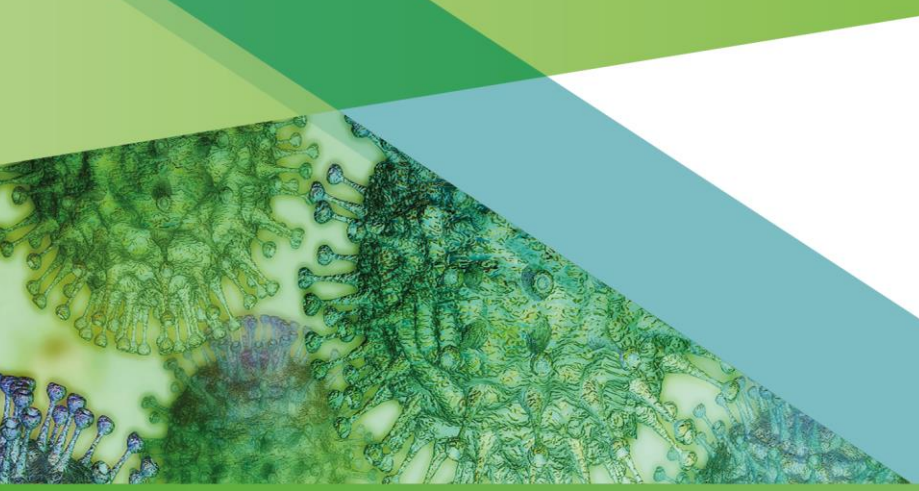


TECHNICAL REPORT

Interim analysis of COVID-19 vaccine effectiveness against Severe Acute Respiratory Infection due to SARS-CoV-2 in individuals aged 20 years and older – third update

8 November 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 assessing vaccine effectiveness against severe acute respiratory infection (SARI) due to laboratory-confirmed SARS-CoV-2 in the hospital setting. This is a case-control study using the test-negative design. As the study is ongoing, this report contains updated results following those previously published on 8 October 2021 [3], 20 January 2022 [4] and 14 March 2022 [5].
- As of 7 July 2022 (end data of data submission), a total of 12 EU countries are participating in the multicentre vaccine effectiveness study: Belgium, Croatia, Czechia, France, Germany, Greece, Ireland, Luxembourg, Malta, the Netherlands, Portugal, and Spain.
- The COVID-19 vaccine effectiveness estimates presented in the report are pooled estimates from eight countries: records from three countries were excluded as fewer than five controls were reported per site, while one country was excluded as the data reported were outside the reporting period. Compared with the previous report, the data presented include a wider age range, including those aged 20-29 years for the first time.
- This report also covers a shorter study period, focusing on vaccine effectiveness estimates for 21 December 2021– 2 July 2022, as a proxy for the Omicron variant-dominant period (further called the 'Omicron period'). This report includes effectiveness estimates for primary series vaccination alone, and primary series vaccination with booster doses in patients who were part of their country's target group for booster dose vaccination at the time of the swab.
- Most individuals enrolled in the study received COVID-19 mRNA vaccine Comirnaty (Pfizer/BioNTech). The effectiveness of full vaccination with the primary series only (two doses for vaccines with a two-dose course and one dose for vaccines with a one-dose course) was lower than for primary series with booster overall in all age groups included in this analysis (20 years of age and older).
- The adjusted vaccine effectiveness against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients during the Omicron period observed ≥150 days after full vaccination with only the primary series of any vaccine product was 45% (95% confidence interval (CI): 27–58%); while it was 65% (95% CI: 56–72%) with the addition of a booster dose. Adjusted vaccine effectiveness was 41% (95% CI: 19–57%) without booster and 60% (95% CI: 50–69%) with a booster dose for Comirnaty; 49% (95% CI: 13–70%) and 75% (95% CI: 06–84%), respectively, for Vaxzevria.

Suggested citation: European Centre for Disease Prevention and Control. Interim analysis of COVID-19 vaccine effectiveness against Severe Acute Respiratory Infection due to SARS-CoV-2 in individuals aged 20 years and older – third update. ECDC: Stockholm; 2022.

European Centre for Disease Prevention and Control. Stockholm, 2022.

- Results of the analysis by age group for all vaccine products combined during the Omicron period indicated that adjusted vaccine effectiveness point estimates for complete primary series vaccination without a booster dose was higher in those aged 20–59 years than in other age groups, although all confidence intervals overlap. A similar pattern was observed for full vaccination with primary series plus a booster dose. Estimated results were in the range published in other studies for similar outcomes in this population during the Omicron period.

Scope of this document

This current report builds on previous analyses [3,4,5] and extends the age groups included. An overview of outcomes, study period and age groups included in the analysis are presented in Table 1

Previous ECDC publications on COVID-19 vaccine effectiveness against hospitalisation with Severe Acute Respiratory Infection laboratory-confirmed with SARS-CoV-2, are available [3,4]. This third update contains vaccine effectiveness results among individuals aged 20 years and older for the Omicron period) for the first time as well as estimates by COVID-19 vaccine product (i.e. Comirnaty and Vaxzevria).

Table 1. Overview of outcomes, study period and age groups included in the analysis

Reference	Date of publication	Study population age groups	Study period	Variant dominant circulating period	Vaccination series evaluated	Vaccination scheme	Vaccine products
[3]	8 October 2021	65+	Until 30 June 2021	Pre-Delta	Partial and complete primary vaccination series	Homologous	Any Comirnaty Vaxzevria
[4]	20 January 2022	50+	Until 30 June 2021	Pre-Delta	Partial and complete primary vaccination series	Homologous	Any Comirnaty Vaxzevria
[5]	14 March 2022	30+	Until 15 December 2021	Pre-Delta and Delta	Partial and complete primary vaccination series	Homologous	Any Comirnaty Vaxzevria
Current report	November 2022	20+	27 December 2021–20 June 2022	Omicron	Complete Primary vaccination series plus booster	Homologous	Any Comirnaty Vaxzevria

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 (SARS-CoV-2), which causes coronavirus disease (COVID-19) emerged. On 11 March 2020, the World Health Organization declared COVID-19 a pandemic. Since 31 December 2019 and as of week 28 2022, 155 430 083 cases of COVID-19 (in accordance with the applied case definitions and testing strategies in the affected countries) have been reported in the EU, including 1 124 471 deaths [6].

