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Short communication

Effectiveness of JN.1 monovalent COVID-19 vaccination in EU/EEA countries between October 2024 and January 2025: a VEBIS electronic health record network study

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ABSTRACT

We estimated vaccine effectiveness (VE) of Omicron JN.1-adapted COVID-19 vaccines administered during the 2024 autumnal vaccination campaign against COVID-19 hospitalisation and death among eligible individuals aged ≥65 years. The study period was October 2024–January 2025. Using a common protocol across six EU/EEA study sites, we linked electronic health records to construct retrospective cohorts and applied Cox modelling to estimate VE via confounder-adjusted hazard ratios.

The majority of vaccines administered during the study period were Omicron JN.1-adapted COVID-19 vaccines (99 %). VE against hospitalisation was 60 % (95 % Confidence Interval: 48–70 %) and against COVID-19-related death was 78 % (95 %CI: 64–87 %) among individuals aged 65–79 years; 58 % (95 %CI: 48–66 %) and 62 % (95 %CI: 32–79 %) among those aged ≥80 years.

These results indicate high effectiveness in the initial months of the campaign. Continued monitoring is necessary to confirm these results, including estimates of VE in those with longer time since vaccination and during different variant predominance periods.

1. Introduction

Two monovalent COVID-19 vaccines targeting the Omicron JN.1 and KP.2 subvariants received marketing authorisation in the European Union/European Economic Area (EU/EEA) respectively in July and September 2024, for use during the 2024 autumnal campaigns. In the EU/EEA, the Omicron JN.1- adapted COVID-19 vaccine was most frequently administered (99 %), with elderly individuals aged ≥60 or ≥

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65 years and adults with underlying health conditions those primarily targeted by national vaccination campaigns [1].

Surveillance data show that SARS-CoV-2 positivity rates remained below 3 % between October 2024 and January 2025 in the EU/EEA. Omicron BA.2.86 sublineages circulated during this period, including KP.3 and XEC — a recombinant of KS.1.1 and KP.3.3. Countries later detected an increase in LP.8.1, and dominance patterns continued to vary across the EU/EEA [2].

As part of the ECDC funded VEBIS studies, we used data extracted from population electronic health records (EHR) to estimate vaccine effectiveness (VE) of the 2024 autumn COVID-19 dose against severe COVID-19 outcomes, including hospitalisation due to COVID-19 and COVID-19-related deaths across six EU/EEA countries [3]. VE was estimated overall, by age group and by time since vaccination.

2. Methods

2.1. Study design, population and data sources

The study period was between 1st October 2024 and 25th January 2025. Data from six study sites were included in the analysis: Belgium, Denmark, Spain (Navarre), Portugal, Italy and Sweden. Detailed methods and results have been published elsewhere previously [3–5]. Briefly, using a common protocol, we constructed fixed retrospective cohorts with data from each participating country by deterministically linking population and health databases. We included individuals eligible for the 2024 autumnal COVID-19 dose at the beginning of each respective study site's vaccination campaign, ranging between September 18 to October 15, 2024 (Annex, Table 1). We further restricted the analysis to community-dwelling individuals aged ≥65 years old and with no history of COVID-19 vaccine administration, no documented SARS-CoV-2 infection, and no hospitalisation due to COVID-19 in the 90 days preceding the start of the vaccination campaign.

2.2. Vaccination status and outcome definitions

Vaccination was defined as having received any authorised COVID-19 vaccine dose from the start of the vaccination campaign according to each study site recommendations. Vaccinated individual time at risk began 14 days after receiving a qualifying dose, with the first 13 days post-vaccination being excluded from the analysis. Vaccination was classified as a time-dependent exposure, with one individual able to change vaccination status multiple times during follow-up defined by time since vaccination, which was stratified into 14–59, 60–119, 120–179, and ≥ 180 days since vaccination intervals.

