variables	Other*	Total
Belgium	22	72	554	135	180	22	985
Croatia	29	66	471	133	84	280	1 063
Czechia	5	6	0	1	0	1	13
France	6	160	181	10	5	38	400
Greece	3	18	0	0	0	0	21
Ireland	–	–	–	–	–	–	–
Luxembourg	–	—	–	–	–	–	–
Malta	2	236	133	0	0	172	543
Portugal	1	2	20	6	0	13	42
Spain	3 941	1 960	945	793	67	234	7 940
Total	**4 009**	**2 520**	**2 304**	**1 078**	**336**	**760**	**11 007**

** Other includes SARI patients swabbed >10 days after symptom onset, vaccinated within 14 days of onset, with vaccination date errors or non-recommended delays between doses, as well as controls with previous positive results, who lived in long-term care facilities, or with symptom onset >3 days after swab.*