International collaborative efforts have accelerated the development of COVID-19 vaccines. As of 22 July 2022, six COVID-19 vaccines – five 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 [[]: Comirnaty (BNT162b2), Spikevax (mRNA-1273), Vaxzevria (AZD1222), Jcovden (Ad26.COV 2.5, (previously COVID-19 Vaccine Janssen) and Nuvaxovid (NVX-CoV2373) and the non-spike protein based COVID-19 Vaccine (inactivated, adjuvanted) Valneva (VLA2001). All vaccine products authorised in the EU/EEA were initially registered for use in people aged 18 years and older, except for Comirnaty (approved for those aged 16 years and older). Comirnaty and Spikevax indications were the first to be 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 [7, 8].

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), Jcovden (on 11 March 2021), Nuvaxovid (20 December 2021) and – most recently – COVID-19 Vaccine Valneva (24 June 2022). Countries prioritised different risk groups at different dates. Uptake as of week 31, 2022 is reported in Table 2.

Table 2. Uptake (%) of full vaccination with the primary series of COVID-19 vaccine*, first and second booster dose in participating EU/EEA countries, as of week 31 2022 (ending 7 August 2022)**

Country	Full vaccination with primary series /first /second booster vaccination uptake (%)		
	25-49 years of age	50-59 years of age	≥ 60 years of age
Belgium	84.6/65.6/1.1	91.4/81.6/3.2	98.1/92.1/15.8
Croatia	58.6/14.2/0	71.7/27.7/0	77.2/47/0.2
Czechia	66.2/34.1/0.2	77.1/53.2/0.4	86/71.72.2
France	88.8/67/0.9	91.6/79.7/4.3	91/83.5/26.5
Greece	78/57.8/0.6	82.9/70.4/1.9	89.6/78.7/14
Ireland	88.8/64.9/0.5	98.2/86.2/1.6	100/97.9/65.4
Luxembourg	77.8/59.7/1	86.1/76.4/2	90.1/83.8/29.7
Malta	93/77.3/0.2	90.4/89.9/12	97.3/87.4/38
Netherlands	71.4/51.1/0.4	83.4/71.4/4.1	90.5/85.9/54.7
Portugal	95.1/67.1/0.1	95.1/86.7/0.3	99.7/97.2/14.8
Spain	79.2/48.8/0.9	88.4/75.4/0.8	96.8/91.4/0.4
Median EU/EEA	**78.6/51.5/0.4**	**83.9/72.4/0.8**	**90.7/83.6/13.7**

Source: ECDC Vaccine Tracker [9]
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.*
*** First and second booster refer to the first or second additional dose of COVID-19 vaccine administered after the standard primary series*

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 20 years and older who received:

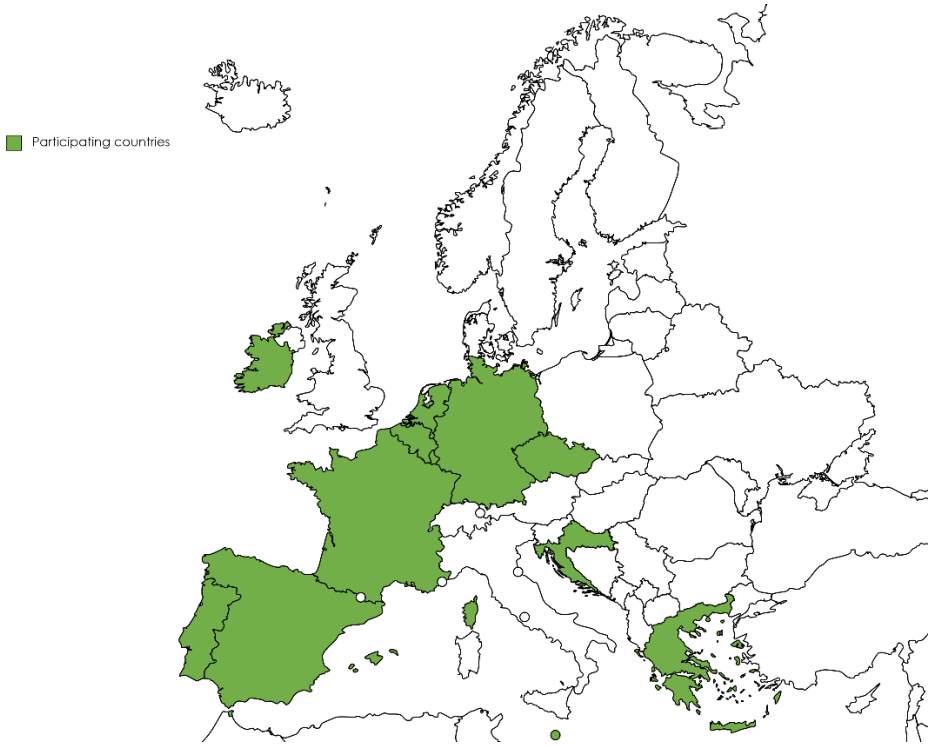
- **full vaccination with the primary series:** one dose for vaccine products with a one-dose course, two doses for vaccine products with a two-dose course (homologous), or three doses for those who are immunocompromised[1], as per the manufacturer's instructions).
- **full vaccination plus first booster dose:** full vaccination with primary series as above plus one booster dose, as per the manufacturer's instructions. Booster dose may be any product.

