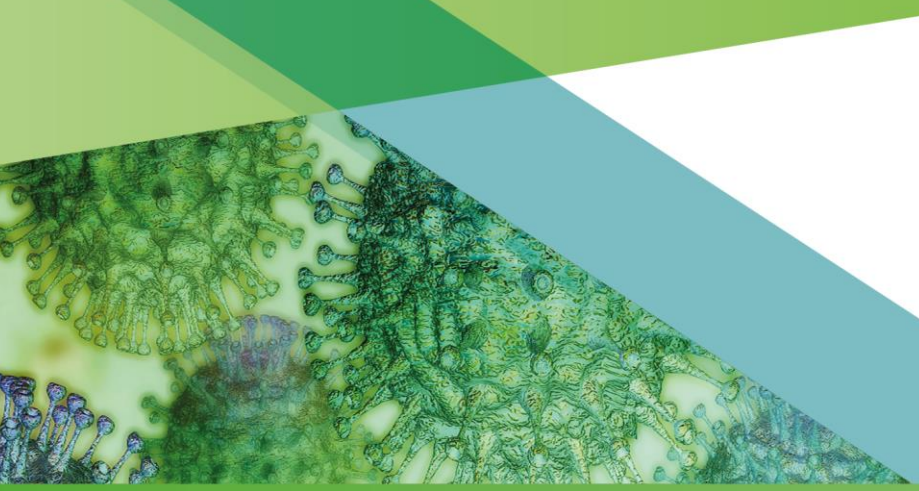


TECHNICAL REPORT

Interim analysis of COVID-19 vaccine effectiveness against Severe Acute Respiratory Infection due to laboratory-confirmed SARS-CoV-2 among individuals aged 30 years and older, ECDC multi-country study – second update

14 March 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. As the study is ongoing, this report contains updated results following those previously published on 8 October 2021 [3] and 20 January 2022 [4].
- As of 16 January 2022, a total of 11 EU countries are participating in the multicentric study (Belgium, Croatia, Czechia, France, Greece, Ireland, Luxembourg, Malta, the Netherlands, Portugal, Spain).
- In this third report, results for the 30-49 years age group have been added. As one of the conditions for individuals to be included in the study was their eligibility for COVID-19 vaccination, this age group was previously ineligible for inclusion.
- The COVID-19 vaccine effectiveness estimates presented are pooled estimates from eight countries (records from three countries were excluded, as fewer than five controls were reported). Compared with the previous report, two additional countries have provided data. This report also covers a longer study period, with vaccine effectiveness estimates for two periods of the pandemic in 2021 (3 January–31 May and 1 July–15 December), as a proxy for the pre-Delta and Delta-dominant periods, respectively.
- Most individuals enrolled in the study received COVID-19 mRNA vaccine Comirnaty (Pfizer/BioNTech). The effectiveness of full vaccination with the primary series (two doses for vaccines with a two-dose course and one dose for vaccines with a one-dose course) was higher than for partial vaccination (a single dose for those vaccines with a two-dose course) in all age groups included in this analysis (30 years and older), regardless of the study period (pre-Delta and Delta-dominant periods).
- The results presented in this report suggest a high adjusted vaccine effectiveness in preventing SARI associated with laboratory-confirmed SARS-CoV-2 infection for COVID-19 vaccines deployed during the first 12 months of the vaccination campaign across EU/EEA countries in all age groups 30 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 the primary series of any vaccine product was 93% (95% confidence interval (CI): 86–96%) during the pre-Delta period and 83% (95% CI: 78–87%) during the Delta-dominant period. For Comirnaty, vaccine effectiveness was 94% (95% CI: 88–97%) in the pre-Delta period and 82% (95% CI: 76–87%) in the Delta period. For Vaxzevria, there were no reports of full vaccination with the primary series during the pre-Delta period, but vaccine effectiveness during the Delta period was 79% (95% CI: 69–86%).

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 30 years and older, ECDC multi-country study – second update. ECDC: Stockholm; 2022.

- Results of the analysis by age group, for all vaccine products combined and during the pre-Delta period, showed that adjusted vaccine effectiveness for partial vaccination was higher in those aged 65–79 years than in the other age groups, although all confidence intervals overlap. A similar pattern was observed for full vaccination with the primary series, but very low numbers of fully vaccinated cases in the youngest age group (30–49 years) make these estimates difficult to interpret. For the Delta period, adjusted vaccine effectiveness for full vaccination with the primary series was higher in younger age groups than in older age groups: 55% (95% CI: 25–74) in those aged 80 years and older compared to 91% (95% CI: 81–95) in those aged 30–49 years (for all products combined, although the results for Comirnaty were very similar). The adjusted vaccine effectiveness for Vaxzevria observed ≥14 days after full vaccination with the primary series was 79% (95% CI: 60–89%) in those aged 50–64 years and 87% (95% CI: 73–94%) in those aged 65–79 years. Sample size was insufficient to estimate vaccine effectiveness in other age groups for Vaxzevria during the Delta period.
- Estimated results were in the range of estimates published in other studies for similar outcomes in this population during the pre-Delta and Delta periods [5–7].

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]. 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.

In the initial 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 until 30 June 2021, across the participating EU/EEA countries.

The first update, published on 20 January 2022, included vaccine effectiveness results among individuals aged 50 years and older [4]. These estimates covered mainly the pre-Delta dominant period (until 30 June 2021), adding further evidence to the existing literature on COVID-19 vaccine effectiveness during this time.

This second update contains vaccine effectiveness results among individuals aged 30 years and older, for the pre-Delta and the Delta-dominant periods (3 January–31 May 2021 and 1 July–15 December 2021, respectively). It also contains estimates by COVID-19 vaccine product (i.e. Comirnaty and Vaxzevria). Compared with the previous report, two additional countries submitted data retrospectively (Ireland and the Netherlands); therefore, estimates for the pre-Delta period may differ slightly from those published previously.

Detailed objectives of the multi-country study can be found in the ECDC core protocol [2], as well as in Annex 1. A detailed description of both the methods used and the characteristics of the cases and controls enrolled in the study was provided in the second report [4], with a summary of the main elements presented in Annex 2. Additional details regarding the methods of the study can also be found in the ECDC core 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. Since 31 December 2019 and as of week 4 2022, 376 229 546 cases of COVID-19 (in accordance with the applied case definitions and testing strategies in the affected countries) have been reported, including 5 681 828 deaths [8].

International collaborative efforts have accelerated the development of COVID-19 vaccines. As of 16 January 2022, 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 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 and 12-17 years, respectively, and subsequently Comirnaty indications were extended further to include children aged 5–11 years [10,11].

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), COVID-19 Vaccine Janssen (on 11 March 2021) and – most recently – Nuvaxovid (20 December 2021). Countries started vaccination programmes on different dates, prioritising specific risk groups. By week 49 2021 (ending 12 December 2021, the end of the study period for the current report), the uptake of full vaccination with the primary series in each participating country was high in all age groups 60 years and older (Table 1).

Table 1. Uptake of full vaccination with the primary series of COVID-19 vaccine* in participating EU/EEA countries, as of week 49 2021 (ending 12 December 2021)

Country	Age group			
	50–59 years Full vaccination with primary series	60–69 years Full vaccination with primary series	70–79 years Full vaccination with primary series	≥ 80 years Full vaccination with primary series
Belgium	90.7	93.9	96.2	90.2
Croatia	64.9	75.1	79	61
Czechia	75.5	77.3	90.2	88.2
France	83.5	85.5	94.5	83.5
Greece	77.6	82.1	83.7	75.4
Ireland	98.8	100	100	100
Luxembourg	83.1	87.8	88.7	92.1
Malta	88.1	93.2	100	100
Netherlands	NA	NA	NA	NA
Portugal	93.6	97.8	100	99.5
Spain	88.8	95	98.6	100
Median EU/EEA	**83.1**	**87.6**	**89.1**	**90.2**

Source: ECDC Vaccine Tracker [12]
NA: not available
** Full vaccination with the primary series of COVID-19 vaccine is defined according to the manufacturer's instructions for each vaccine product.*

Objectives 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 and product-specific COVID-19 vaccines against SARI due to laboratory-confirmed SARS-CoV-2 in hospitalised patients aged 30 years and older who received:

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

Direct effectiveness estimates are calculated by age group (30-49 years, 50–64 years, 65–79 years, ≥80 years), as well as by the variant that was dominant during a specific period (pre-Delta or Delta).

