

Interim analysis of COVID-19 vaccine effectiveness against Severe Acute Respiratory Infection due to laboratory-confirmed SARS-CoV-2 among individuals aged 20 years and older, ECDC multi-country study – fourth update

16 March 2023

Key facts

- 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 within the ECDC Vaccine Effectiveness, Burden and Impact Studies infrastructure (VEBIS) [1,2]. 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], 14 March 2022 [5], and 8 November 2022 [6]. Compared with the previous report, the data presented include a longer period of Omicron dominance, from 21 December 2021 to 30 September 2022.
- This report includes vaccine effectiveness estimates for first booster doses of COVID-19 vaccines and relative vaccine effectiveness estimates of first booster dose, using those with complete primary series vaccination at least 150 days before onset as the reference group.
- As of 18 November 2022 (data submission deadline for the current analysis), a total of 13 EU countries were participating in the multicentre vaccine effectiveness study: Belgium, Croatia, Czechia, France, Germany, Hungary, Ireland, Lithuania, Luxembourg, Malta, Portugal, Romania, and Spain.
- The COVID-19 vaccine effectiveness estimates presented in this report are pooled estimates from seven countries: records from six countries were excluded as fewer than five cases or controls or fewer than 20 total patients were reported after applying exclusion criteria.
- The adjusted vaccine effectiveness of first booster dose vaccination in preventing SARI hospitalisations associated with laboratory-confirmed SARS-CoV-2 infection was moderate at 54% (95% CI: 45–61%), and relative to complete primary series vaccination adjusted relative effectiveness of the first booster dose was 29% (95% CI: 14–42%).
- The results presented in this report suggest a lower relative vaccine effectiveness for the first booster dose vaccination among younger adults (20–59 years of age) compared with older adults (60–79 and ≥80 years), albeit with wide overlapping confidence intervals.
- Vaccine effectiveness and relative vaccine effectiveness of the first booster dose vaccination remained high in the first four months after vaccination, but reduced substantially after four months. A similar pattern was observed for 60–79 and ≥80 years of age groups. Limited sample size did not allow vaccine effectiveness estimation of time since booster dose for the youngest age group (20–59 years).
- A longer time since receiving a booster dose coincided with onset during the dominance of BA.4/BA.5 Omicron sublineages, and it is challenging to attribute the apparent decrease in vaccine effectiveness to either the impact of waning immunity alone or to the immune escape properties of these Omicron sublineages.

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Scope of this document

This document reports the pooled estimates from the ECDC test-negative case-control study of COVID-19 vaccine effectiveness against hospitalisation with SARS-CoV-2, 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 2.0* [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 European Union/European Economic Area (EU/EEA).

For a brief outline of previous published vaccine effectiveness reports, see Table A1 in Annex 1. This fourth update contains booster dose vaccine effectiveness results among individuals aged 20 years and older for the Omicron-dominant period (20 December 2021 to 30 September 2022). It also contains estimates by age group. Compared with the previous report, there are additional estimates for vaccine effectiveness by time since vaccination and for relative vaccine effectiveness of the booster dose versus primary series.

Detailed objectives of the multi-country study can be found in the ECDC core protocol [2], as well as in Annex 2. 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 here in Annex 3. Additional details regarding the methods of the study can also be found in the ECDC core protocol [2].

Background

As of 30 September 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 [7]: Comirnaty (BNT162b2), Spikevax (mRNA-1273), Vaxzevria (AZD1222), Jcovden (Ad26.COV 2.5), Nuvaxovid (NVX-CoV2373), and the non-spike protein based COVID-19 vaccine (inactivated, adjuvanted) Valneva (VLA2001).

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 started vaccination programmes on different dates, prioritising specific risk groups. By the start of week 39, 2022 (30 September 2022, the end of the study period for the current report), the uptake of full vaccination with the primary series and of first booster dose 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*, first and second booster dose in participating EU/EEA countries, as of week 4 2023 (ending 29 January 2023)

Country	Full vaccination with primary series /first booster/second booster vaccination uptake (%)		
	25–49 years	50–59 years	≥60 years
Belgium	84.9/66.1/23.3	91.5/82/47.3	98.2/92.6/70.9
Croatia	58.7/14.6/0.2	71.7/28.5/0.5	77.3/50.3/3
Czechia	66.3/35/2.2	77.2/54/5.7	86/72.6/22.3
France	89.1/67.1/3.5	91.7/80.4/12.4	91.1/84.3/43.8
Germany	NA	NA	NA
Hungary	66/35.9/1.4	74.7/50.3/2.8	81.9/67.4/12.6
Ireland	90/65.3/9.4	100/88.2/38.2	100/100/76.7
Lithuania	80.1/31.9/0.6	80.9/37.8/0.8	78.2/51.8/3.3
Luxembourg	77.7/59.9/2.7	84.8/75.4/6.9	91.1/85.3/49.1
Malta	93/77.7/1.4	90.4/90/4.3	97.3/87.5/44.1
Portugal	91.1/69.2/5.3	94.8/88.8/42.1	99/98.8/74.7
Romania	51.4/9.5/0.1	56/13.5/0.2	46.7/13.3/0.3
Spain	79.2/50.5/3.9	88.4/76.8/10.7	96.7/92.8/58.6
Median EU/EEA	79.2/52.6/2.7	83.9/73.2/6.8	91.1/84.9/35

Source: ECDC Vaccine Tracker [8]. 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 effectiveness of COVID-19 vaccine booster dose against SARI due to laboratory-confirmed SARS-CoV-2 in hospitalised patients aged 20 years and older over time since vaccination. COVID-19 vaccinations were compared between SARI patients who were **fully vaccinated and received the first booster dose** (as per the manufacturer’s instructions) and SARI patients who were either **unvaccinated** or **fully vaccinated** with the primary series (one dose for vaccine products with a one-dose course, two doses for vaccine products with a two-dose course, or three doses for those who are immunocompromised¹, as per the manufacturer’s instructions) for ≥150 days.

The above full vaccination with primary series for two-dose course vaccines excludes heterologous vaccination (i.e. vaccination with two different vaccine products). Direct effectiveness estimates are calculated by age group (20–59 years, 60–79 years, ≥80 years), and by time since vaccination (14–59 days, 60–119 days, 120–179 days, 180–239 days, 240–299 days).