Above vaccination status may include heterologous scheme. Direct effectiveness estimates are calculated by age group (20–59 years, 60–79 years, ≥80 years). All effectiveness estimates are adjusted for (Annex 2)

Countries participating in the study and in this analysis

As of 11 July 2022 (the deadline for the latest submission of data), a total of 41 hospitals across 12 countries (Belgium, Croatia, Czechia, France, Germany, Greece, Ireland, Luxembourg, Malta, the Netherlands, Portugal and Spain) participated in the ECDC study (Figure 1; Table 2). All countries submitting eligible data by this deadline for the Omicron-dominant period were included in this report, which comprised 33/41 (80%) participating hospitals from 8/12 (66.6%) participating countries. Three countries with fewer than five controls were excluded as per protocol; one was excluded as their data were missing key variables for analyses (e.g. sex, age, see paragraph below and Figure 2).

Figure 1. Map of the 12 participating EU/EEA countries, ECDC multi-country COVID-19 vaccine effectiveness among hospitalised SARI patients, as of 3 July 2022



Ethical approval has been obtained in all 12 countries.

[1] This is country-specific and only one country currently provides information on a third dose for the immunocompromised.

The start and end weeks of Omicron dominance are reported in Table 2, based on data collected by ECDC on the distribution of variants of concern (VOCs) by week and country [10,11], using cut-offs of 80% to define 'dominance' in any given week. Once the proportions of variants sequenced reached at least 80% Omicron in each participating country, data were included from the first date of that week and up to the end of the last week where the proportion remained at least 80%.

For the individual country vaccination campaign start dates, see the previous report [5].

Table 2. Participating hospitals and start dates of Omicron dominance in participating EU/EEA countries Omicron-dominant period (20 December 2021–7 July 2022)

Country	Participating hospitals	Start week of Omicron variant dominance*	First day of start week	End week of study period†	Last day of end week
Belgium	Cliniques Universitaires Saint-Luc	week 1 2022	3 Jan 2022	week 26 2022	3 Jul 2022
	Algemeen Ziekenhuis Sint-Jan Brugge-Oostende				
	Centre Hospitalier Universitaire Saint-Pierre				
	Universitair Ziekenhuis Brussel				
	Jessa Ziekenhuis				
	Grand Hôpital de Charleroi				
Croatia	Clinical Hospital Centre Split	week 2 2022	10 Jan 2022	week 22 2022	5 Jun 2022
Czechia	University Hospital Brno	week 2 2022	10 Jan 2022	week 24 2022	19 Jun 2022
France	Hôpital Cochin, Paris	week 1 2022	3 Jan 2022	week 25 2022	26 Jun 2022
	CHU of Montpellier, Saint Eloi Hospital, Montpellier				
	CHU Rennes, Rennes				
Greece	Hippocratio General Hospital	week 51 2021	20 Dec 2021	week 21 2022	29 May 2022
Germany	Helios Klinikum Emil von Behring	week 2 2022	10 Jan 2022	week 26 2022	3 Jul 2022
Ireland	Saint Vincent's University Hospital	week 51 2021	20 Dec 2021	week 26 2022	3 Jul 2022
Luxembourg	Centre Hospitalier de Luxembourg	week 1 2022	3 Jan 2022	week 22 2022	5 Jun 2022
Malta	Mater Dei Hospital	week 1 2022	3 Jan 2022	NO DATA**	NO DATA**
Netherlands	Sint Antonius Ziekenhuis	week 1 2022	3 Jan 2022	week 25 2022	26 Jun 2022
	Onze Lieve Vrouwe Gasthuis				
	Catharina Ziekenhuis				
	Meander Medisch Centrum				
	Noordwest Ziekenhuisgroep Alkmaar				
	Rijnstate Ziekenhuis				
	Martini Ziekenhuis				
Portugal	Centro Hospitalar Universitário de São João	week 52 2021	27 Dec 2021	week 24 2022	19 Jun 2022
	Centro Hospitalar e Universitário de Lisboa Norte				
	Centro Hospitalar e Universitário de Lisboa Central				
Spain	Hospital Universitario Virgen de las Nieves – Andalucía	week 1 2022	3 Jan 2022	week 26 2022	3 Jul 2022
	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 Clínic de Barcelona – Catalunya				
	Hospital Sant Joan de Déu – Catalunya				
	Hospital Clínico Universitario de Santiago – Galicia				
	Hospital Universitario La Paz – 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				
	Complejo Hospital Universitario Doctor Negrín – Canarias				
	Complejo Hospitalario de Cáceres – Extremadura				
	Complejo Hospitalario de Badajoz – Extremadura				

** Source: ECDC website reporting GISAID results: https://www.ecdc.europa.eu/en/publications-data/data-virus-variants-covid-19-eueea. "Start week" represents the first week when the proportion of named variants sequenced was ≥80%. "End week" represents the last week in which the proportion of named variants sequenced was ≥80%. All but one country was still at 100% Omicron dominance at the end of their data collection period (no data for Luxembourg after week 22).*
*** No data for Malta after week 1, 2022.*

Descriptive analysis[2]