Countries participating in the study

As of 16 January 2022, a total of 42 hospitals across 11 countries (Belgium, Croatia, Czechia, France, Greece, Ireland, Luxembourg, Malta, the Netherlands, Portugal and Spain; Figure 1) were participating in the study.

All countries that submitted data by the 16 January deadline were included in this report. The earliest vaccination campaign start date among the 11 countries was 27 December 2020 (for five countries; see Table 2).

The start week of Delta dominance is reported in Table 2, based on data collected by ECDC on the distribution of variants of concern (VOCs) by week and country [13,14].

Figure 1. Map of the 11 participating EU/EEA countries, ECDC multi-country COVID-19 vaccine effectiveness study among hospitalised SARI patients, as of 16 January 2022

Ethical approval has been obtained by all 11 countries. All countries have started to recruit SARI patients, with start dates ranging from the end of December 2020 to January 2022 (Table 1).

Table 2. 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 2020–15 December 2021

Country	Participating hospitals	Vaccination campaign start date	Study start date	Start of Delta variant dominance*
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	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
Netherlands**	Sint Antonius Ziekenhuis	6 Jan 2021	1 Sep 2021	Week 26, 2021
	Onze Lieve Vrouwe Gasthuis			
	Catharina Ziekenhuis			
	Meander Medisch Centrum***			
	Noordwest Ziekenhuisgroep Alkmaar***			
	Meander Medisch Centrum		1 Oct 2021	
	Noordwest Ziekenhuisgroep Alkmaar			
	Rijnstate Ziekenhuis			
	Martini Ziekenhuis		15 Jan 2022	
Portugal	Centro Hospitalar Universitário de São João (CHUSJ)	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			

** Source: The European Surveillance System (TESSy) data results*
*** Retrospective data collection*
****Two hospitals in the Netherlands contributed data initially but no longer participate (highlighted in grey).*

Descriptive analysis[1]

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

Hospital and SARI patient recruitment

As of 16 January 2022, data were available from 42 hospitals in 11 countries: Belgium (6 hospitals), Croatia (3), Czechia (1), France (3), Greece (1), Ireland (1), Luxembourg (1), Malta (1), the Netherlands (9), Portugal (3) and Spain (13). By 16 January 2022, there were 18 407 records submitted from all 11 countries.

This analysis estimates vaccine effectiveness among hospitalised SARI patients aged 30 years and older, over two distinct periods [13,14]:

- **The pre-Delta period**, from the first vaccination campaign start date (27 December 2020; Table 1) to 31 May 2021. This end date was selected to provide a study period before wide circulation of the Delta VOC in the European region and to allow the month of June as a transition period.
- **The Delta period**, for SARI patients swabbed between 1 July and 15 December 2021.

After excluding 7 308 records for patients that did not have an RT-PCR test or had a missing RT-PCR test result (3 658), were not SARI patients (1 889), or were recruited outside of the study period (1 761), there were 11 099 remaining SARI patient records within the overall study period. Of these, a further 6 221 were excluded from this analysis: 1 669 were not part of a vaccine target group at the time of their swab (and were therefore unable to receive vaccination and ineligible for inclusion in the study); 1 375 were <30 years of age; 668 were swabbed during the June transition period; 682 were swabbed >10 days after symptom onset; 660 were missing key variable information (age; sex; swab, onset or admission date; and vaccine information/dates); 407 lived in long-term care facilities; 365 had symptom onset within 14 days of their first, second or booster vaccine dose; 148 had symptom onset >3 days after their swab; 160 were controls with a prior positive result; 52 had errors in vaccination information/date or a non-recommended delay between their two vaccine doses; 22 had symptom onset >7 days after admission; 7 had inconsistent dates (e.g. discharge before admission date); and 6 were duplicate records. A detailed description of the exclusion by countries is available in Annex 3.

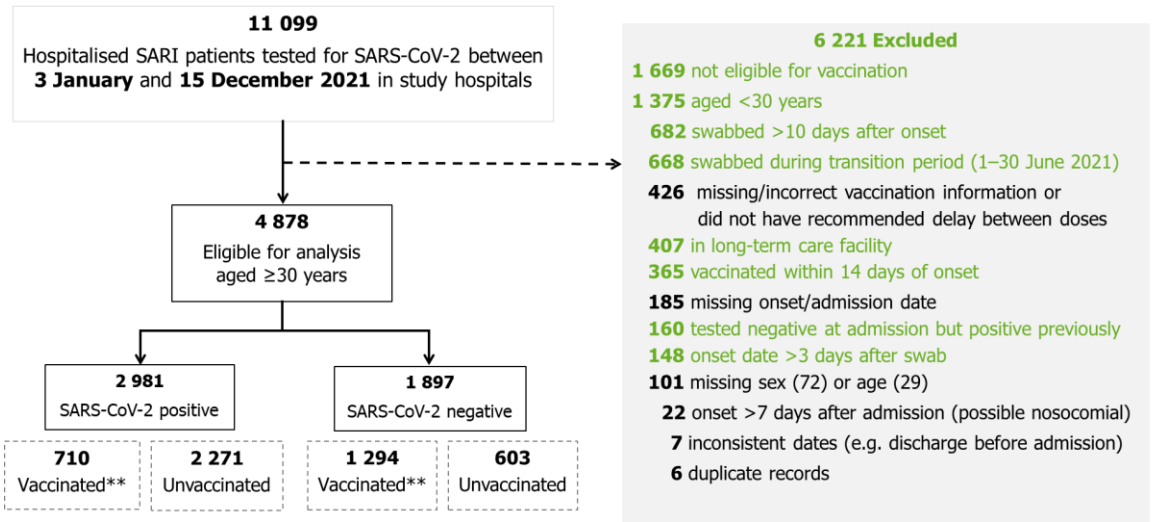
This left 4 878 records eligible for descriptive analyses. After excluding a further 50 records from three sites that had fewer than five controls, there were 4 828 records eligible to be included in the vaccine effectiveness estimates (Table 3 and Figure 2; see Table A1 in Annex 3 for details of exclusions by country).

Table 3. Number of submitted records, exclusions and inclusions for vaccine effectiveness estimates among SARI patients aged 30 years and older, by participating EU/EEA country, from the start of the vaccination campaign in each country to 15 December 2021

Country	Number of submitted records for SARI patients aged ≥30 years	Number of records within transition period*	Number of exclusions	Total number of included records		Number of cases	Number of controls
				Descriptive analysis	Vaccine effectiveness analysis		
Belgium	1 347	96	619	632	632	429	203
Croatia	2 179	100	1 075	1 004	1 004	893	111
Czechia	67	3	37	27	0**	27	0
France	862	29	304	529	529	311	218
Greece	30	0	16	14	0**	14	0
Ireland	213	0	61	152	152	97	55
Luxembourg	15	0	6	9	0**	7	2
Malta	935	52	415	468	468	172	296
Netherlands	618	68	224	326	326	110	216
Portugal	762	106	217	429	429	231	208
Spain	2 696	214	1 204	1 278	1 278	690	588
Total	**9 724**	**668**	**4 178**	**4 878**	**4 828**	**2 981**	**1 897**

** Transition period: 1–30 June 2021*
*** Vaccine effectiveness analysis could not be completed for these countries due to the low number of controls.*

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, 3 January–15 December 2021



** Included data are from 42 hospitals in 11 countries. Analysis exclusions are indicated in green text. A further 50 records were excluded from the vaccine effectiveness analysis due to the exclusion of three countries that contributed fewer than five controls. After exclusions, the first swab date was on 3 January 2021.*
*** Vaccinated with at least one dose of COVID-19 vaccine*

Hospitalised SARI patients

The 4 878 eligible hospitalised SARI patients were from 41 hospitals across all 11 participating countries. Almost one-third (1 433; 29%) of the hospitalised SARI patients from participating countries were aged 80 years and older. Two in five cases (1 201; 40%) and one in four controls (496; 26%) were younger than 65 years of age. More than half of both cases and controls were male (1 703 cases and 1 081 controls; 57% for each). Three out of four (1 391; 73%) controls and more than half (1 643; 55%) of cases had at least one of four commonly collected chronic conditions (diabetes, heart disease, lung disease, asthma). More controls than cases were vaccinated (1 294 controls; 68% vs 710 cases; 37%) (Table 4).