Countries participating in the study and in this analysis

As of 18 November 2022 (data submission deadline), a total of 42 hospitals across 13 countries (Belgium, Croatia, Czechia, France, Germany, Hungary, Ireland, Lithuania, Luxembourg, Malta, Portugal, Romania, and Spain) were participating in the ECDC study (Figure 1; Annex 4). All countries submitting eligible data by this deadline for the Omicron-dominant period were included in this report, which comprised 30/42 (71%) participating hospitals from 7/13 (54%) participating countries. Six countries with fewer than five cases or controls or fewer than 20 cases and controls combined after applying exclusion criteria (Figure 2) were excluded as per protocol.

Figure 1. Map of the 13 participating EU/EEA countries, ECDC multi-country COVID-19 vaccine effectiveness among hospitalised SARI patients, as of 18 November 2022



Ethical approval has been obtained in all 14 sites: Belgium, Croatia, Czechia, France, Germany, Hungary, Ireland, Lithuania, Luxembourg, Malta, Portugal, Romania, and Spain (2 sites: national site and regional Navarra site).

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 and Omicron sublineage (BA.1, BA.2, BA.4/BA.5) dominance are reported in Annex 5, based on data collected by ECDC on the distribution of variants of concern by week and country [9,10], 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%.

Descriptive analysis²

Hospital and SARI patient recruitment

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

As of 18 November 2022, data were available from 42 hospitals in 13 countries: Belgium (6 hospitals), Croatia (2), Czechia (1), France (3), Germany (1), Hungary (1), Ireland (1), Lithuania (2), Luxembourg (1), Malta (1), Portugal (3), Romania (2), and Spain (national site: 15 hospitals; regional Navarra site: 3 hospitals). There were 12 227 records submitted from all 13 countries with a swab date after 20 December 2021 or before 30 September 2022 inclusive, before exclusions (using admission date as a proxy for those with missing swab date).

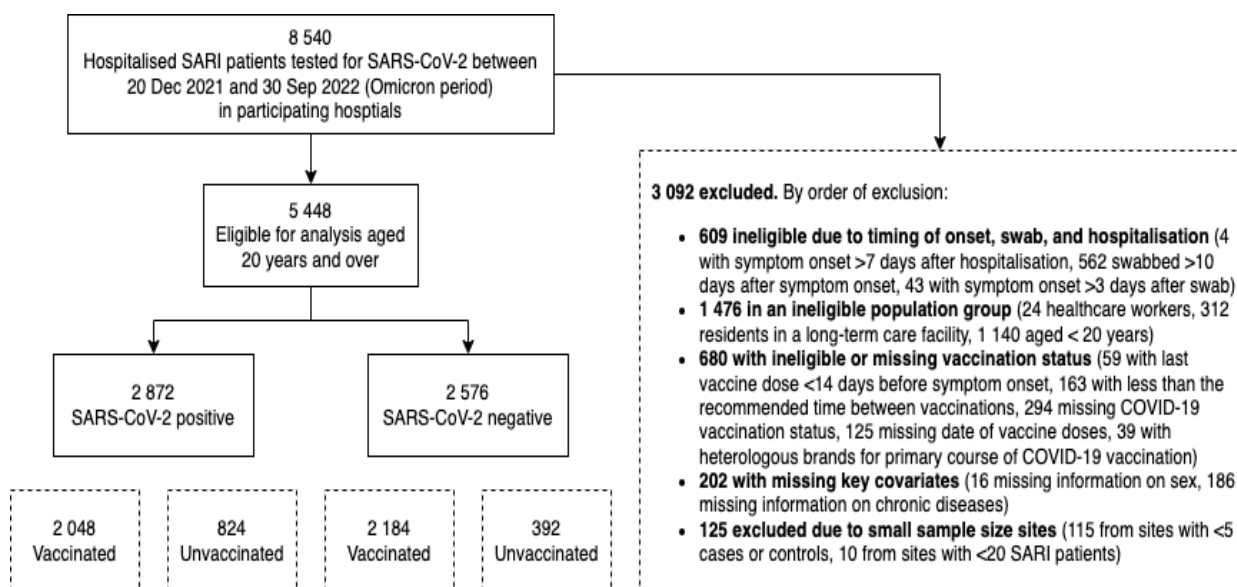
After excluding 2 562 records for patients with missing information to determine inclusion (114 missing consent information, 1 559 missing information on SARI case definition, 409 missing symptom onset date, 8 missing hospital admission date, 442 missing swab date, and 30 missing age), 196 did not meet the ECDC SARI case definition and 929 had a missing RT-PCR test result/did not have an RT-PCR test. There were 8 540 remaining SARI patient records. Of these, a further 3 092 were excluded from this analysis: 609 ineligible due to timing of onset, swab, and hospitalisation (4 with symptom onset >7 days after hospitalisation, 562 swabbed >10 days after symptom onset, 43 with symptom onset >3 days after swab), 1 476 in an ineligible population group (24 healthcare workers, 312 residents in a long-term care facility, 1 140 aged <20 years), 680 with ineligible or missing vaccination status (59 with last vaccine dose <14 days before symptom onset, 163 with less than the recommended time between vaccinations, 294 missing COVID-19 vaccination status, 125 missing date of vaccine doses, 39 with heterologous brands for primary course of COVID-19 vaccination), and 202 with missing key covariates (16 missing information on sex and 186 missing information on common chronic diseases (diabetes, heart disease, lung disease and asthma)). After excluding a further 115 from sites with <5 cases or controls and 10 from sites with <20 SARI patients, there were 5 448 records eligible for descriptive analyses (Figure 2).

For vaccine effectiveness of primary series plus first booster dose, those who were partially vaccinated, had received only primary series vaccination, or had received more than one booster dose were excluded. For relative vaccine effectiveness of primary series plus booster dose compared with primary series only with their last dose ≥ 150 days before onset, those who were unvaccinated, partially vaccinated, received last complete primary course vaccination dose <150 days before symptom onset (if vaccinated with primary course only), or who had received more than one booster dose were excluded. For both analyses, those who were not in the booster target group or received a booster dose <150 days after last complete primary course vaccination dose were excluded. Sites with <5 cases or controls and with <20 SARI patients after restricting to appropriate vaccination status were further excluded.

This left 3 971 SARI patients for the booster dose vaccine effectiveness analysis and 3 494 for the relative vaccine effectiveness analysis.