Hospital and SARI patient recruitment

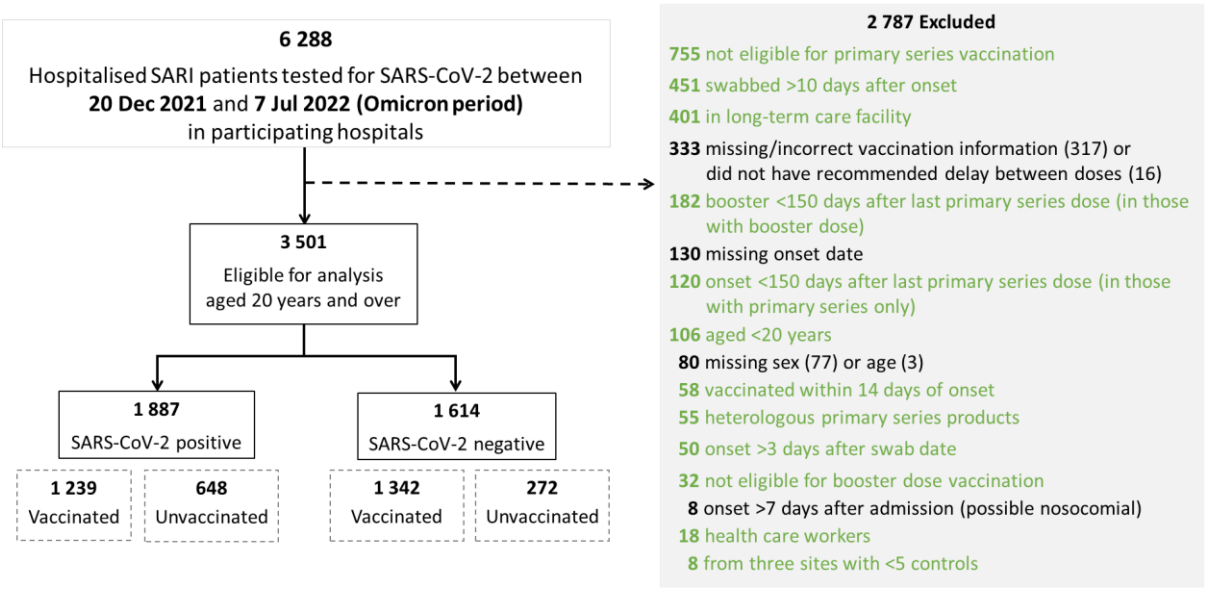
This analysis estimates COVID-19 vaccine effectiveness among hospitalised SARI patients aged 20 years and older.

As of the data deadline (11 July 2022), data were available from 41 hospitals in 12 countries: Belgium (six hospitals), Croatia (one hospital), Czechia (one hospital), France (three hospitals), Germany (one hospital), Greece (one hospital), Ireland (one hosptial), Luxembourg (one hospital), Malta (one hospital), the Netherlands (six hospitals), Portugal (three hospitals) and Spain (16 hospitals). There were 10 027 records submitted from all 12 countries with a swab date later than between 20 December 2021 and 7 July 2022 inclusive, before exclusions (using admission date as a proxy for those with missing swab date).

There were 6 288 remaining SARI patient records among which, 3 501 records were eligible for descriptive analyses. An extensive description of reasons for patient's exclusion is presented in Figure 2.

For primary series vaccine effectiveness estimates, those who received their second dose (or first dose for Jcovden[3]) <150 days before onset were excluded to allow comparability with vaccine effectiveness in those who had received their first booster dose (most countries had recommended booster dose at five months after the last primary series dose). Those receiving a booster were not included in this analysis of primary series effectiveness. For vaccine effectiveness of primary series plus booster dose, those who had received primary series only were excluded as well as those receiving a second booster dose.

Figure 2. Flowchart of inclusion and pooled data of participating EU/EEA countries, Omicron-dominant period (20 December 2021–7 July 2022)*



** Final included data after the exclusions above are from 33 hospitals in eight countries, with swab dates from 21 December 2021 to 2 July 2022. Analysis exclusions are indicated in green text.*

Hospitalised SARI patients

The 3 501 eligible hospitalised SARI patients were from 33 hospitals across 8/12 (67%) participating countries. Forty-one percent (1 420) of the hospitalised SARI patients were aged 80 years and older. Fifty-seven percent of cases (1 080) and 54% of controls (875) were male. Sixty-eight percent of cases (1 276) and 77% of controls (1 250) had at least one of four commonly collected chronic conditions (diabetes, heart disease, lung disease, asthma). More controls than cases were vaccinated (1 342 controls; 83% vs 1 239 cases; 66%) (Table 4).

[2] All data presented in this section might be updated in future reports

[3] Booster effectiveness analysis not done for Jcovden (not enough SARI cases)

The number of eligible cases recruited into the study between week 51, 2021 and week 26, 2022 peaked at 194 cases in week 2, 2022. There were two further (smaller) peaks in week 14, 2022 (76 cases) and week 25 (71 cases). The number of controls recruited fluctuated between 39 and 92 in all but three weeks, in which the total did not reach 25. Most SARI patients vaccinated only with a primary course (330; 57%) received their last dose between weeks 17 and 27, 2021. Most of those who had received a first booster dose (1 973; 65%) received this between weeks 43 and 50, 2021 (Figure 3).