The median delay between receiving the first and second vaccine doses was 28 days for cases and 27 days for controls, as per vaccine manufacturer's instructions (Table 4). The longest delays between the first two doses were 182 days for both cases and controls (Figure 3). The median number of days from the administration of the first vaccine dose to the onset of SARI symptoms was 170 days in cases and 172 days in controls (p=0.106) (Table 4). Almost two-thirds of vaccinated cases (460; 65%) and controls (788; 61%) had a delay of 115 to 250 days between the first dose and symptom onset. 70% of cases (376/539) and 61% of controls (671/1 101) with a second dose had a delay of 115 to 250 days between the second dose and symptom onset (Figures 4 and 5). The median delay from second dose to booster dose was longer in controls (196 days) than in cases (134 days; p<0.001), although numbers of cases and controls with a booster dose were low (Table 4).

The number of eligible cases recruited into the study between week 52 2020 and week 50 2021 peaked in week 14 at 160 cases. The number of controls recruited fluctuated by week but was higher in the Delta period than in the pre-Delta period. There was a low of fewer than 10 controls swabbed per week between the end of 2020 and week 3 2021, and a high of 83 in week 45 2021. Most vaccinated SARI patients received their vaccine between weeks 11 and 22 (Figure 6).

Vaccine effectiveness is described below for the pre-Delta period (3 January–31 May 2021), for which five countries were excluded for not having enough cases or controls during this time, and the Delta-dominant period (1 July–15 December 2021), for which data from eight countries were included.

Table 4. Characteristics of eligible SARI patients aged 30 years and older in EU/EEA participating countries[a], ECDC multi-country COVID-19 vaccine effectiveness study among hospitalised SARI patients, 3 January–15 December 2021 (n = 4 878)[b]

Characteristics		Cases (N = 2 981) n (%)	Controls (N = 1 897) n (%)	p-value
Sex	Male	1 703 (57.1)	1 081 (57.0)	0.929[c]
	Female	1 278 (42.3)	816 (43.0)	
Age (years)	Median	68	74	–
	30–49	405 (13.6)	143 (7.5)	<0.001[c]
	50–64	796 (26.7)	353 (18.6)	
	65–79	1 038 (34.8)	710 (37.4)	
	≥80	742 (24.9)	691 (36.4)	
Any of the four chronic conditions[d]	Yes	1 643 (55.1)	1 391 (73.3)	<0.001[c]
	No	1 338 (44.9)	506 (27.7)	
COVID-19 vaccination status[e]	Unvaccinated	2 271 (76.2)	603 (31.8)	<0.001[c]
	Partially vaccinated	126 (4.2)	162 (8.5)	
	Fully vaccinated with primary series	567 (19.0)	1 062 (56.0)	
	Fully vaccinated with primary series plus booster dose	17 (0.6)	71 (3.7)	
Number of COVID-19 vaccine doses administered	None	2 271 (76.2)	603 (31.8)	–
	One dose	171 (5.6)	192 (10.1)	
	Two doses	522 (17.5)	1 031 (54.3)	
	Three doses	17 (0.6)	71 (3.7)	
Median time delay in days (IQR)	From first dose to symptom onset	170 (99–210)	172 (103–216)	0.106[f]
	From second dose to symptom onset	151 (180–186)	147 (90–190)	0.2767[f]
	From booster dose to symptom onset	40 (27–62)	31 (24–43)	0.093[f]
	From first to second dose	28 (21–36)	27 (21–35)	0.005[f]
	From second to booster dose	134 (118–178)	196 (175–225)	<0.001[f]

[a] All 11 participating countries submitted eligible data by 16 January 2022: Belgium, Croatia, Czechia, France, Greece, Ireland, Luxembourg, Malta, the Netherlands, Portugal and Spain.
[b] Excluding data from the transition period (1–30 June 2021)
[c] Fisher's exact test
[d] The four chronic conditions are: diabetes, heart disease, lung disease and asthma.
[e] Patients were considered fully vaccinated with the primary series if they received two 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 symptom onset. 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 symptom onset.
[f] Wilcoxon rank-sum (Mann-Whitney)

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, 11 EU/EEA countries, 3 January–15 December 2021 (n = 1 640)

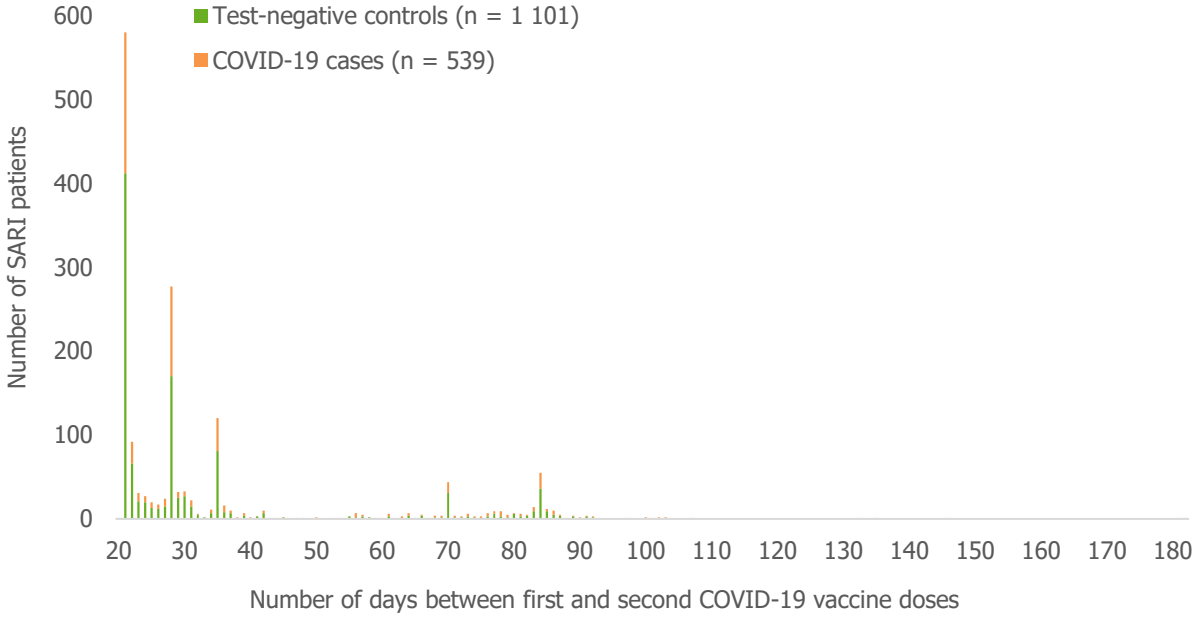


Figure 4. Number of days between first COVID-19 vaccine dose and SARI symptom onset among cases and controls, pooled data for ECDC multi-country COVID-19 vaccine effectiveness study among hospitalised SARI patients, 11 EU/EEA countries, 3 January–15 December 2021 (n = 2 004)