Follow-up in both groups continued until the date of any outcome of interest: date of any subsequent COVID-19 vaccination after receipt of the autumn 2024/25 dose, date of death from any cause, or the end of the study follow-up, whichever occurred first. Hospitalisation due to COVID-19 was defined as a severe acute respiratory infection (SARI) admission with a positive SARS-CoV-2 test within 14 days before and up to 1 day after admission, or with a primary COVID-19 diagnosis noted in admission or discharge records. Death related to COVID-19 was defined as a death with the main cause coded as COVID-19, or death for any cause with a SARS-CoV-2 positive laboratory result in the 30 days preceding death. Further information regarding outcome definitions can be found in Table 1 of the annex.

2.3. Statistical analysis

We used Cox regression with calendar time as the underlying time scale to estimate the confounder-adjusted hazard ratios (HR) for vaccination and to derive VE using the formula VE = (1 – HR) x100, along with 95 % confidence intervals (CIs). Besides vaccine status, models included as confounders 5-year age group, sex, region within each country, comorbidity status as defined at study site level, according to presence of one or more conditions at vaccination campaign start date and relevant to local COVID-19 vaccine recommendations (none, medium-risk and high-risk/immunocompromising), and number of previous COVID-19 booster doses. Further details regarding included covariates and their definitions can be found in the Annex, Tables 2 and 3, and in the full study protocol published elsewhere [3]. VE was estimated overall (≥14 days post-vaccination) and by time since vaccination (14–59 days and 60–119 days) stratified by age groups (65–79 and 80+ years). Estimates from study sites based on fewer than 5 events among the unexposed reference strata were excluded. We pooled estimates of VE produced at the study site level via a two-stage random-effects meta-analysis, and calculated the anticipated heterogeneity arising from variations in study design and disease epidemiology. Heterogeneity was assessed using the I^2 index [6]. We employed a fixed-effects model as a secondary analysis for comparative purposes.

Table 1
Distribution of sex, comorbidities, and vaccine product according to autumn 2024/25 COVID-19 vaccination status by the end of follow-up (25th January 2025).

Variable	Characteristic	Unvaccinated N (%)	Vaccinated (≥14d) N (%)
Overall	Total	14,747,206 (100)	3,753,959 (100)
Sex	Female	8,191,662 (55.5)	1,989,396 (53)
	Male	6,555,544 (44.5)	1,764,563 (47)
Comorbidity	No comorbidity	9,200,360 (62.4)	1,729,756 (46.1)
	Medium-risk	5,051,739 (34.3)	1,686,574 (44.9)
	High risk (immune compromising)	495,107 (3.4)	337,625 (9)
COVID-19 boosters received before vaccination campaign start date	0	1,765,450 (12.0)	120,631 (3.2)
	1	7,658,631 (51.9)	109,547 (2.9)
	2	3,562,952 (24.2)	383,667 (10.2)
	3	1,470,605 (10.0)	1,800,669 (48.0)
	4	257,720 (1.7)	910,761 (24.3)
	≥5	31,848 (0.2)	428,684 (11.4)
Vaccine product	Comirnaty JN.1		3,635,185 (96.8)
	Spikevax (JN.1)		92,425 (2.5)
	Comirnaty KP.2		17,565 (0.5)
	Comirnaty XBB.1.5		5117 (0.1)
	Other		3620 (0.1)
	Missing		47 (0)

3. Results

We included 14.8 million unvaccinated and 3.8 million vaccinated individuals across both age groups according to vaccination status by the end of the study period (25th January 2025). Prevalence of comorbidities (medium or high-risk) was higher in those vaccinated (54 %) compared with unvaccinated individuals (38 %). The Comirnaty JN.1 monovalent dose was the most-commonly-administered vaccine (97 %) (Table 1).

Among 65–79-year-old unvaccinated individuals, we counted 3021 hospitalisations due to COVID-19 and 282 COVID-19 deaths among 39,930,332 person-months at risk. Among those vaccinated, we counted 323 COVID-19 hospitalisations and 34 deaths among 6,457,751 person-months at-risk. Overall estimated VE was 60 % (48 % to 70 %) against

Table 2
Vaccine effectiveness against hospitalisation due to COVID-19, including median days since autumn 2024/25 vaccination.