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

Figure 2. Flowchart of inclusion of pooled data from participating EU/EEA countries providing interim data to the ECDC multi-country COVID-19 vaccine effectiveness study among hospitalised SARI patients, Omicron-dominant period (20 December 2021–30 September 2022)*



* Final included data after the exclusions above are from 30 hospitals in seven countries, with swab dates from 21 December 2021 to 30 September 2022.

Hospitalised SARI patients

The 5 448 eligible hospitalised SARI patients were from 30 hospitals across 7/13 (54%) participating countries. Of the 2 872 hospitalised SARI patients who tested positive for SARS-CoV-2 (cases), 46% (1 331) were aged 80 years and older. Of the 2 576 hospitalised SARI patients who tested negative with SARS-CoV-2 (controls), 37% (954) were aged 80 years and older. Fifty-seven percent of cases (1 628) and 55% of controls (1 424) were male. Seventy-five percent of cases (2 149) and 79% controls (2 042) had at least one of four commonly collected chronic conditions (diabetes, heart disease, lung disease, asthma). Between one-fifth and one-third of SARI patients were swabbed during each of the Omicron sublineage periods (BA.1, BA.2, BA.4/BA.5), or the transition period. More cases than controls were unvaccinated (824 cases; 29% vs 392 controls; 15%) or received only the primary series of COVID-19 vaccination (468 cases; 16% vs 357 controls; 14%) (Table 2).

The number of eligible cases recruited into the study between weeks 51, 2021 and 39, 2022 peaked in week 2, 2022 at 209 cases (BA.1 sublineage dominance period). There were two further (smaller) peaks in week 14, 2022 (97 cases) during the BA.2 sublineage dominance period, and week 27 (104 cases) during the BA.4/BA.5 sublineage dominance period. The number of controls recruited fluctuated between 25 and 119 in all but two weeks (at the end of 2021), in which the total did not reach 25. Most SARI patients vaccinated only with a primary course received their last dose between weeks 10 and 33, 2021 (648; 79%). Most of those who had received a first booster dose received this between week 42, 2021 and week 5, 2022 (2 694; 97%) (Figure 3).

The median delay between last primary series dose and symptom onset for cases who received primary series vaccination only was 248 days (IQR: 190–309 days); for controls, the median delay was 263 days (210–341). For cases who received a booster, the median delay between booster dose and symptom onset was 170 days (105–219); for controls, this was 143 days (96–204). For both cases and controls, time between vaccination and onset was higher during the BA.2 and substantially higher during the BA.4/BA.5 period compared to BA.1 sublineage dominance period. For booster dose, this varied from <80 days during the BA.1 period to >240 days during the BA.4/BA.5 period (Table 2, Figure 3).

Table 2. Characteristics of eligible SARI patients aged 20 years and older in EU/EEA participating countries^a, ECDC multi-country COVID-19 vaccine effectiveness study among hospitalised SARI patients, Omicron-dominant period (21 December 2021–30 September 2022; n=5 448)

Characteristics		Cases (N=2 872) n (%)	Controls (N=2 576) n (%)
Sex	Male	1 628 (56.7)	1 424 (55.3)
Age (years)	Median (IQR)	78 (68–86)	75 (64–84)
	20–59	399 (13.9)	450 (17.5)
	60–79	1 142 (39.8)	1 172 (45.5)
	≥80	1 331 (46.3)	954 (37.0)
Any of the four chronic conditions^b	Yes	2 149 (74.8)	2 042 (79.3)
Omicron sublineage periods^c	BA.1	968 (33.7)	379 (14.7)
	BA.2	595 (20.7)	840 (32.6)
	BA.4/BA.5	622 (21.7)	526 (20.4)
	Sublineage transition period	687 (23.9)	831 (32.3)
COVID-19 vaccination status^d	Unvaccinated	824 (28.7)	392 (15.2)
	Partially vaccinated	30 (1.0)	31 (1.2)
	Fully vaccinated with primary series only	468 (16.3)	357 (13.9)
	Fully vaccinated with primary series plus first booster dose	1 525 (53.1)	1 751 (68.0)
	Fully vaccinated with primary series plus second booster dose	25 (0.9)	45 (1.7)
Vaccine product: first dose	Comirnaty	1 573 (76.8)	1 614 (73.9)
	Vaxzevria	232 (11.3)	305 (14.0)
	Spikevax	179 (8.7)	188 (8.6)
	Jcovden	58 (2.8)	63 (2.9)
	Other/unknown	6 (0.3)	14 (0.6)
Vaccine product: second dose^e	Comirnaty	1 552 (79.1)	1 591 (76.1)
	Vaxzevria	227 (11.6)	299 (14.3)
	Other/unknown	7 (0.4)	16 (0.8)
Vaccine product: first booster dose	Comirnaty	1 214 (78.3)	1 303 (72.5)
	Spikevax	327 (21.1)	477 (26.5)
	Other/unknown	9 (0.6)	17 (0.9)
Vaccine product: second booster dose	Comirnaty	14 (56.0)	21 (46.7)
	Spikevax	11 (44.0)	24 (53.3)
	Unknown	0 (0.0)	0 (0.0)
Days from vaccination Median (IQR)	Last primary series dose to onset, Omicron period	248 (190–309)	263 (210–341)
	BA.1 period	219 (178–255)	212 (184–252)
	BA.2 period	312 (252–359)	274 (240–328)
	BA.4/BA.5 period	389 (318–438)	421 (331–454)
	First booster dose to onset, Omicron period	170 (105–219)	143 (96–204)
	BA.1 period	75 (53–96)	61 (39–84)
	BA.2 period	150 (123–174)	138 (113–163)
	BA.4/BA.5 period	240 (217–266)	256 (231–283)

^a Seven participating countries submitted eligible data by 30 November 2022: Belgium, Croatia, France, Ireland, Malta, Portugal, and Spain.