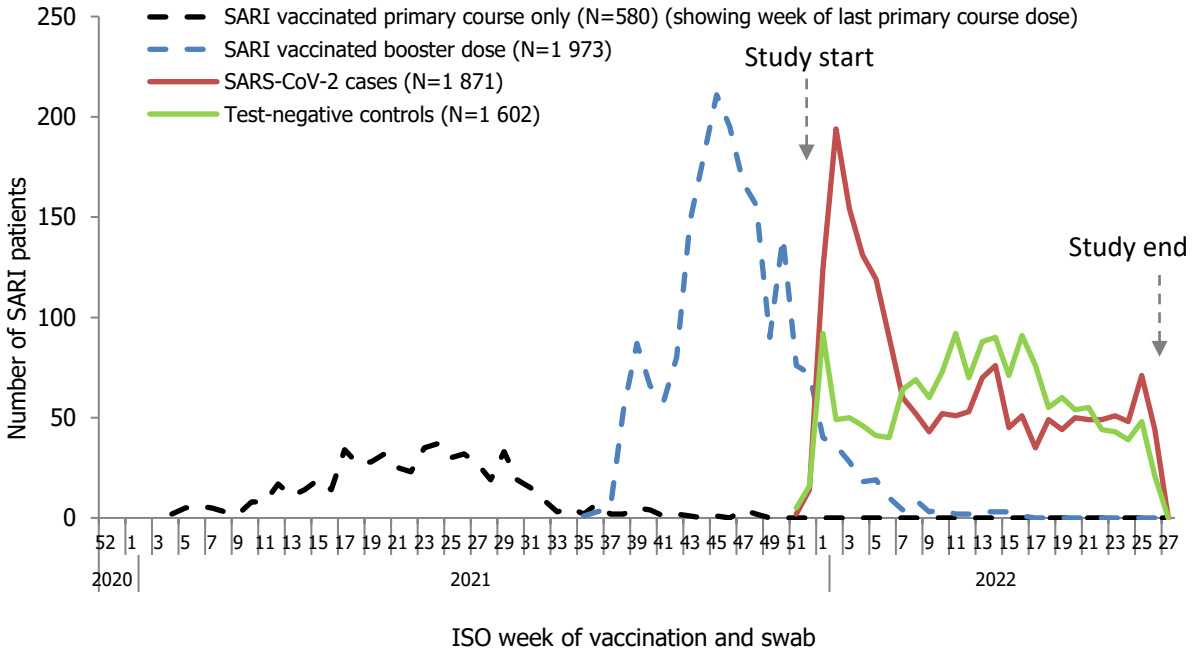
Vaccine effectiveness is described below for the Omicron period for which data were available e.g 21 December 2021–2 July 2022 (Figure 2).

Table 4. Characteristics of eligible SARI patients aged 20 years and older in EU/EEA participating countries[a], Omicron-dominant period (21 December 2021–2 July 2022; n = 3 501)

Characteristics		Cases (N = 1 887) n (%)	Controls (N = 1 614) n (%)	p-value
Sex	Male	1 080 (57.2)	875 (54.2)	0.113 [b]
	Female	807(42.8)	739 (45.8)	
Age (years)	Median	77	75	–
	20–59	284 (15.1)	297 (18.4)	<0.001 [b]
	60–79	778 (41.2)	722 (44.7)	
	≥80	825 (43.7)	595 (36.9)	
Any of the four chronic conditions[c]	Yes	1 276 (67.6)	1 250 (77.4)	<0.001 [b]
	No	611 (32.4)	364 (22.6)	
COVID-19 vaccination status[d]	Unvaccinated	648 (34.3)	272 (16.9)	<0.001 [b]
	Fully vaccinated with primary series only	337 (27.2)	243 (18.1)	
	Fully vaccinated with primary series plus first booster dose[e]	886 (71.5)	1 087 (81.0)	
	Fully vaccinated with primary series plus second booster dose[e]	16 (1.3)	12 (0.9)	
Vaccine product: first dose	Comirnaty	1 008 (81.4)	1 030 (76.8)	Na [g]
	Vaxzevria	99 (8.0)	147 (11.0)	
	Spikevax	103 (8.3)	123 (9.2)	
	Jcovden	28 (2.3)	39 (2.9)	
	Other/unknown	1 (0.1)	3 (0.2)	
Vaccine product: second dose[e]	Comirnaty	1 009 (83.3)	1 027 (78.8)	Na [g]
	Vaxzevria	99 (8.2)	147 (11.3)	
	Spikevax	102 (126)	126 (9.7)	
	Other/unknown	1 (0.1)	3 (0.2)	
Vaccine product: first booster dose	Comirnaty	723 (80.2)	751 (68.3)	Na [g]
	Spikevax	176 (19.5)	335 (30.5)	
	Other/unknown	3 (0.3)	12 (1.1)	
Vaccine product: second booster dose	Comirnaty	14 (87.5)	11 (91.7)	Na [g]
	Spikevax	1 (6.3)	1 (8.3)	
	Unknown	1 (6.3)	0 (0.0)	

[a] Eight participating countries submitted eligible data by 07 July 2022: Belgium, Croatia, France, Ireland, Malta, the Netherlands, Portugal and Spain.
[b] Fisher's exact test
[c] The four chronic conditions are: diabetes, heart disease, lung disease and asthma.
[d] Patients were considered fully vaccinated with the primary series if they received two doses of a vaccine with a two-dose course (or three doses if immunocompromised, in one country) or one dose of a vaccine with a one-dose course at least 14 days before symptom onset.
[e] Any product
[f] Fourteen cases and 24 controls received Janssen as first dose, with second dose ≥5 months later (entered as first booster dose).
[g] Not applicable

Figure 3. Number of cases and controls by ISO week of specimen collection and number of patients vaccinated with complete primary course and primary course plus booster, by ISO week of vaccination, eight EU/EEA countries, 21 December 2021–2 July 2022 (n = 3 473*)