Age group	Status (days since)	Vaccine effectiveness (95 % CI)	Events/person-months	I^2	Study site VE range	Time since vaccination (days) - median (IQR)
	Not vaccinated during the 2024 autumn campaign	***REF***	3021/39,853,839	***REF***	***REF***	***REF***
65–79	Vaccinated (≥14 days ago; overall)	60.3 % (47.6 to 69.9 %)	323/6,340,543	50 %	33–70 %	98 (82;107)
	Vaccinated (≥14 and ≤ 59 days ago)	58.9 % (50.6 to 65.8 %)	218/3,619,957	0 %	55–66 %	52 (45;58)
	Vaccinated (60–119 days ago)	58.6 % (−12.7 to 84.8 %)	105/2,709,500	88 %	−89-85 %	99 (86;107)
	Not vaccinated during the 2024 autumn campaign	***REF***	4842/17,981,299	***REF***	***REF***	***REF***
80+	Vaccinated (≥14 days ago; overall)	57.5 % (47.5 to 65.6 %)	718/3,284,589	57 %	39–67 %	100 (85;108)
	Vaccinated (≥14 and ≤ 59 days ago)	59.1 % (51.8 to 65.3 %)	438/1,851,994	21 %	49–64 %	52 (45;58)
	Vaccinated (60–119 days ago)	53.7 % (21.8 to 72.5 %)	280/1,427,830	82 %	15–73 %	101 (87;107)

Table 3
Vaccine effectiveness against death related to COVID-19, including median time since autumn 2024/25 vaccination.

Age group	Status (days since)	Vaccine effectiveness (95 % CI)	Events/person-months	I^2	Study site VE range	Time since vaccination (days) - median (IQR)
	Not vaccinated during the 2024 autumn campaign	***REF***	282/39,715,508	***REF***	***REF***	***REF***
65–79	Vaccinated (≥14 days ago; overall)	78.1 % (64.1 to 86.6 %)	34/6,341,610	7 %	62–86 %	98 (82;107)
	Vaccinated (≥14 and ≤ 59 days ago)	82.2 % (67.7 to 90.2 %)	16/3620,499	0 %	75–90 %	52 (45;58)
	Vaccinated (60–119 days ago)	74.1 % (45.1 to 87.8 %)	17/2,710,024	12 %	36–88 %	99 (86;107)
	Not vaccinated during the 2024 autumn campaign	***REF***	726/17,954,772	***REF***	***REF***	***REF***
80+	Vaccinated (≥14 days ago; overall)	62.1 % (32.4 to 78.8 %)	110/3,286,745	77 %	21–77 %	100 (85;108)
	Vaccinated (≥14 and ≤ 59 days ago)	59.8 % (30.5 to 76.7 %)	69/1,853,042	66 %	19–75 %	52 (45;58)
	Vaccinated (60–119 days ago)	68.6 % (40.2 to 83.5 %)	40/1,428,934	55 %	27–83 %	100 (87;107)

COVID-19 hospitalisations, and 78 % (64 % to 87 %) against COVID-19-related death (Tables 2 & 3). By time since vaccination, VE against COVID-19 hospitalisation was 59 % (51 % to 66 %) in the 14–59 days post-administration. It remained stable at 59 % in the following 60–119 days, but with wide confidence intervals (−13 % to 85 %). Against COVID-19 related death, VE was 82 % (68 % to 90 %) in the 14–59 days post-administration and 74 % (45 % to 88 %) in the following 60–119 days.