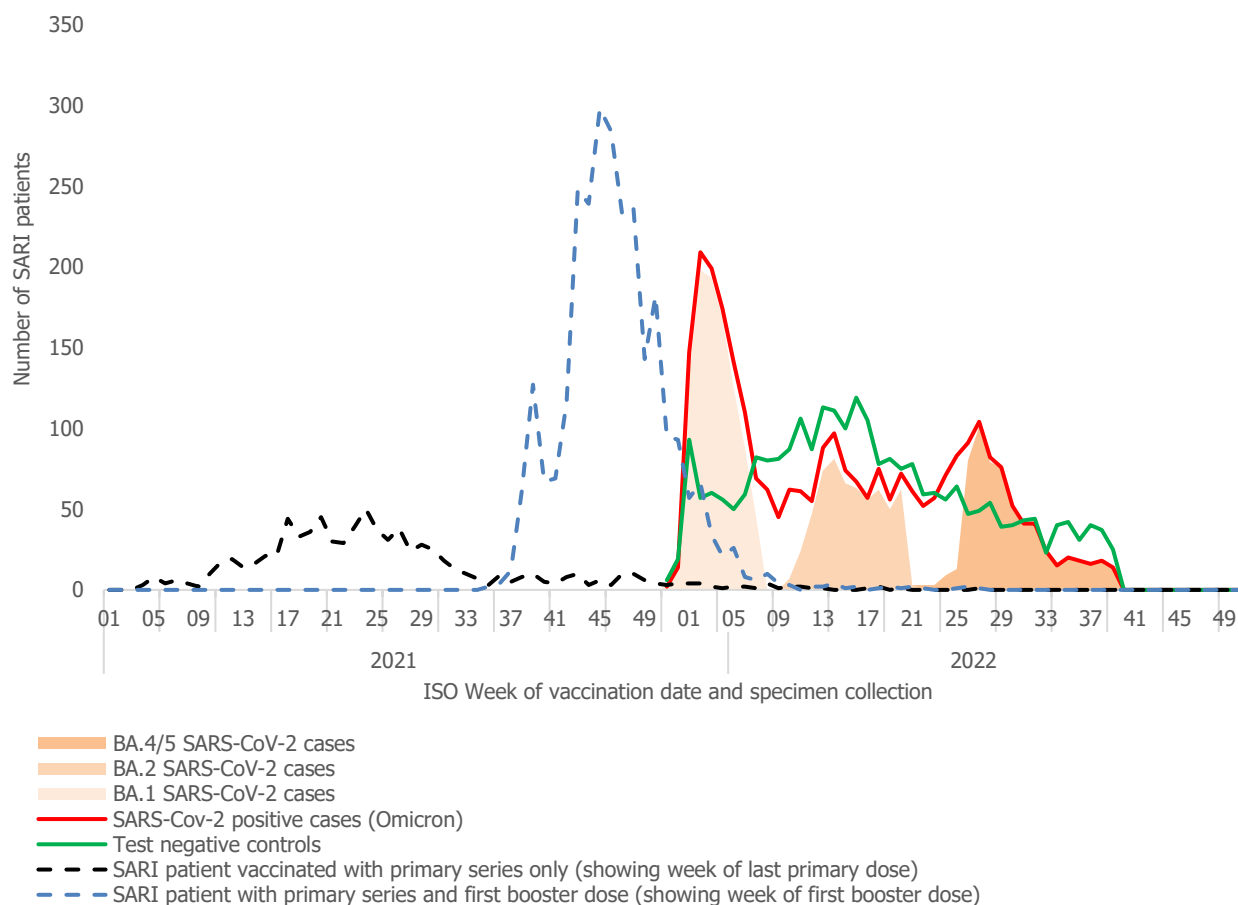
^b The four chronic conditions are: diabetes, heart disease, lung disease and asthma.

^c Patients were grouped into Omicron sublineage dominance periods based on their swab date. The start and end weeks of Omicron and Omicron sublineage (BA.1, BA.2, BA.4/BA.5) dominance are reported in Annex 5.

^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 Twenty-two cases and 37 controls received Jcovden as first dose, with second dose ≥5 months later (entered as first booster dose).

Figure 3. Number of cases and controls by ISO week of specimen collection, number of cases by Omicron sublineage dominance period, and number of patients vaccinated with complete primary series and primary series plus booster by ISO week of vaccination date, ECDC multi-country COVID-19 vaccine effectiveness study among hospitalised SARI patients, seven EU/EEA countries, 21 December 2021–30 September 2022 (n=5 317*)



* Note: The 61 SARS-CoV-2 cases listed in Table 4 who were partially vaccinated and the 70 SARS-CoV-2 cases who had received a second booster dose were not included in the VE analyses or this figure. Cases were grouped into Omicron sublineage dominance periods based on their swab date. The start and end weeks of Omicron and Omicron sublineage (BA.1, BA.2, BA.4/BA.5) dominance by participating countries are reported in Annex 5.