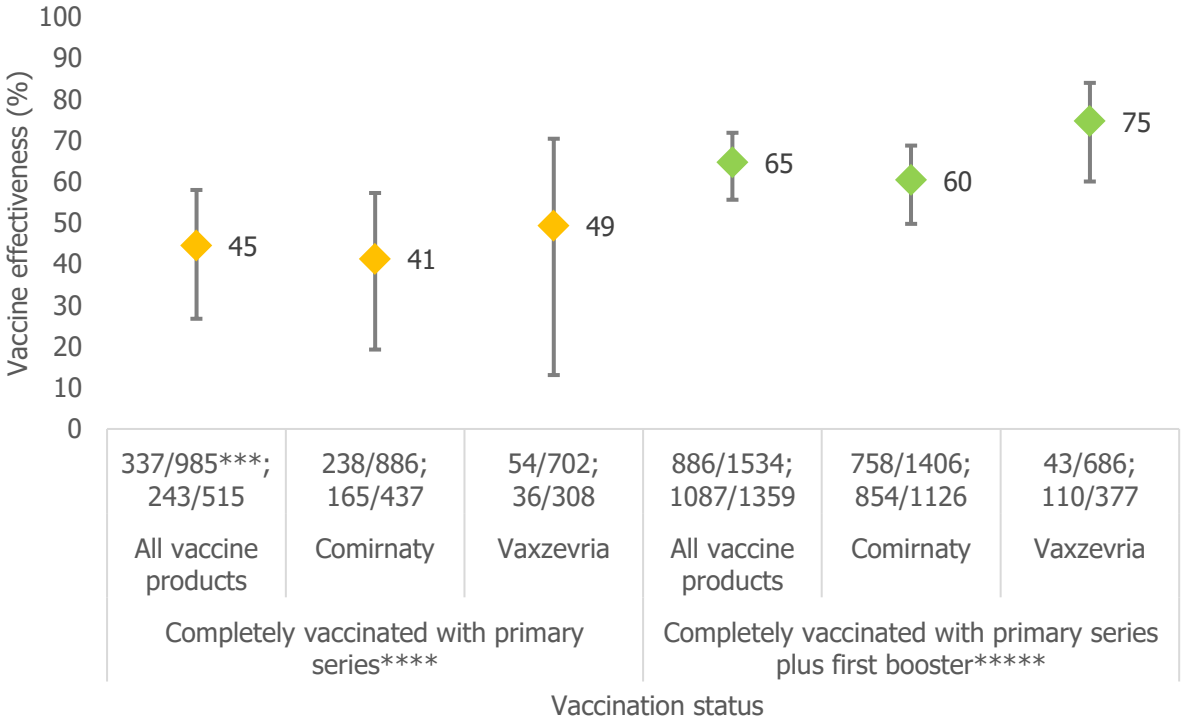
**Note: The 28 SARS-CoV-2 cases listed in Table 4 who had received a second booster dose were not included in the VE analyses or this figure.*

COVID-19 vaccine effectiveness estimates in the Omicron period

Vaccine effectiveness for all ages (≥ 20 years)

The adjusted vaccine effectiveness of complete primary series of any homologous vaccine product against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients aged 20 years and older, swabbed during the Omicron period, in the booster dose target group, ≥150 days after complete primary series was 45% (95% CI: 25–58%). Complete primary series vaccine effectiveness by product was 41% (95% CI: 19–57%) for Comirnaty and 49% (95% CI: 13–71%) for Vaxzevria. For complete primary series plus booster, vaccine effectiveness for all products combined was 65% (95% CI: 56–72%); 60% (95% CI: 50–69%) for Comirnaty and 75% (95% CI: 60–84%) for Vaxzevria (Figure 4).

Figure 4. Overall adjusted vaccine effectiveness of any COVID-19 vaccine product against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients aged 20 years and older at specimen collection date, by vaccination status, eight EU/EEA countries*, 21 December 2021–2 July 2022 (n = 3 473)**