In the ≥80-year-old unvaccinated cohort, we counted 4842 hospitalisations and 726 deaths among 18,015,812 person-months at risk. In vaccinated we counted 718 COVID-19 hospitalisations and 110 deaths among 3,351,335 person-months at-risk. Overall, VE was 58 % (48 % to 66 %) against hospitalisations, and 62 % (32 % to 79 %) against COVID-19-related death. By time since vaccination, VE against hospitalisations was 59 % (52 % to 65 %) 14–59 days post-administration, decreasing slightly to 54 % (22 % to 73 %) 60–119 days thereafter. VE against COVID-19 related death increased over time, from 60 % (31 % to 77 %) to 69 % (40 % to 84 %), respectively, in the first 14–59 days compared to 60–119 days post-administration. Estimates of VE were based on data from four study sites (Italy, Sweden, Portugal, and Denmark), as numbers of reference group events in Belgium and Navarra were too low (<5) to estimate VE. There was moderate-to-high heterogeneity in all models (max I^2: 21–88 %), except in those estimating death among the 65–79-year age group, where heterogeneity was low (I^2 = 0–12 %).

4. Discussion

Our estimates indicate that among the EU/EEA population aged 65 years or more, a moderate-to-high level of protection was conferred by the 2024/25 autumn COVID-19 vaccine dose against hospitalisations due to COVID-19 and COVID-19-related deaths between 1st October 2024 and 25th January 2025. VE against COVID-19 hospitalisation was estimated to be between 58 and 60 % across both age groups. Against COVID-19-related death, VE ranged from 78 % in those aged 65–79 to 62 % among those aged ≥80 years. By time since vaccination, we observed small variations in VE over time, though there was not a clear decreasing trend between the first 14–59 days and the following 60–119 days post-vaccination, defying the anticipated trend of decreasing VE over time. Evaluating whether this trend persists with longer time since vaccination will require analysis of longer observational periods later in the season.

Our VE estimates are higher than estimates reported in the United States (VE: 45 %, among those aged ≥65 years) which were based on a comparable study period and similar methods, though with differences in study design, including the covariates used to adjust estimates. In North America, both KP.2- and JN.1-adapted vaccines were approved, though KP.2 was used more frequently in autumn 2024, which may explain these contrasting findings. In the U.S., KP.3.1.1 was similarly dominant in October 2024, with XEC gaining in dominance up to January 2025, when the proportion of LP.8.1 detections began to increase, reaching 31 % by mid-February [7]. Our estimates are also higher than those reported in the United Kingdom, where VE was estimated at 44 % in the first 2–4 weeks, decreasing to 42.8 % in the 10 to 14 weeks post-vaccination. In the United Kingdom, where the JN.1 vaccine was also offered from October 2024, XEC was dominant towards the end of November, having increased in proportion versus KP.3.1.1 [8]. In Denmark, which participates in the VEBIS EHR study, VE was separately reported to be approximately 70 % against hospitalisation, and slightly higher at 76 % against COVID-19 death among those aged 65+ and using a different inclusion methodology to the present study [9].

In our study population we found that 99 % of administered doses contained the JN.1 component. Our estimates of VE are based on a period in which the Omicron JN.1 lineage descendants KP.3 and XEC shared dominance in the EU/EEA. These findings are reassuring given earlier concerns over the potential for immune escape [10].

Several limitations should be considered when interpreting the findings. We did not exclude the small proportion (<1 %) of those who received non-JN.1 adapted vaccines, though we do not anticipate that this small proportion of individuals will impact the overall

interpretation of the estimates presented here. Measures of heterogeneity ranged between 0 % and 88 %, depending on model. Although all study sites followed a common protocol, differences in vaccine campaigns, Omicron SARS-CoV-2 sublineage circulation patterns, and the information available in source EHRs for use in confounder-adjusted HR estimates may have introduced this moderate observed heterogeneity between study sites. It is likely that unmeasured confounding is present in the estimates we present, as registries may not record all covariates necessary to adjust estimates for all possible sources of confounding. The use of negative control outcomes (e.g., non-COVID-19 mortality) or exposures (e.g., the first 0–13 days post-vaccination) could be used to evaluate the presence and degree of unmeasured confounding, though was outside the scope of the present study [11]. Differences in outcome definitions, for instance the use of positive tests within 30 days of death versus death with COVID-19 recorded as main cause, may introduce heterogeneity between study sites. It was not possible to estimate VE against death using one definition versus the other, though this would aid interpretation of the main VE estimate, which is a pooled composite of estimates based on both definitions. Pooled estimates only included sites where a sufficient number of events were found in the unvaccinated cohort. The exclusion of certain sites due to limited sample size may affect the generalisability of results across the EU/EEA, given the relatively low number of contributing countries. Finally, the choice of study period did not allow us to analyse waning, which is key when interpreting estimates of VE. In future analyses, we intend to include measures of waning over time throughout the season.