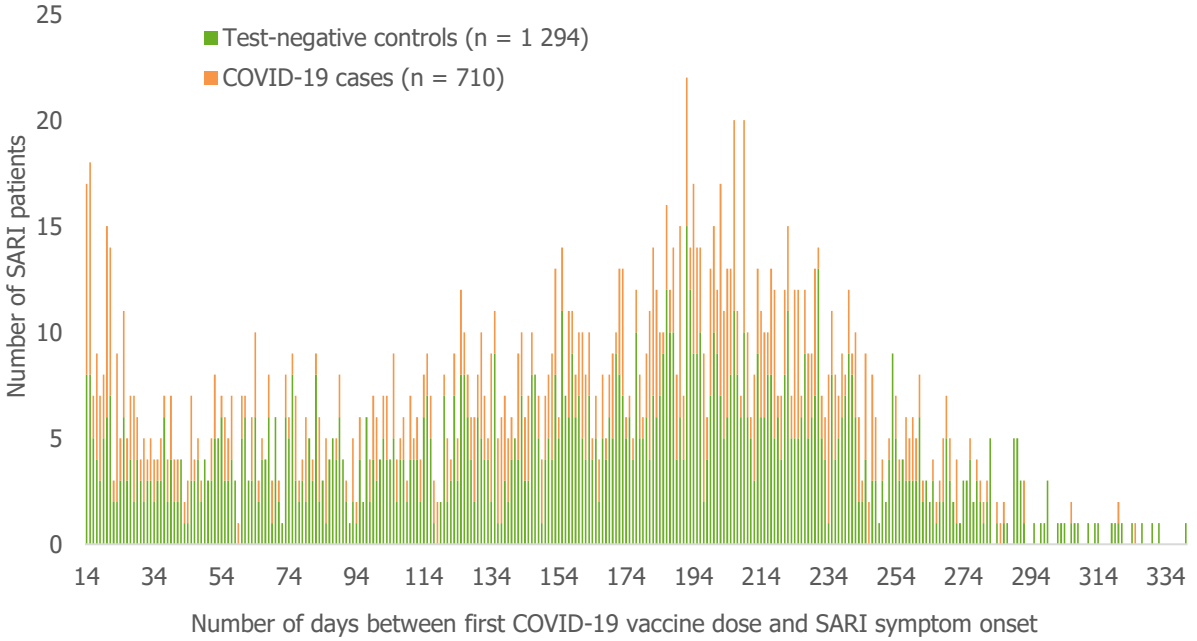


Figure 5. Number of days between second COVID-19 vaccine dose and SARI symptom onset among cases and controls, pooled data for ECDC multi-country COVID-19 vaccine effectiveness study among hospitalised SARI patients, 11 EU/EEA countries, 3 January–15 December 2021 (n = 1 640)

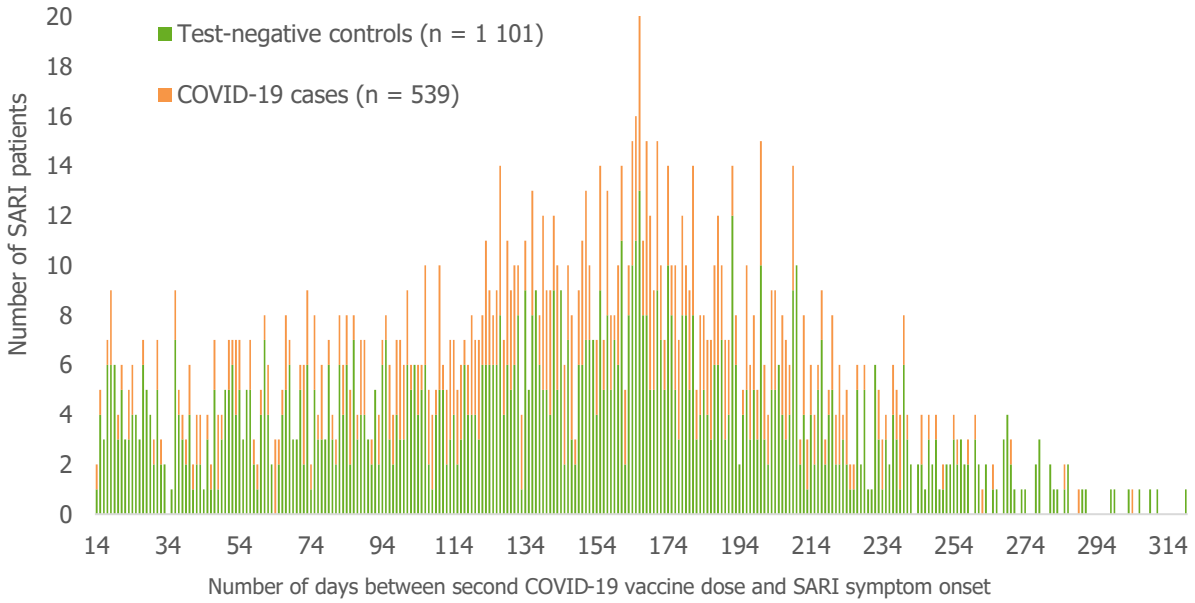
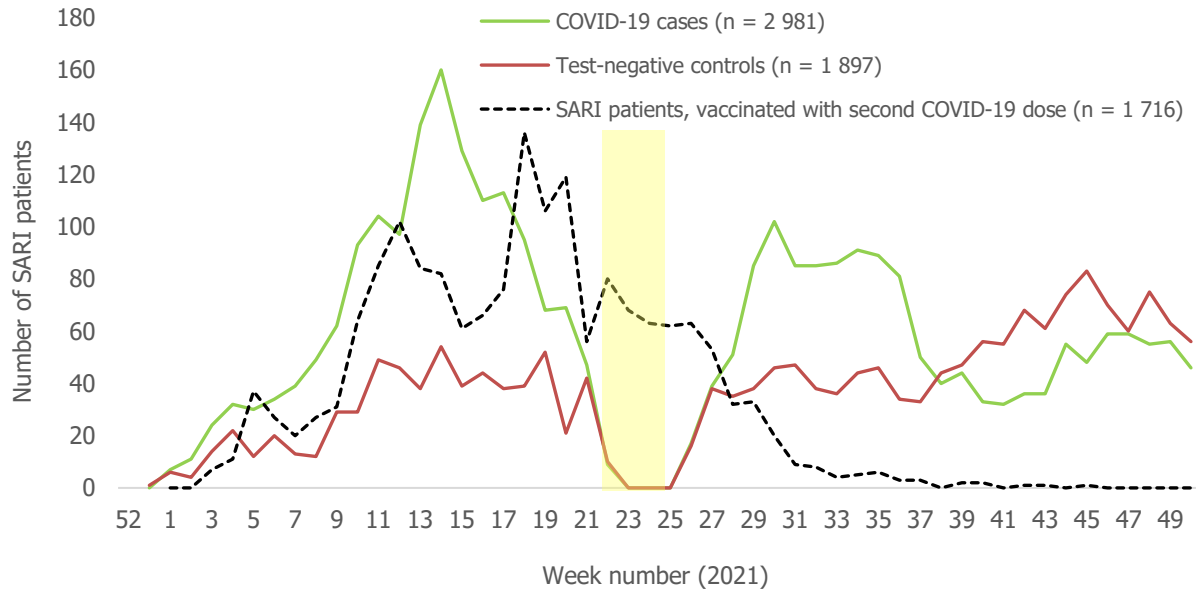


Figure 6. Number of cases and controls by ISO week of specimen collection and number of patients vaccinated with second dose by ISO week of vaccination, ECDC multi-country COVID-19 vaccine effectiveness study among hospitalised SARI patients, 11 EU/EEA countries, 3 January–15 December 2021 (n = 4 878)



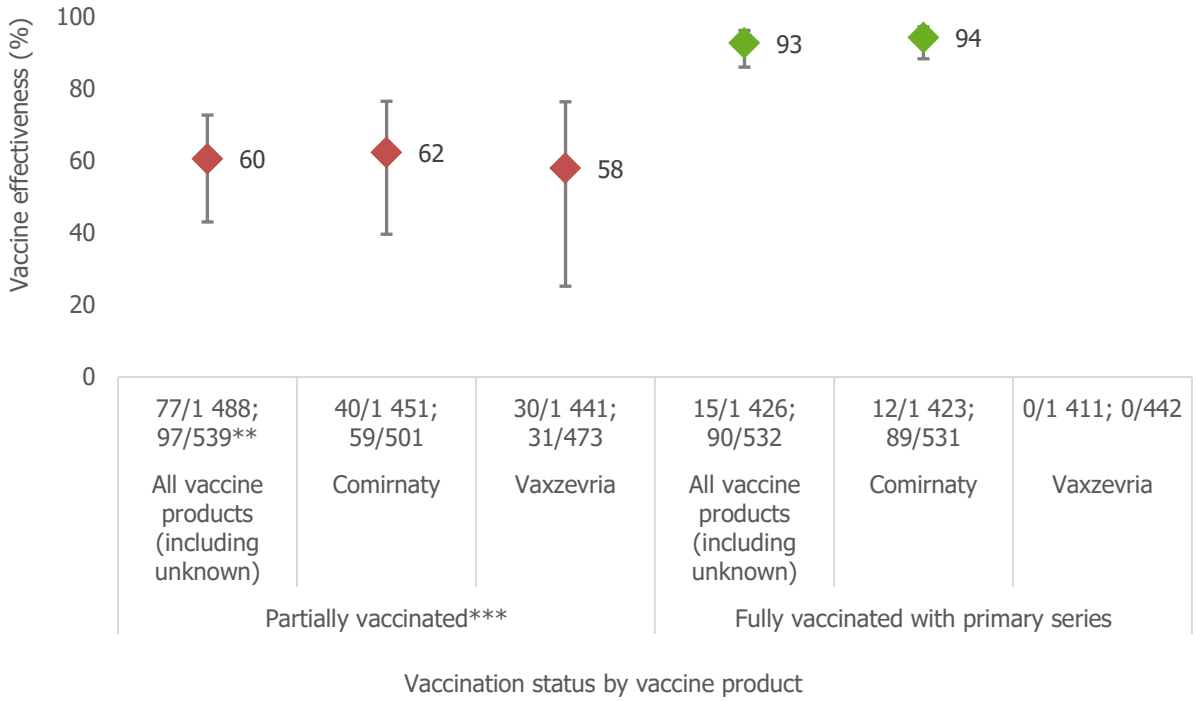
** The yellow shading indicates the transition period (1–30 June 2021) between the pre-Delta and Delta-dominant periods. SARI patients from this period have been excluded.*