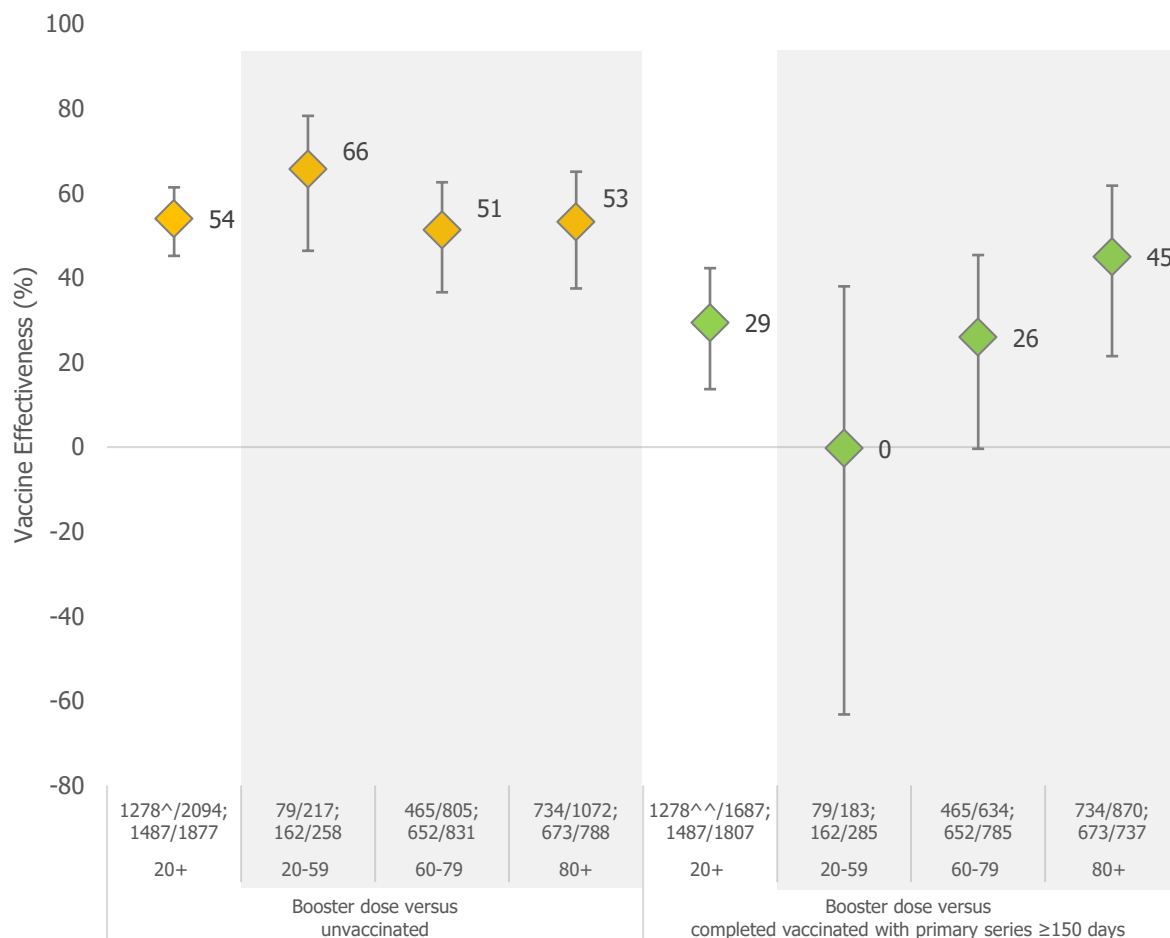
COVID-19 vaccine effectiveness estimates: Omicron period (21 December 2021–30 September 2022)

Vaccine effectiveness is described below for the Omicron period under study for which data were available (21 December 2021–30 September 2022).

Vaccine effectiveness of COVID-19 mRNA booster dose for all ages (≥ 20 years)

The adjusted vaccine effectiveness of the first mRNA booster dose vaccine against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients aged 20 years and older swabbed during the Omicron period was 54% (95% CI: 45–61%). Relative vaccine effectiveness of the first booster dose vaccine compared with complete primary series vaccination only was 29% (14–42%) (Figure 4).

Figure 4. Adjusted* vaccine effectiveness and relative vaccine effectiveness of COVID-19 vaccine mRNA booster against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients aged 20 years and older, by age, seven EU/EEA countries, 21 December 2021–30 September 2022 (n=4 700[†])**



*For all vaccine effectiveness estimates, study site (country) was included in the logistic regression as a fixed effect, with time modelled as a categorical variable (swab month) or as a restricted cubic spline of swab date. Additional adjustments included sex, age (as a categorical variable in 5-year age bands, a continuous variable, or as a restricted cubic spline), and at least one of four commonly collected chronic conditions (diabetes, heart disease, lung disease, and asthma).

** Seven participating countries submitted eligible data by 30 November 2022: Belgium, Croatia, France, Ireland, Malta, Portugal, and Spain.

[†]Patients who were not in the target group for receiving booster dose vaccination or who were vaccinated with the last primary series vaccination <5 months from onset or before booster dose receipt were excluded from this analysis. Note that the total number of cases and controls within each vaccine effectiveness dose analysis excludes the other (i.e. booster vs unvaccinated N = 3 971 as those with primary series only were excluded; booster vs complete primary course N = 3 494 as those unvaccinated were excluded).

[^]Numbers in the x-axis show boosted cases/all cases (total of unvaccinated cases and cases with one booster); boosted controls/all controls (total of unvaccinated controls and controls with one booster), for each age group.

^{^^} Numbers in the x-axis show boosted cases/all cases (total of cases vaccinated with complete primary course only and cases with one booster); boosted controls/all controls (total of controls vaccinated with complete primary course only and cases with one booster), for each age group. Complete primary course indicates patients who received one dose of a one-dose schedule or two/three of a two- or three-dose (if immunocompromised) schedule.

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

Results of the analysis by age group during the Omicron period indicated that the adjusted vaccine effectiveness point estimate for booster dose was above 50% for all age groups. Relative effectiveness of the booster dose versus complete primary series for ≥ 150 days before symptom onset was the highest among patients aged 80 and older (45%, CI: 22–62%), lower for 60–79 years (26%, CI: 0–45%), and the lowest (0%, CI: -63–38%) in the 20–59 age group, although all confidence intervals overlap (Figure 4).