Our findings support that vaccination of individuals aged 65 years or older is of ongoing benefit, though these estimates are based on data from a period of remarkably low COVID-19 activity compared with the same period in the preceding year [2,4]. Surveillance data highlight the dynamic nature of SARS-CoV-2 evolution, with a variable trend in dominance between LP.8.1 (a descendant of KP.1.1.3) and XEC across many EU/EEA countries [2].

Monitoring the effectiveness of the COVID-19 vaccine deployed as part of the 2024 autumnal campaign is key to inform timely public health recommendations. We report high intermediate VE estimates of the JN1 adapted vaccine against severe COVID-19 outcomes. Effectiveness of the vaccine must be confirmed with longer time since vaccination and against emerging subvariants of Omicron BA2.86 [12].

CRediT authorship contribution statement

James Humphreys: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Alexandre Blake:** Writing – review & editing, Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Nathalie Nicolay:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Toon Braeye:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Izaak Van Evercooren:** Writing – review & editing, Visualization, Validation, Software, Resources, Methodology, Investigation, Data curation, Conceptualization. **Christian Holm Hansen:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Ida Rask Moustsen-Helms:** Writing – review & editing, Visualization, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Chiara Sacco:** Writing – review & editing, Visualization, Validation, Software, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Alberto Mateo-Urdiales:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Jesús Castilla:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Iván Martínez-Baz:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Ausenda Machado:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Andre Brito:** Writing – review & editing, Visualization, Validation, Formal analysis, Data curation, Conceptualization. **Rickard Ljung:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Nicklas Pihlstrom:** Writing – review & editing, Visualization, Validation, Formal analysis, Data curation, Conceptualization. **Yohann Mansiaux:** Writing – review & editing, Visualization, Validation, Software, Formal analysis, Data curation. **Susana Monge:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Sabrina Bacci:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Baltazar Nunes:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Ethics

All study sites participating in this study conformed with their respective national and EU ethical and data protection requirements. Ethical statements for each of the participating study sites:

Belgium: Data linkage and collection within the data-warehouse have been approved by the information security committee. The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was granted for the gathering of data from hospitalised patients by the Committee for Medical Ethics from the Ghent University Hospital (reference number BC-07507) and authorisation for possible individual data linkage using the national register number from the Information Security Committee (ISC) Social Security and Health (reference number IVC/KSZG/20/384). Linkage of hospitalised patient data to vaccination and testing within the LINK-VACC project was approved by the Medical Ethics Committee UZ Brussels–VUB on 3 February 2021 (reference number 2020/523), and authorisation from the ISC Social Security and Health (reference number IVC/KSZG/21/034).

Denmark: Only administrative register data was used for the study. According to Danish law, ethics approval is exempt for such research, and the Danish Data Protection Agency, which is dedicated ethics and legal oversight body, thus waives ethical approval for the study of administrative register data when no individual contact of participants is necessary, and only aggregate results are included as findings. The study is, therefore, fully compliant with all legal and ethical requirements, and there are no further processes available regarding such studies.

Navarre (Spain): The study was approved by Navarre's Ethical Committee for Clinical Research, which waived the requirement of obtaining informed consent.

Portugal: The study received approval from the Ethical Committee and the Data Protection Officer of the Instituto Nacional de Saúde Doutor Ricardo Jorge. Given that data was irreversibly anonymised, the

need for the participants' informed consent was waived by the Ethical Committee.