COVID-19 vaccine effectiveness estimates: pre-Delta period (3 January–31 May 2021)

Vaccine effectiveness for all ages (≥ 30 years)

The adjusted vaccine effectiveness against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients aged 30 years and older, swabbed during the pre-Delta period and observed ≥14 days after only one dose of any vaccine product was 60% (95% CI: 33–73%). The adjusted vaccine effectiveness observed ≥14 days after full vaccination with the primary series of any vaccine product during this period was 93% (95% CI: 86–96%). For partial vaccination, vaccine effectiveness by product was: 62% (95% CI: 40–76%) for Comirnaty and 58% (95% CI:25–76%) for Vaxzevria. For full vaccination with the primary series, vaccine effectiveness was 94% (95% CI: 88–97%) for Comirnaty. During this period there were no reports of full vaccination with Vaxzevria (Figure 7).

Figure 7. Overall vaccine effectiveness of any COVID-19 vaccine product against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients aged 30 years and older at specimen collection date, by dose and product, six EU/EEA countries*, 3 January–31 May 2021 (n = 2 027)

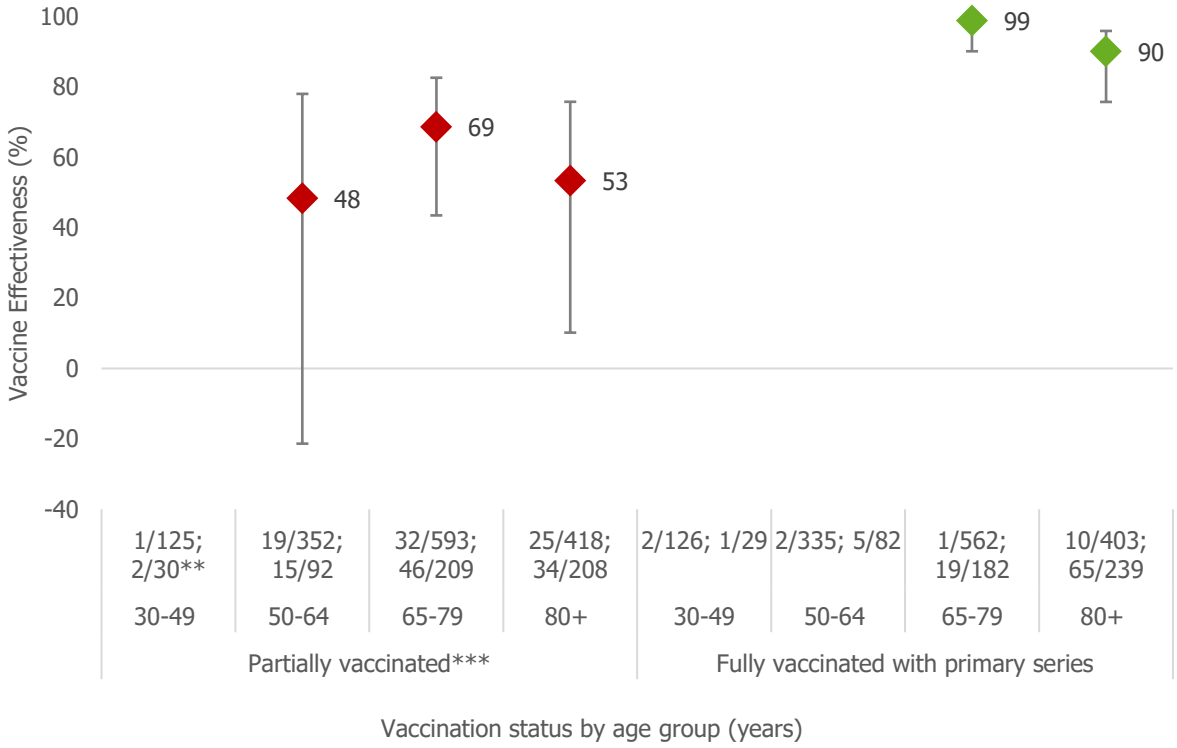


** Data from two additional participating EU/EEA countries were excluded from this vaccine effectiveness analysis because the sample size was insufficient (<5 cases or controls) for the pre-Delta period.*
*** Data are given as vaccinated cases/all cases; vaccinated controls/all controls.*
**** Partially vaccinated indicates patients who received one dose of a vaccine with a two-dose course.*

Vaccine estimates by age group (30–49 years, 50–64 years, 65–79 years, ≥80 years)

Results of the analysis by age group for all products combined during the pre-Delta period showed that adjusted vaccine effectiveness for partial vaccination was higher in those aged 65–79 years than in the other age groups, although all confidence intervals overlap. A similar pattern was observed for full vaccination with the primary series, but very low numbers of fully vaccinated cases in the youngest age group (39–40 years) make these vaccine effectiveness estimates difficult to interpret (Figure 8).

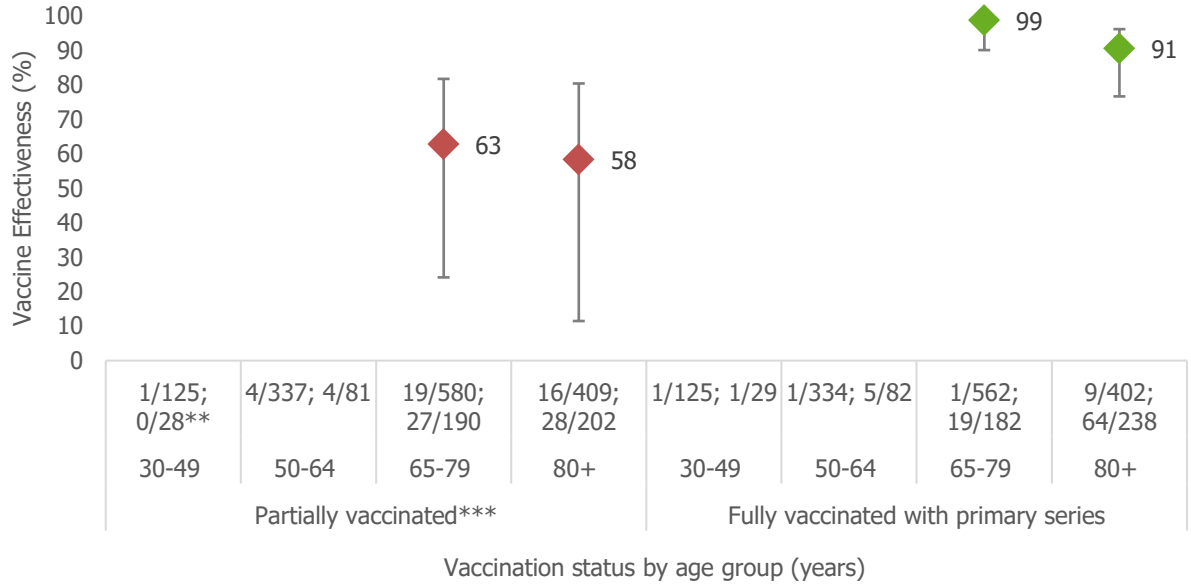
Figure 8. Overall vaccine effectiveness of any COVID-19 vaccine product against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients aged 30 years and older at specimen collection date, by dose and age group, six EU/EEA countries*, 3 January–31 May 2021 (n = 2 027)



** Data from two additional participating EU/EEA countries were excluded from this vaccine effectiveness analysis because the sample size was insufficient (<5 cases or controls) for the pre-Delta period.*
*** Data are given as vaccinated cases/all cases; vaccinated controls/all controls.*
**** Partially vaccinated indicates patients who received one dose of a vaccine with a two-dose course.*

Results of the analysis by age groups for individual vaccine products showed that vaccine effectiveness for partial vaccination with Comirnaty was 63% (95% CI: 24–82%) for those aged 65–79 years and 58% (95% CI: 11–80%) for those aged 80 years and older. For other age groups, the sample size was insufficient to calculate vaccine effectiveness for partial vaccination or full vaccination with the primary series of Comirnaty during this period (Figure 9). Adjusted vaccine effectiveness for full vaccination with the primary series of Comirnaty was 99% in those aged 65–79 years (95% CI: 90–100%) and 91% (95% CI: 77–96%) in those aged 80 years and older.