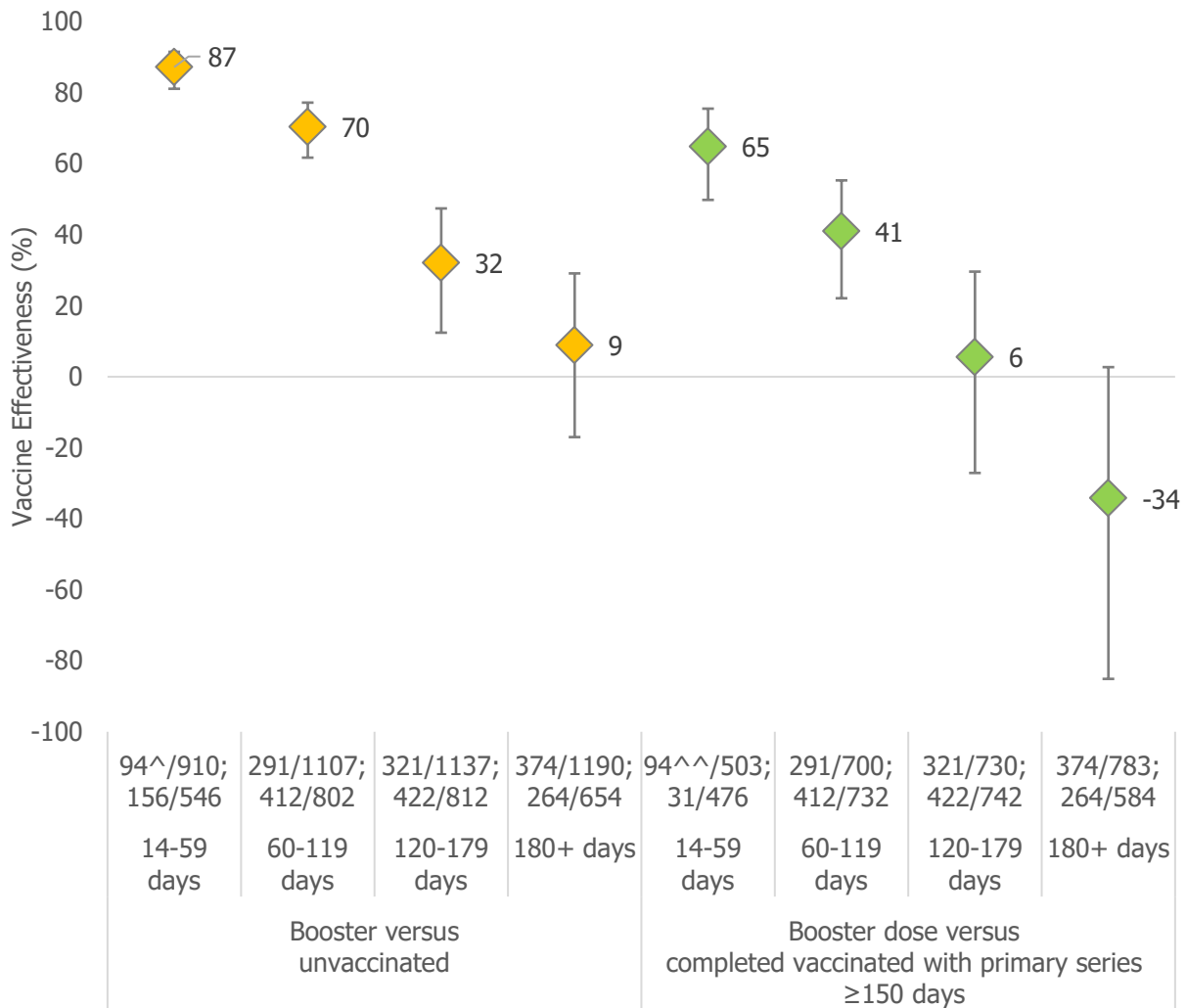
Vaccine effectiveness estimates by time since vaccination (14–59, 60–119, 120–179, 180–239 and ≥ 180 days)

Estimated mRNA booster dose effectiveness was the highest within two months (14–59 days) and for two to four months after vaccination (87%, CI: 81–92%; 70%, CI: 62–77%). The effectiveness of the booster dose vaccination decreased over time and was close to zero at ≥ 6 months or more (≥ 180 days) following vaccination (9%, CI: 17–29%;). Observed vaccine effectiveness was 36% (3–85%) at ≥ 6 months or more (≥ 180 days) following booster dose vaccination (Figure 5).

Relative to receiving the complete primary course vaccination for ≥ 150 days before symptom onset, booster dose effectiveness was the highest within two months (14–60 days) and two to four months of vaccination (65%, CI: 50–76%; 41%, CI: 22–55%), being close to zero at four to six months (120–179 days) following vaccination (6%, CI: -27–30%). Observed relative vaccine effectiveness remained low from six months following vaccination (Figure 5).

Similar trends were observed for older age groups (60–79 years and ≥ 80 years) (results not shown). Sample size was too low to estimate vaccine effectiveness by time since vaccination for the 20–59 age group.

Figure 5 (alternative). Adjusted* vaccine effectiveness and relative vaccine effectiveness of COVID-19 mRNA booster vaccine against laboratory-confirmed SARS-CoV-2 among hospitalised SARI patients aged 20 years and older, by time since vaccination, seven EU/EEA countries, 21 December 2021–30 September 2022 (n = 4 700†)**



*For all vaccine effectiveness estimates, study site (country) was included in the logistic regression as a fixed effect, with time modelled as a categorical variable (swab month) or as a restricted cubic spline of swab date. Additional adjustments included sex, age (as a categorical variable in 5-year age bands, a continuous variable, or as a restricted cubic spline), and at least one of four commonly collected chronic conditions (diabetes, heart disease, lung disease, and asthma).

**Belgium, Croatia, France, Ireland, Malta, Portugal, and Spain.

†Patients who were boosted ≥300 days prior to SARI symptom onset, who were not in the target group for receiving booster dose vaccination, and who were vaccinated with the last primary series vaccination <5 months from onset or before booster dose receipt were excluded from this analysis. Note that the total number of cases and controls within each vaccine effectiveness dose analysis excludes the other (i.e. booster vs unvaccinated N = 3 971 as those with primary series only were excluded; booster vs complete primary course N = 3 494 as those unvaccinated were excluded).

[^]Numbers in the x-axis show boosted cases/all cases (total of unvaccinated cases and cases with one booster); boosted controls/all controls (total of unvaccinated controls and controls with one booster), for each age group.

^{^^}Numbers in the x-axis show boosted cases/all cases (total of cases vaccinated with complete primary course only and cases with one booster); boosted controls/all controls (total of controls vaccinated with complete primary course only and cases with one booster), for each age group. Complete primary course indicates patients who received one dose of a one-dose schedule or two/three of a two- or three-dose (if immunocompromised) schedule.

Challenges, limitations, and interpretations

As the primary course and booster dose COVID-19 vaccines were rolled out across the 13 participating countries, vaccination coverage among target groups increased. As a result, vaccinated and unvaccinated patients in observational studies became increasingly incomparable, even after adjusting for confounding variables such as calendar time, age, sex, and common comorbid conditions. We attempted to address this concern in this report by estimating relative vaccine effectiveness for the booster dose vaccination versus complete primary series vaccination (in addition to against unvaccinated individuals), also estimating relative vaccine effectiveness by age group [11].

One major challenge for the interpretation of results presented is the lack of information on prior SARS-CoV-2 infections. An estimated 47.9% of the population in high-income European countries has been infected by SARS-CoV-2 as of March 2022 [12]. Although many participating countries collect prior infection status of included SARI patients, this field is rarely complete, and we do not systematically adjust for prior infection status. We conducted a sensitivity analysis which showed that including prior infection status in our model adjustment resulted in minimal changes in vaccine effectiveness estimates. The longer the time since vaccination, the more likely an individual will have had SARS-CoV-2 infection, potentially conferring some hybrid immunity [13]. This was especially pertinent during the Omicron period, when transmission was rapid and widespread [13]. As a result, there would be an increase in the estimated vaccination effectiveness after the initial observed early waning. This hypothesis could be tested with detailed data on the timing and number prior infection status for SARI patients.