Italy: This study, based on routinely collected data, will not be submitted for approval to an ethical committee because the dissemination of COVID-19 surveillance data was authorised by the Italian law N. 52 of 19 May 2022, following the law decree N. 24 of 24 March 2022 (Article n. 13). Based on the same acts, the information on COVID-19 vaccination was retrieved by the Italian National Institute of Health using data from the National Immunisation Information System of the Italian Ministry of Health. Because of the retrospective design and the large size of the population under study, in accordance with the Authorisation n. 9 released by the Italian data protection authority on 15 December 2016, the individual informed consent was not requested for the conduction of this study.

Sweden: The Swedish study is approved by the Swedish Ethical Review Authority (2020–06859, 2021–02186) and has conformed to the principles embodied in the Declaration of Helsinki. Consent to participate is not applicable as this is a register-based study.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: All authors report that financial support was provided by European Centre for Disease Prevention and Control (ECDC). Funding: All the public health organisations involved received funding from the European Centre for Disease Prevention and Control (ECDC) implementing Framework Contract ECDC/2021/018 'Vaccine effectiveness and impact of COVID-19 vaccines through routinely collected exposure and outcome using health registries' (RS/2022/DTS/24104). In Portugal, this work was also supported by FCT – Fundação para a Ciência e Tecnologia, I.P. by project reference CEECINST/00049/2021/CP2817/CT0001 and DOI identifier 10.54499/CEECINST/00049/2021/CP2817/CT0001 If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Annex

Table 1
Autumn 2024/25 COVID-19 vaccination recommendations for each study site.

Study site	Recommended groups	Season start date
Belgium	Aged 65+ and risk groups	15th September 2024
Denmark	Aged 65+ and risk groups	1st October 2024
Italy	Aged 65+ and risk groups	18th September 2024
Navarra	Aged 60+ and risk groups	14th October 2024
Portugal	Aged 60+ and risk groups	20th September 2024
Sweden	Aged 65+ and risk groups	15th October 2024

Table 2
Outcome definitions at study site level.

Study site	Outcome definition	
	Hospitalisation due to COVID-19	Death related to COVID-19
Belgium	Hospitalisation due to COVID-19 related symptoms **with** a laboratory-confirmed SARS-CoV-2 infection up to 14 days before admission or within 24 h after.	COVID-19–related death is not analysed by Belgium due to data constraints.
Italy	Patients presenting with symptoms compatible with severe acute respiratory infections (SARI—based on criteria similar to SARI surveillance) **with** a laboratory-confirmed SARS-CoV-2 infection up to 14 days before admission or within 24 h after (RT-PCR or antigen test).	Laboratory-confirmed SARS-CoV-2 infection with death within 30 days after a positive test, in concomitance with a clinical picture suggestive of COVID-19 and absence of a clear non-COVID-19 cause of death (e.g., trauma).
Denmark	Admission with criteria compatible with SARI (based on SARI surveillance–like criteria, ICD codes or similar) **with** a laboratory-confirmed SARS-CoV-2 infection up to 14 days before admission or within 24 h after.	Laboratory-confirmed SARS-CoV-2 infection with death within 30 days after a positive test.
Portugal	(a) Admission where COVID-19 is the main diagnosis in the discharge record (e.g., per ICD coding or similar) **OR** (b) admission with criteria compatible with SARI (based on SARI surveillance–like criteria, ICD codes or similar) **with** a laboratory-confirmed SARS-CoV-2 infection up to 14 days before admission or within 24 h after.	(a) Death for which COVID-19 is recorded as the main cause of death **OR** (b) if cause of death is unavailable, laboratory-confirmed SARS-CoV-2 infection with death within 30 days after a positive test.
Navarra	Admission with criteria compatible with SARI (based on SARI surveillance–like criteria, ICD codes or similar) **with** a laboratory-confirmed SARS-CoV-2 infection up to 14 days before admission or within 24 h after.	Deaths caused by or *triggered* [sic] by COVID-19, based on medical review of all laboratory-confirmed SARS-CoV-2 infections with death within 30 days after a positive test.