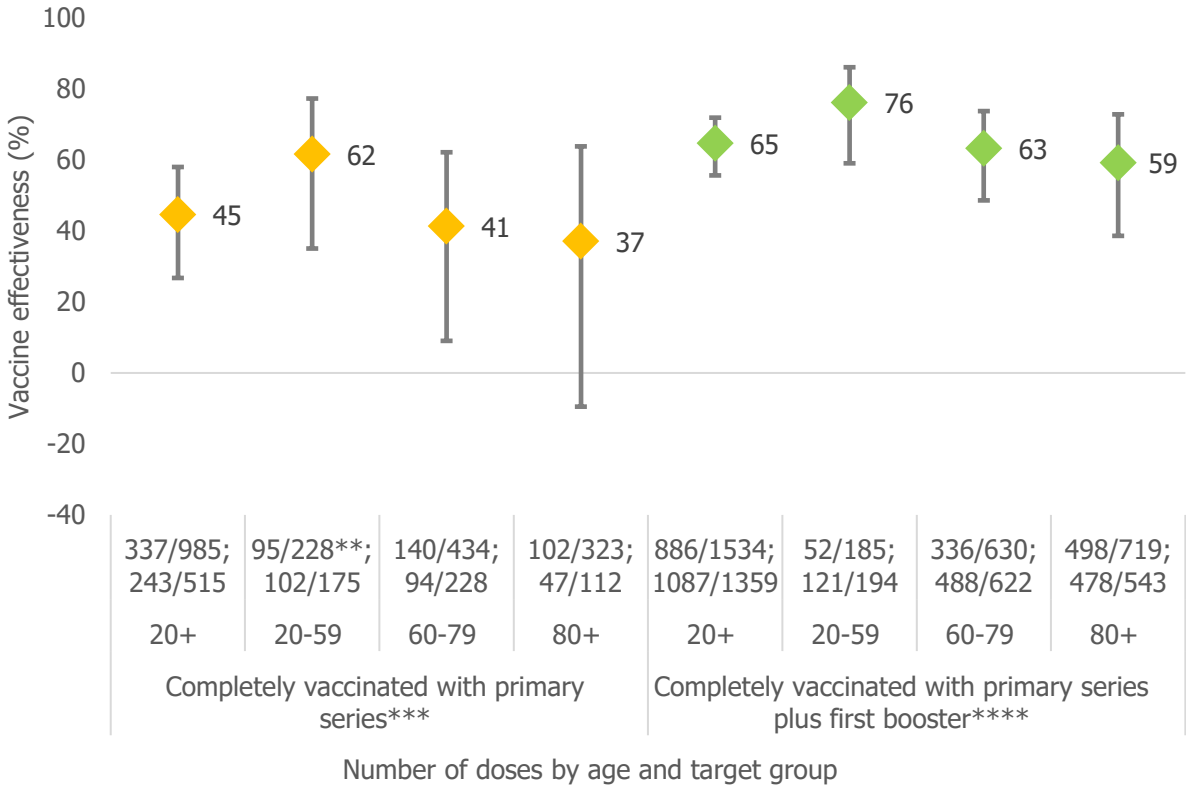


** Eight participating countries submitted eligible data by 7 July 2022: Belgium, Croatia, France, Ireland, Malta, the Netherlands, Portugal and Spain.*
*** Note that the total number of cases and controls within each vaccine effectiveness dose analysis excludes the other (i.e. complete primary course for all products N =1 500 as those with booster dose were excluded; complete primary course + booster for all products N = 2 893 as those with primary course alone were excluded).*
**** Numbers in the x-axis show vaccinated cases/all cases; vaccinated controls/all controls, for each vaccine product.*
***** Completely vaccinated with primary series indicates patients who received one dose of a one-dose schedule or two/three of a two- or three-dose (if immunocompromised) schedule.*
****** Any product*

Vaccine estimates by age group (20–59 years, 60–79 years, ≥80 years)

The results of the analysis by age group for all products combined during the Omicron period, indicated that adjusted vaccine effectiveness point estimate for complete vaccination with primary series alone was higher in those aged 20–59 years than in the older age groups, although all confidence intervals overlap. A similar pattern was observed for complete vaccination with the primary series plus booster (Figure 5).

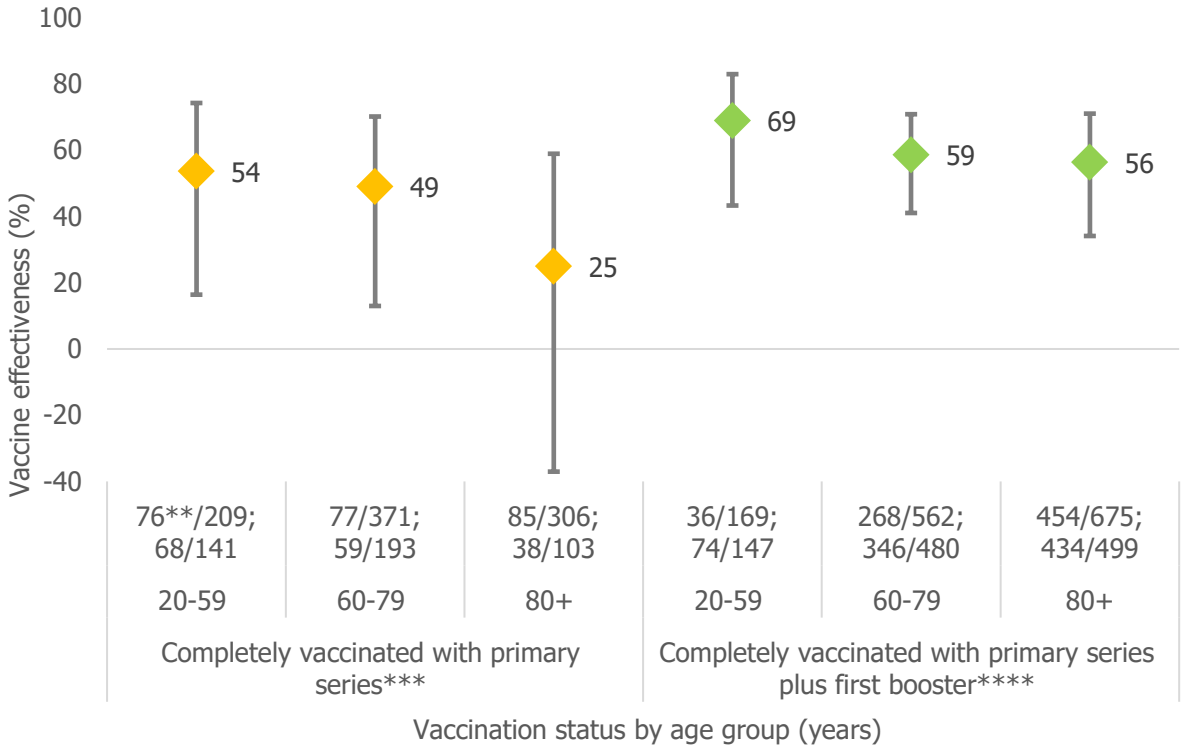
Figure 5. Overall adjusted vaccine effectiveness of any COVID-19 vaccine product against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients aged 20 years and older at specimen collection date, by dose and age group, eight EU/EEA countries*, 21 December 2021–2 July 2022 (n = 3 473)



** Eight participating countries submitted eligible data by 7 July 2022: Belgium, Croatia, France, Ireland, Malta, the Netherlands, Portugal and Spain.*
*** Numbers in the x-axis show vaccinated cases/all cases; vaccinated controls/all controls, for any vaccine product.*
**** Completely vaccinated with primary series indicates patients who received one dose of a one-dose schedule or two/three of a two- or three-dose (if immunocompromised) schedule.*
***** Any product*

Adjusted vaccine effectiveness for complete vaccination alone with Comirnaty among those aged 20–59 years was 54% (95% CI: 16–74%) for primary series alone and 69% (95% CI: 43–83%) for primary series plus booster. For those aged 60–79 years, primary series adjusted vaccine effectiveness was 49% (95% CI: 13–70%); while it was 59% (95% CI: 41–71%) with the addition of a booster dose. Among those aged 80 years and older, adjusted vaccine effectiveness for primary series alone was 25% (95% CI: -37–59%); 56% (95% CI: 34–71%) with a booster dose (Figure 6).