Another major challenge for interpreting COVID-19 booster dose vaccine effectiveness by time since vaccination is confounding by calendar time, which coincides with different Omicron sublineages that dominated 2022 [14,15]. Most patients who received a booster dose received it between week 42, 2021 and week 5, 2022. Most SARI patients who received a booster four to six months (120–179 days) before onset were admitted during the BA.2 dominance period, and most of those receiving a booster dose more than six months (≥ 180 days) before onset were admitted during the BA.4/BA.5 dominance period, likely explaining the low booster dose effectiveness observed (≥ 180 days after vaccination). As these Omicron sublineages may possess higher immune evasion properties, it is challenging to disentangle the impact of waning immunity over time and the increasing immune-escape properties of different Omicron sublineages [16]. In a sensitivity analysis, we estimated vaccine effectiveness ≥ 180 days after booster dose for BA.2 and BA.4/BA.5 sublineages separately and did not find statistically significant differences, and our current sample size did not permit further disentangling of their impact.

Logistically, 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 reported in the current study to date, and we used dates of sequences of viruses from national surveillance that were uploaded to 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 [17]. 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, or the varying ways that different SARS-CoV-2 variants circulate in each country over time, but also the immunological landscape of the populations related to infection. To help mitigate any differences in processes, all hospital study sites followed the same protocol. Adjustment by time and site as fixed effects in analyses should minimise some of the remaining heterogeneity, as well as stratifying vaccine effectiveness estimates by 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 statistical heterogeneity.

Next steps

The next interim analysis is being conducted based on data reported as of 27 January 2023. 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 (as done in this report);
- by different variant or sublineage periods, as a proxy for circulation of different variants/sublineages (as done for the Omicron variant in this report);
- by different and potentially longer delays from vaccination during different pandemic periods;
- for individuals < 18 years of age;
- for those with different individual comorbidities;
- using the WHO SARI case definition, as included in the core ECDC protocol [2]; and
- 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 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 in mid-November 2022, provided estimates using data from the first half of 2022 on SARI patients aged 20 years and older [6]; this report presents data up to the end of September 2022 and provides estimates using data for Omicron period including BA.1, BA.2, and BA.4/BA.5 sublineage periods. Thirteen countries participated in this multi-country, test-negative, case-control study and all participating countries submitted data by 18 November 2022. A tremendous amount of work continues to be done at the country level to reduce the time from data collection to submission. The reported effectiveness estimates are those for the original mRNA vaccines [15] as bivalent adapted vaccines were only approved by the European Medicines Agency in September 2022 [7].

During the Omicron dominance period in EU/EEA countries, among 4 700 hospitalised SARI patients aged 20 years and older who were eligible to receive an mRNA COVID-19 booster dose vaccine at the time of sample collection, results suggest moderate (54%) vaccine effectiveness for full vaccination with the primary series plus booster dose vaccination against laboratory-confirmed SARS-CoV-2 for COVID-19 vs unvaccinated patients, and 29% relative booster dose effectiveness versus full vaccination with primary series only (last primary series dose received ≥ 150 days before symptom onset). The adjusted vaccine effectiveness for full vaccination with the primary series plus booster dose was similar for all three age groups studied (20–59 years, 60–79 years and ≥ 80 years), and the relative vaccine effectiveness was higher for patients in the older age groups (60–79 years and ≥ 80 years) than in the youngest age group (20–59 years, for whom relative booster dose vaccine effectiveness against hospitalisation with SARS-CoV-2 was not statistically significantly different from zero). The booster dose vaccine effectiveness point estimates presented in this report are lower compared with those already published in other (mostly single country) studies [19–21]. Other (single country) study results have indicated rapid waning of booster dose with increasing time from vaccination [22], and, to the best of our knowledge, there has been no report on relative booster dose vaccine effectiveness against hospitalisation in younger age groups, limiting our ability to compare our estimates with other populations.

In our study, vaccine effectiveness of the booster dose vaccination remained high in the first four months after vaccination, but reduced substantially after four months. Longer time since booster dose coincided with the dominance of BA.4/BA.5 Omicron sublineages and it is challenging to attribute the apparent decrease in vaccine effectiveness to either the impact of waning immunity alone or to immune escape properties of Omicron sublineages [20,21]. Other studies showed similar decrease over time in vaccine effectiveness, with effectiveness against hospitalisation >4 months after first booster dose ranging between 0% and 60% and relative vaccine effectiveness compared to complete primary series between 0% and 30% [18,22–23]. We plan to study vaccine effectiveness by delays since vaccination during different Omicron sublineage periods in the next report (if sample size permitting).

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

While this study included the ECDC clinical case definition for a SARI patient (possible COVID-19 case), further investigations 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 the various sites has provided a powerful platform to monitor and further investigate vaccine effectiveness and inform the development of key vaccine policy issues in 2022. Continuation and expansion of this vaccine effectiveness study is vital to maintain this important work.

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Disclaimer

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

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Annex 1. Previous ECDC vaccine effectiveness reports

Table A1. Previous ECDC publications on COVID-19 vaccine effectiveness against hospitalisation with severe acute respiratory infection laboratory-confirmed with SARS-CoV-2, VEBIS project, 2021

Reference	Date of publication	Study population age groups	Study period	Variant dominance	Vaccination series	Vaccine products	Time since vaccination
[3]	8 October 2021	65+	Up to and including 30 June 2021	Pre-Delta	Primary	<ul style="list-style-type: none"> Any product mRNA brand-specific estimates 	N/A
[4]	20 January 2022	50+	Up to and including 30 June 2021	Pre-Delta	Primary	<ul style="list-style-type: none"> Any product mRNA brand-specific estimates 	N/A
[5]	14 March 2022	30+	Up to and including 15 December 2021	Pre-Delta and Delta	Partially vaccinated; primary	<ul style="list-style-type: none"> Any product mRNA brand-specific estimates 	N/A
[6]	8 November 2022	20+	Up to and including 7 July 2022	Omicron	Primary; first booster	<ul style="list-style-type: none"> Any product mRNA brand-specific estimates 	N/A

Annex 2. 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 3. 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:

- were living in a long-term care facility;
- 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 (whether homologous or heterologous vaccine products were received).
- **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.