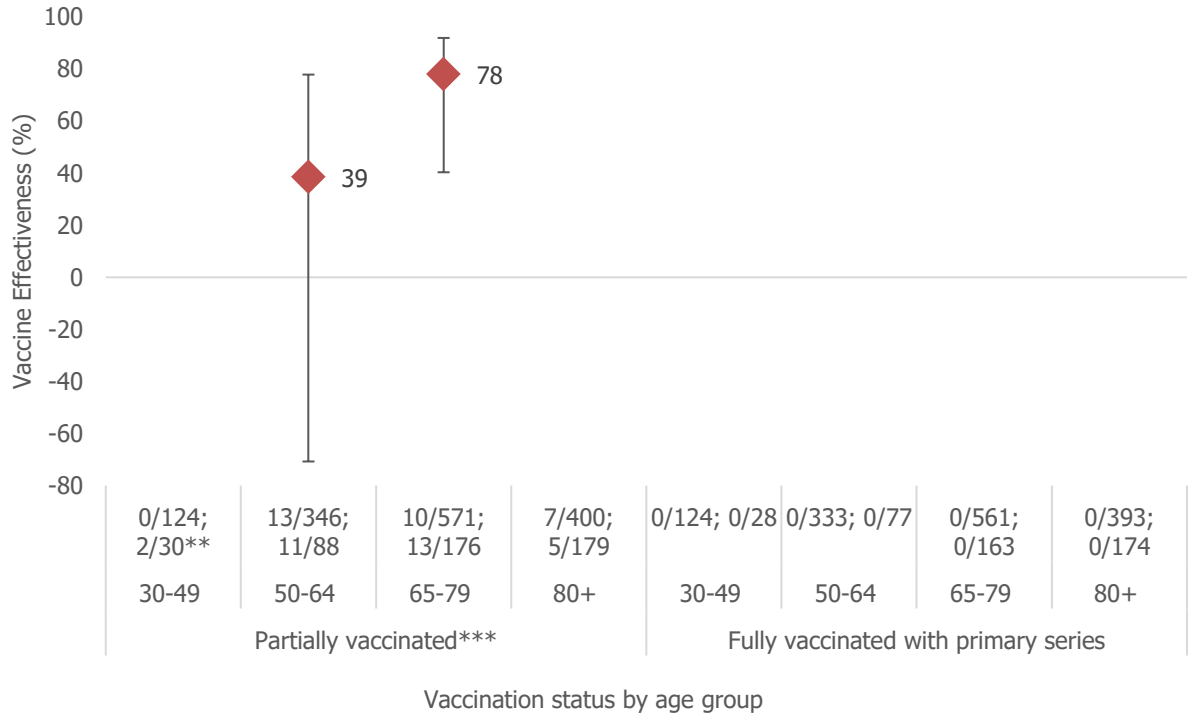
Figure 9. Adjusted vaccine effectiveness of the Comirnaty COVID-19 vaccine against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients aged 30 years and older at specimen collection date, by dose and age group, six EU/EEA countries*, 3 January–31 May 2021 (n = 1 952)



** Data from two additional participating EU/EEA countries were excluded from this vaccine effectiveness analysis because the sample size was insufficient (<5 cases or controls) for the pre-Delta period.*
*** Data are given as vaccinated cases/all cases; vaccinated controls/all controls.*
**** Partially vaccinated indicates patients who received one dose of a vaccine with a two-dose course.*

For Vaxzevria, the number of cases and controls who were fully vaccinated with the primary series was too low to provide these estimates in all age groups. There were also too few partially vaccinated cases and controls in the 30–49 years and 80 years and older age groups to provide these estimates. Vaccine effectiveness for partial vaccination with Vaxzevria in the pre-Delta period was 39% in those aged 50–64 years (95% CI: -71–78%) and 78% (95% CI: 40–92%) in those aged 65–79 years (Figure 10).

Figure 10. Adjusted vaccine effectiveness of the Vaxzevria COVID-19 vaccine against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients aged 30 years and older at specimen collection date, by dose and age group, six EU/EEA countries*, 3 January–31 May 2021 (n = 1 914)



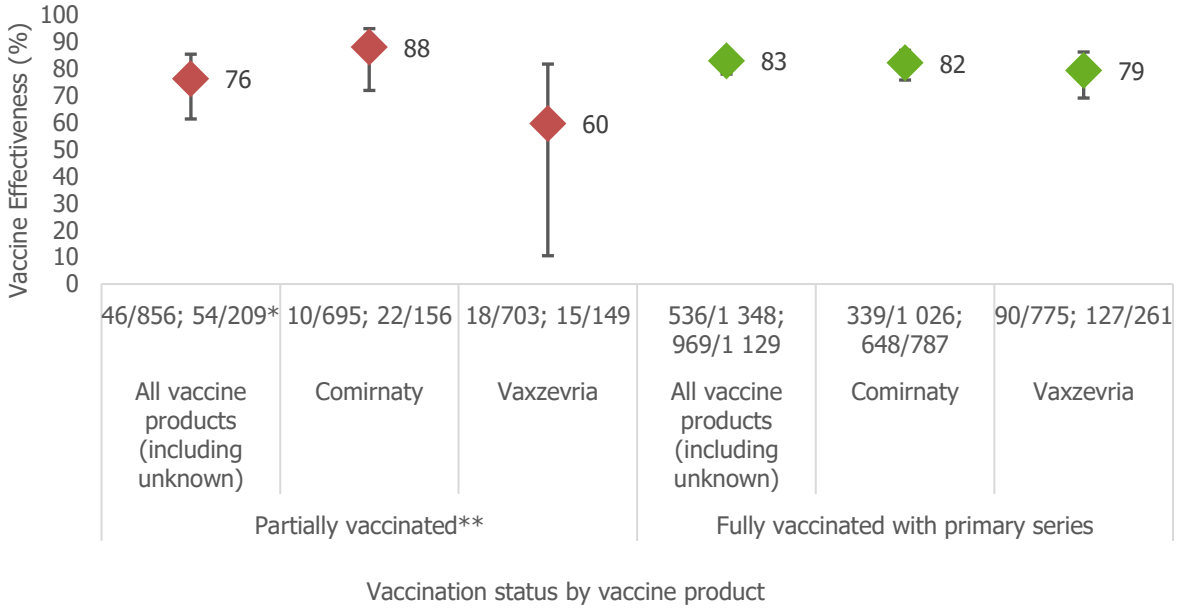
** Data from two additional participating EU/EEA countries were excluded from this vaccine effectiveness analysis because the sample size was insufficient (<5 cases or controls) for the pre-Delta period.*
*** Data are given as vaccinated cases/all cases; vaccinated controls/all controls.*
**** Partially vaccinated indicates patients who received one dose of a vaccine with a two-dose course.*

COVID-19 vaccine effectiveness estimates: Delta period (1 July–15 December 2021)

Vaccine effectiveness for all ages (≥30 years)

The adjusted vaccine effectiveness against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients aged 30 years and older, swabbed during the Delta period and observed ≥14 days after only one dose of any vaccine product was 76% (95% CI: 61–85%). After full vaccination with the primary series of any vaccine product, adjusted vaccine effectiveness observed ≥14 days was 83% (95% CI: 78–87%). For partial vaccination by product, vaccine effectiveness was 88% (95% CI: 72–95%) for Comirnaty and 60% (95% CI: 11–82%) for Vaxzevria. For full vaccination with the primary series, vaccine effectiveness was 82% (95% CI: 76–87%) for Comirnaty and 79% (95% CI: 69–86%) for Vaxzevria (Figure 11).