Figure 6. Adjusted vaccine effectiveness of the Comirnaty COVID-19 vaccine against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients aged 20 years and older at specimen collection date, by dose and age group, eight EU/EEA countries*, 21 December 2021–2 July 2021 (n = 2 937)



** Eight participating countries submitted eligible data by 7 July 2022: Belgium, Croatia, France, Ireland, Malta, the Netherlands, Portugal and Spain.*
*** Numbers in the x-axis show vaccinated cases/all cases; vaccinated controls/all controls, for Comirnaty vaccine product.*
**** Completely vaccinated with primary series of Comirnaty indicates patients who received two/three of a two- or three-dose (if immunocompromised) schedule.*
***** Any product*

For Vaxzevria, adjusted vaccine effectiveness for complete vaccination alone among those aged 20–59 and 80 years and older was not calculated for primary series alone or for primary series plus a booster dose, as the total number of vaccinated cases and controls in each of these categories was below 20 (see Annex 2). For those aged 60–79 years, primary series adjusted vaccine effectiveness was 31% (95% CI: -41–66%); while it was 73% (95% CI: 50–86%) with addition of a booster dose.

Challenges and limitations

As the vaccines were rolled out across the 12 participating countries, vaccination coverage among target groups increased. As a result, there has been an increasingly small group of unvaccinated controls and current unvaccinated controls may not be representative of those from earlier in 2021. 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 Omicron period, there was a small number of cases and controls that were vaccinated with Vaxzevria outside of the age group 60–79 years. This made interpreting the vaccine effectiveness estimates for these age groups difficult.

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 sometimes 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. Consequently, there have been very few sequences provided to date, hence the use of dates from GISAID as a proxy to estimate vaccine effectiveness during the Omicron period in this report.

In any multi-country study such as this, heterogeneity between sites is always a potential limitation. This is caused not only by differences in data collection processes and vaccination rollout 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 a 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, including 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 September, based on data reported as of 5 September 2022. Additional analyses will estimate vaccine effectiveness against SARS-CoV-2 among hospitalised SARI patients as follows (sample size permitting):

- by different delays from vaccination to symptom onset (e.g. 0–59 days vs ≥60 days);
- 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;
- using the WHO SARI case definition, as included in the core ECDC protocol [2];
- via a two-stage analysis (once individual site sample sizes permit), to assess heterogeneity.

Site visits are also being undertaken to understand potential qualitative heterogeneity (e.g. different vaccination rollout strategies, different mixes of vaccines at different times, circulation of different variants at different times). Planning of additional meetings with participating countries 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 in mid-March 2022, provided estimates using data from the second half of 2021 on SARI patients aged 30 years and older [5]; this report presents data up to early July 2022 and provides estimates using data for the Omicron period, for SARI patients aged 20 years and older. Twelve countries participated in this multi-country, test-negative, case–control study and all participating countries submitted data by 10 July 2022. A tremendous amount of work continues to be done at the country level to reduce the time from data collection to submission.

Among 3 501 hospitalised SARI patients aged 20 years and older who were eligible to receive the COVID-19 vaccine at the time of sample collection, results suggest moderate 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 of the vaccination campaign across EU/EEA countries. The adjusted vaccine effectiveness for full vaccination with the primary series plus booster dose was higher than vaccine effectiveness for primary series alone. Our results are in the lower range of published estimates, e.g. some studies show around 80−90% protection for up to two to three months after receiving the booster dose [12-14]. Few studies reported lower estimates for Vaxzevria (below 80%) [15-17]. When making comparisons across different studies, it is important to account for differences in study populations (e.g. the age differences), varying time since vaccination (not yet available in the current analysis), different study designs and settings, and study limitations (see above). In addition, our study shows a difference in VE for the sub-lineages of Omicron, with VE for BA.1 being higher than that for BA.2. The sub-lineage period is important to consider when measuring Omicron VE. The more sensitive case definition used for the purpose of the current analysis may have lowered the overall estimated level of effectiveness, as compared to other studies. Differences in effectiveness by vaccine product need to be further investigated as confidence intervals overlapped.

Vaccine effectiveness was higher among those in the youngest age group (20–59 years) than those in the older age groups (60–79 years and ≥80 years), for all products combined and for Comirnaty and Vaxzevria separately which is in line with published data [14, 18, 19]. Those in the older age groups, however, having been targeted for primary series and booster doses earlier, would have likely had more time since last vaccination than those in the youngest age group. Time since vaccination will be investigated in the next update, as there is probably a range of time since vaccination for those becoming ill within the Omicron period (current data are from the end of December 2021 to early July 2022). It will also be important to look at vaccine effectiveness at the sub-lineage level as the Omicron period was marked by several sub-lineages of the virus (so far, from BA.1 to BA.5). The vaccine effectiveness estimates for older adults presented in this report are similar to those already published in other studies, and results for Comirnaty and Vaxzevria fall within the range of results already published [20].

This ECDC multi-country study complements other international efforts to respond to COVID-19 vaccine effectiveness questions, both globally and in Europe [20]. Use of the same approach to study design and data collection can contribute to a more comprehensive discussion of 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 are being 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 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 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;
- 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:

- 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;
- 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[4] 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[4] 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[4] before symptom onset or received the second dose on the same day as or after symptom onset.

[4] The period <14 days from last dose to onset was the exclusion cut-off in the protocol. However, in this Omicron analysis, as adjusted vaccine effectiveness was being compared between patients receiving booster doses and those with primary series vaccination alone, SARI patients with onset <150 days from last primary series dose were excluded (as they would not have been able to have received a booster dose vaccination, due to too short a time since last primary series dose).

- **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.

The period between December 2021 and July 2022 was used as a proxy for the Omicron-dominant period, using GISAID data to define week numbers for each participating country when ≥80% or <80% sequenced samples belonged to the Omicron variant.

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 20 years and older, who were swabbed between 27 December 2021 and 2 July 2022. 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 three age groups: 20–59 years, 60–79 years and ≥80 years. To avoid sparse data bias, vaccine effectiveness estimates were not calculated where the total number of vaccinated cases and controls was fewer than 20.