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

** 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).*

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.

Analysis

The vaccine effectiveness estimated in this analysis was among hospitalised SARI patients aged 20 years and older, who were swabbed between 20 December 2021 and 30 September 2022. Vaccine effectiveness for fully vaccinated with the primary series plus booster was calculated relative to unvaccinated patients. Relative vaccine effectiveness for fully vaccinated with the primary series plus booster was calculated relative to patients who were fully vaccinated with the primary series (single or two-dose vaccination).

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. For time-since-vaccination-specific vaccine effectiveness estimates, vaccinated SARI patients were stratified into 14-59 days, 60-119 days, 120-179 days, 180-239 days and 240-299 days since booster dose vaccination.

To avoid sparse data bias, vaccine effectiveness estimates were not calculated where the total number of vaccinated cases and controls was fewer than 20.

Annex 4. Participating hospitals, ECDC multi-country COVID-19 vaccine effectiveness studies among hospitalised SARI patients, Omicron-dominant period (20 December 2021–30 September 2022)

Country	Participating hospitals
Belgium	Cliniques universitaires (UCL)
	Algemeen Ziekenhuis Sint-Jan Bugge-Oostende
	Centre Hospitalier Universitaire Saint-Pierre
	Universitair Ziekenhuis Brussel
	Jessaziekenhuis
	Grand Hôpital de Charleroi
Croatia	Clinical Hospital Centre Split
	Zabok General Hospital and Croatian Veterans Hospital*
Czechia	University Hospital Brno
France	CIC Cochin Hospital
	CIC Montpellier University Hospital
	CIC Rennes University Hospital
Germany	Helios hospital
Hungary	Semmelweis University Hospital
Ireland	Saint Vincent's University Hospital
Lithuania	Lithuanian University of Health Sciences Hospital
	Vilnius University Hospital
Luxembourg	Centre Hospitalier de Luxembourg
Malta	Mater Dei Hospital
Portugal	Centro Hospitalar Universitário de São João
	Centro Hospitalar e Universitário de Lisboa Norte
	Centro Hospitalar e Universitário de Lisboa Central
Romania	Clinical Hospital of Infectious and Tropical Diseases "Dr Victor Babes"
	Infectious Diseases Hospital "Sf Parascheva"
Spain	Hospital Universitario Virgen de las Nieves – Andalucía
	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 Clínico Universitario Virgen de la Arrixaca – Murcia
	Complejo Hospital Universitario Doctor Negrín – Canarias
	Complejo Hospitalario de Cáceres – Extremadura
	Hospital de San Pedro – La Rioja
	Hospital Universitario de Navarra
Hospital Reina Sofía de Tudela	
Hospital García Orcoyen de Estella	

*Hospital contributed data to this report, but has ceased participating in the study after June 2022.

Annex 5. Start dates of Omicron and Omicron sublineage dominance in participating EU/EEA countries, ECDC multi-country COVID-19 vaccine effectiveness studies among hospitalised SARI patients, Omicron-dominant period (20 December 2021–30 September 2022)

Country	First day of start week of Omicron variant dominance*	First day of start week of BA.1 sublineage dominance*	Last day of last week of BA.1 sublineage dominance*	First day of start week of BA.2 sublineage dominance*	Last day of last week of BA.2 sublineage dominance*	First day of start week of BA.4/BA.5 sublineage dominance*	End date of study period [†]
Belgium	3 Jan 2022	3 Jan 2022	31 Jan 2022	14 Mar 2022	23 May 2022	20 Jun 2022	30 Sep 2022
Croatia	10 Jan 2022	10 Jan 2022	21 Feb 2022	21 Mar 2022	30 May 2022	4 Jul 2022	30 Sep 2022
Czechia	10 Jan 2022	10 Jan 2022	7 Feb 2022	14 Mar 2022	30 May 2022	20 Jun 2022	30 Sep 2022
France	3 Jan 2022	3 Jan 2022	14 Feb 2022	14 Mar 2022	23 May 2022	20 Jun 2022	30 Sep 2022
Germany	10 Jan 2022	17 Jan 2022	31 Jan 2022	14 Mar 2022	30 May 2022	20 Jun 2022	30 Sep 2022
Hungary	10 Jan 2022	10 Jan 2022	NO DATA [‡]	NO DATA [‡]	NO DATA [‡]	NO DATA [‡]	NO DATA [‡]
Ireland	20 Dec 2021	20 Dec 2021	7 Feb 2022	7 Mar 2022	23 May 2022	20 Jun 2022	30 Sep 2022
Lithuania	10 Jan 2022	10 Jan 2022	31 Jan 2022	7 Mar 2022	NO DATA [‡]	NO DATA [‡]	NO DATA [‡]
Luxembourg	3 Jan 2022	3 Jan 2022	7 Feb 2022	7 Mar 2022	23 May 2022	13 Jun 2022	30 Sep 2022
Malta	3 Jan 2022	3 Jan 2022	NO DATA [‡]	NO DATA [‡]	NO DATA [‡]	NO DATA [‡]	NO DATA [‡]
Portugal	27 Dec 2021	27 Dec 2021	7 Feb 2022	14 Mar 2022	30 May 2022	4 Jul 2022	30 Sep 2022

Country	First day of start week of Omicron variant dominance*	First day of start week of BA.1 sublineage dominance*	Last day of last week of BA.1 sublineage dominance*	First day of start week of BA.2 sublineage dominance*	Last day of last week of BA.2 sublineage dominance*	First day of start week of BA.4/BA.5 sublineage dominance*	End date of study period [†]
Romania	10 Jan 2022	10 Jan 2022	7 Feb 2022	NO DATA [‡]	NO DATA [‡]	NO DATA [‡]	30 Sep 2022
Spain	3 Jan 2022	3 Jan 2022	21 Feb 2022	21 Mar 2022	23 May 2022	27 Jun 2022	30 Sep 2022

*† 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 countries were still at 100% Omicron BA.5 dominance at the end of their data collection period.

*No continuous data for Hungary after week 2, 2022; no continuous data for Malta after week 1, 2022; no continuous data for Lithuania after week 17, 2022.