Figure 11. Overall adjusted vaccine effectiveness of any COVID-19 vaccine product against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients aged 30 years and older at specimen collection date, by dose and vaccine product, eight EU/EEA countries, 1 July–15 December 2021 (n = 2 477)

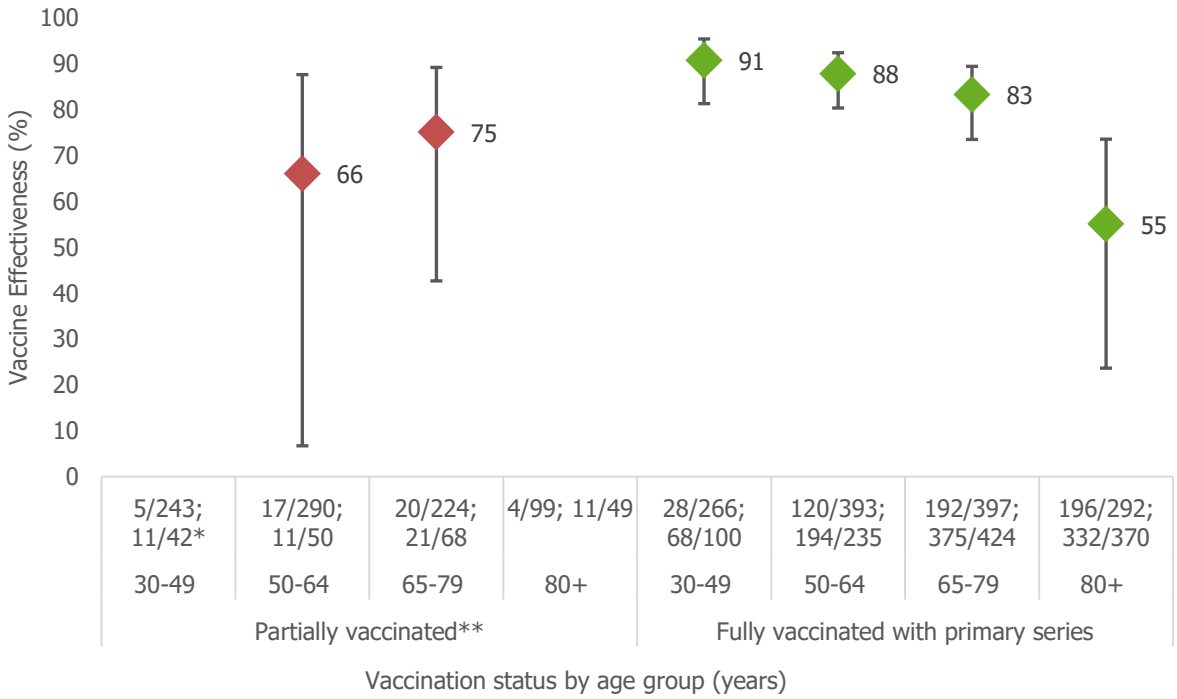


**Data are given as vaccinated cases/all cases; vaccinated controls/all controls.*
*** Partially vaccinated indicates patients who received one dose of a vaccine with a two-dose course.*

Vaccine estimates by age group (30–49 years, 50–64 years, 65–79 years, ≥80 years)

Results of the analysis by age group for all products combined during the Delta period showed that adjusted vaccine effectiveness for partial vaccination was 66% (95% CI: 7–88) in those aged 50–64 years and 75% (95% CI: 43–89) for those aged 65–79 years. Insufficient sample size in the 30–49 years and 80 years and older age groups resulted in no estimates for these groups. For full vaccination with the primary series, adjusted vaccine effectiveness was 91% (95% CI: 81–95) in those aged 30–49 years, 88% (95% CI: 80–92) in those aged 50–64 years, 83% (95% CI: 74–89) in those aged 65–79 years, and 55% (95% CI: 25–74) in those aged 80 years and older (Figure 12).

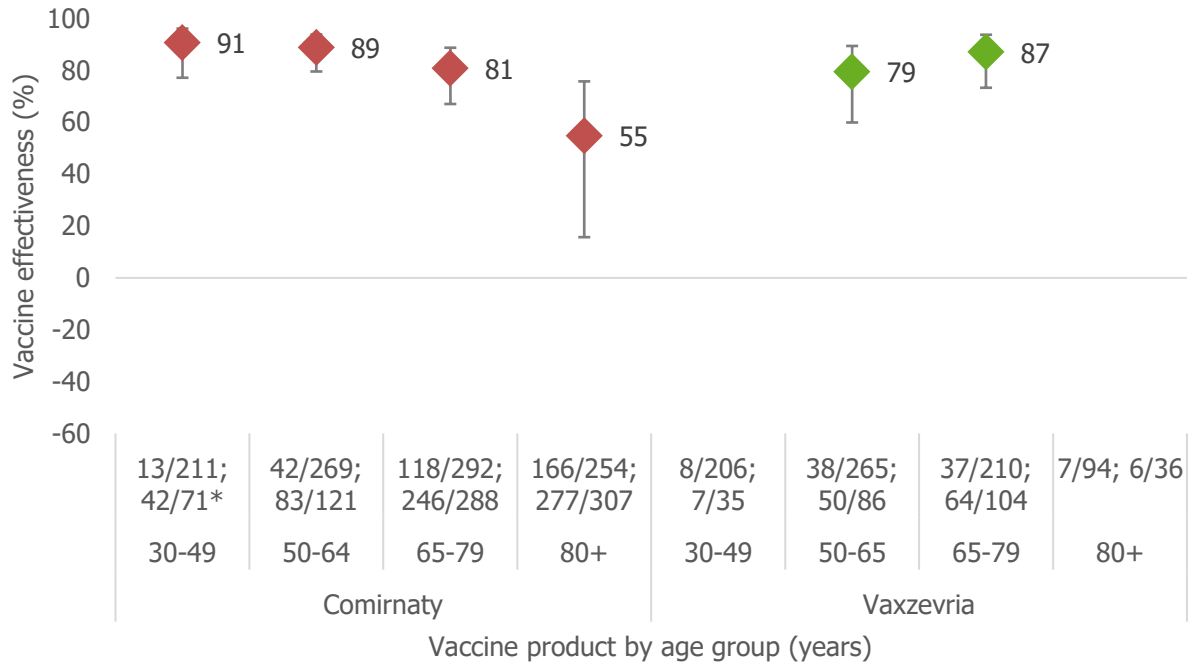
Figure 12. Overall adjusted vaccine effectiveness of any COVID-19 vaccine product against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients aged 30 years and older at specimen collection date, by dose and age group, eight EU/EEA countries, 1 July–15 December 2021 (n = 2 477)



** Data are given as vaccinated cases/all cases; vaccinated controls/all controls.*
*** Partially vaccinated indicates patients who received one dose of a vaccine with a two-dose course.*

Insufficient sample size for partial vaccination with Comirnaty and Vaxzevria during the Delta period resulted in no vaccine effectiveness estimates for partial vaccination by age group for either product during the Delta period (1 July–15 December 2021). Adjusted vaccine effectiveness for full vaccination with the primary series of Comirnaty vaccine was 91% (95% CI: 77–96) in those aged 30–49 years, 89% (95% CI: 80–94) in those aged 50–64 years, 81% (95% CI: 67–89) in those aged 65–79 years, and 55% (95% CI: 16–76) in those aged 80 years and older. For full vaccination with the primary series of Vaxzevria, vaccine effectiveness during the Delta period was 79% in those aged 50–64 years (95% CI: 60–89%) and 87% (95% CI: 73–94%) in those aged 65–79 years. There was insufficient sample size to estimate vaccine effectiveness in other age groups for Vaxzevria during the Delta period (Figure 13).

Figure 13. Adjusted vaccine effectiveness against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients aged 30 years and older who are fully vaccinated with the primary series of Comirnaty or Vaxzevria COVID-19 vaccines at specimen collection date, by age group, eight EU/EEA countries, 1 July–15 December 2021 (n = 1 813)



** Data are given as vaccinated cases/all cases; vaccinated controls/all controls.*

SARS-CoV-2 genetic sequencing

There were 174 strains sequenced from six countries (Belgium, Croatia, Czechia, Ireland, Luxembourg and Portugal). Fifty-six (32%) of these were the Alpha VOC, all in the pre-Delta period. The remaining 118 (68%) were the Delta VOC, all in the Delta period. Samples from all six countries are included in the descriptive analysis below.

Descriptive analysis of sequenced variants of concern (VOCs)

Table 5 provides a brief description of the 174 hospitalised COVID-19 cases whose samples were sequenced. Although the numbers are too low to draw any firm conclusions, most (55/56; 98%) patients infected with the Alpha VOC were unvaccinated, while 53% (62/118) of patients with the Delta VOC were vaccinated. This descriptive analysis will be repeated once additional sample results are received and vaccine effectiveness estimates will be calculated once sample size allows.

Table 5. Characteristics of hospitalised COVID-19 cases infected with variants of concern in six EU/EEA countries*, 3 January–15 December 2021 (n = 174)

Characteristics		Alpha (n = 56)	Delta (n = 118)
Sex	Male	30 (53.6)	72 (61.0)
	Female	26 (46.4)	46 (39.0)
Age (years)	Median	70	66
	30–49	5 (8.9)	25 (21.2)
	50–64	10 (17.9)	29 (24.6)
	65–79	28 (50.0)	39 (33.1)
	≥80	13 (23.2)	25 (21.2)
Any of the four chronic conditions**	Yes	28 (50.0)	56 (47.5)
	No	28 (50.0)	62 (52.5)
Vaccination status	Unvaccinated	55 (98.2)	56 (47.5)
	Partially vaccinated	1 (1.8)	1 (0.9)
	Fully vaccinated with primary series	0	54 (45.8)
	Fully vaccinated plus booster dose	0	7 (5.9)

** Six participating countries submitted eligible data on sequenced samples by 16 January 2022: Belgium, Croatia, Czechia, Ireland, Luxembourg and Portugal.*
*** The four commonly collected chronic conditions are: diabetes, heart disease, lung disease and asthma.*
**** Patients were considered fully vaccinated with the primary series 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 symptom onset. 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 symptom onset.*

Challenges and limitations

As the vaccines were rolled out across the 11 participating countries, vaccination coverage among target groups increased. As a result, there has been an increasingly small 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 peak periods of the pandemic.

During the pre-Delta period, there was a very low number of cases that were fully vaccinated with the primary series. This indicates the effectiveness of the vaccines in reducing serious (hospitalised) events, but also makes interpreting the vaccine effectiveness estimates for some stratified groups difficult. There were also low numbers of vaccinated SARI patients in the youngest (30–49 years) age group in the pre-Delta period. This is understandable, as vaccines were rolled out in older age groups first, so prior to 31 May 2021 the number of people in the general population in this age group who were vaccinated was probably limited. This meant that vaccine effectiveness could not be estimated for this age group in the pre-Delta period.

During the Delta period, there was a low number of partially vaccinated cases and controls. This could indicate that most people aged 30 years and older were fully vaccinated with the primary series by July 2021, as there were sufficient SARI patients to estimate the effectiveness of full vaccination. It is, however, difficult to interpret the effectiveness of partial vaccination during this period.

One of the major challenges in many countries was 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, and sometime served several demanding surveillance systems in parallel (comprehensive surveillance of COVID-19 associated with sentinel surveillance of acute respiratory infections) leading to delays in results. As a result of this, it was difficult to match sequenced samples to epidemiological study results. Hence, there have been very few sequences provided to date, and these have been from only six study sites. Going forward, addressing sequencing issues at individual sites 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 by the varying ways that different SARS-CoV-2 variants circulate in each country over time. To help mitigate any 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. 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 ECDC vaccine effectiveness data or 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 European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE) in 2021.

Next steps

The next interim analysis will be conducted at the end of March, based on data reported as of 1 March 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 (as done in this report);
- with age groups widened to include all adults aged 18 years and older;
- for those with different individual comorbidities;
- by different delays from vaccination to symptom onset (e.g. 0–59 days vs ≥60 days);
- using the WHO SARI case definition, as included in the core ECDC protocol [2];
- including controls with previous positive RT-PCR or serology results 14–28 days and 28–59 days prior vs ≥60 days prior; and
- via a two-stage analysis (once individual site sample sizes permit), to assess heterogeneity.

Site visits are also planned to understand potential qualitative heterogeneity (e.g. 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

The previous update, published at the end of January 2022, provided estimates using data from the first half of 2021 on SARI patients aged 50 years and older [4]; this report presents data up to mid-December 2021 and provides estimates using data for almost all of 2021, for SARI patients aged 30 years and older. Eleven countries participated in this multi-country, test-negative, case–control study and all participating countries submitted data by 16 January 2021. Two additional countries have provided data since the previous update. A tremendous amount of work continues to be done at the country level to reduce the time from data collection to submission.

Among 4 828 hospitalised SARI patients aged 30 years and older who were eligible to receive the COVID-19 vaccine at the time of sample collection, results suggest good vaccine effectiveness for full vaccination with the primary series against laboratory-confirmed SARS-CoV-2 for the COVID-19 vaccines deployed during the first 12 months (pre-Delta and Delta periods) of the vaccination campaign across EU/EEA countries. The adjusted vaccine effectiveness for full vaccination with the primary series was better than vaccine effectiveness for partial vaccination during both periods and was higher in the pre-Delta than the Delta period overall and for each product and age group. The vaccine effectiveness was lower among those in the oldest age group (≥80 years) than those in the younger age groups (30–49 years, 50–64 years and 65–79 years), for all products combined and for Comirnaty and Vaxzevria separately. This was particularly marked during the Delta period, when effectiveness for all products combined and for Comirnaty was only 55% in the 80 years and older age group (vs 81–91% in the younger age groups). The vaccine effectiveness estimates for older adults presented in this report are similar to those already published in other studies, and results fall within the range of results already published for mRNA vaccines [5–7].

This ECDC multi-country study complements other international efforts to respond to COVID-19 vaccine effectiveness questions, both globally and in Europe [15]. 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.

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 [2]. 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 vaccine effectiveness progresses over time.

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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Annexes

Annex 1. 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 vaccine effectiveness 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 vaccine effectiveness: 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.

Annex 2. 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 symptom onset; or
- received the first or second vaccine dose within 14 days of symptom onset.

Exposure

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

- **Fully vaccinated with the primary series (two-dose vaccine):** patients were considered fully vaccinated if they received both doses at least 14 days before symptom onset.
- **Fully vaccinated with the primary series (single-dose vaccine):** patients were considered fully vaccinated if they received one dose at least 14 days before symptom onset.
- **Fully vaccinated with the primary series plus booster:** patients were considered fully vaccinated with the primary series plus booster if they were fully vaccinated (according to the definitions above), followed by a booster dose at least 14 days before symptom onset.
- **Partially vaccinated (two-dose vaccine):** patients were considered partially vaccinated if they received only one of the two primary series doses at least 14 days before symptom onset or received the second dose on the same day as or after symptom onset.
- **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 symptom onset.

Two periods (3 January–31 May 2021 and 1 July–15 December 2021) were used as proxies for the pre-Delta and Delta-dominant periods.

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 (intensive care unit admission, invasive ventilation, death).

Analysis

The vaccine effectiveness estimated in this analysis was among hospitalised SARI patients aged 30 years and older, who were swabbed between the start of the vaccination campaign in their country and 15 December 2021, for each of the two periods (pre-Delta and Delta-dominant), as defined above. 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 (as a categorical variable) or as a restricted cubic spline of swab date. 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 four age groups: 30–49 years, 50–64 years, 65–79 years and ≥80 years. Vaccine effectiveness estimates were not calculated where the total number of vaccinated cases and controls was fewer than 20.

Annex 3. Exclusions by country and category

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 16 January 2021

Country	No lab results or test not RT-PCR	Outside study period	<30 years of age or not in vaccine target group	Not SARI	Missing key variables	Other*	Total
Belgium	105	1 109	971	201	225	177	2 788
Croatia	124	104	635	214	162	407	1 646
Czechia	11	13	15	1	6	17	63
France	18	30	313	14	31	59	465
Greece	1	4	3	1	13	1	23
Ireland	11	38	54	0	5	46	154
Luxembourg	1	12	1	1	0	5	20
Malta	14	170	232	0	0	295	711
Netherlands	76	84	48	0	44	150	402
Portugal	41	191	182	110	22	143	689
Spain	3 256	674	1 323	1 347	90	427	7 117
Total	3 658	2 429	3 777	1 889	598	1 727	14 078

** Other includes SARI patients swabbed >10 days after symptom onset, vaccinated within 14 days of symptom 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.*