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Table 2 (*continued*)

Study site	Outcome definition	
	Hospitalisation due to COVID-19	Death related to COVID-19
Sweden	Patients presenting with symptoms compatible with SARI (based on criteria similar to SARI surveillance) **with** a laboratory-confirmed SARS-CoV-2 infection up to 14 days before admission or within 24 h after (RT-PCR or antigen test).	Laboratory-confirmed SARS-CoV-2 infection with death within 30 days after a positive test, with a clinical picture suggestive of COVID-19 and absence of a clear non-COVID-19 cause of death (e.g., trauma), **or** COVID-19 listed as the underlying cause of death.

Table 3
Confounders included at study site level.

Confounder	Belgium	Denmark	Italy	Navarre	Portugal	Sweden
Age group	X	X	X	X	X	X
Comorbidities	X	X	X	X	X	X
Previous booster doses	X	X	X	X	X	X
Sex	X	X	X	X	X	X
Region	X	X	X		X	X
Socioeconomic status	X				X	X
Country of birth			X	X		
Dependence				X		

Table 4
Definition of common covariates.

Variable	Definitions of common covariates					
	Belgium	Denmark	Italy	Navarre (Spain)	Portugal	Sweden
Age	Age in years at the end of the year in which the study period begins. For adjustment: 5-year age groups.	adjusted in categories: 5-year categories until the final category, 90+ years	Age at the start of study period (for adjustment: 5-year age groups up to 90–94 years and then grouping ≥95 years))	Age at the start of study period (5-year categories)	Age at the start of study period (5-year categories)	Age in years at the end of the year in which the study period begins.
Comorbidities	No comorbidities associated with an increased risk for severe COVID-19 infection. At least one comorbidity which increases the risk for severe COVID-19 infection and not being immunocompromised (medium risk): - *Cardiovascular illness – general* - *Cardiovascular illness-specifically a heart disease* - *Alzheimer* - *Asthma* - *Haemophilia* - *Chronic obstructive pulmonary disease* - *Diabetes with cardiovascular compilations* - *Diabetes Mellitus with insulin treatment* - *Epilepsy and neuropathic pain* - *Chronic hepatitis type B or C* - *Exocrine pancreatic disease* - *Disease of Parkinson* - *Psychosis occurring with people older than 70 years* - *Psychosis occurring with people of 70 year or younger.*	Immunocompromised, including: - *HIV* - *Immunological disease* - *Radiation therapy* - *Organtransplanted* Other, including: - *Diabetes* - *Obesity* - *Cancer* - *Neurological Disease* - *Kidney disease* - *Haematological cancers* - *Heart disease* - *Chronic respiratory disease* - *Liver disease (incl. Alcohol lever)* - *Endocrine Disease* - *Haematological Disease* - *Coagulation Disease* - *Innate Diseases* - *TB* - *Missing a lung* - *Missing a kidney*	Immunocompromised, including: - *Immunocompromised defects of the complement system* - *Other specified disorders involving the immune mechanism* - *Deficiency or dysfunction of a single component (C1-C9)* - *Deficiency of cell-mediated immunity* - *Deficiency of humoral immunity* - *Human immunodeficiency virus [HIV] disease, Human immunodeficiency virus, type 2 [HIV-2], Asymptomatic human immunodeficiency virus [HIV] infection status* - *Disorders involving the immune mechanism* - *Congenital and acquired disorders with poor antibody production* - *Drug-induced immunosuppression* Other comorbidities, including: - *Respiratory diseases requiring oxygen therapy, idiopathic pulmonary fibrosis*	Immunocompromised Other major chronic conditions - *Diabetes* - *Severe Obesity* - *Cancer* - *Ictus* - *Dementia* - *Kidney disease* - *Haematological cancers* - *Heart disease* - *Chronic respiratory disease* - *Liver disease* - *Rheumatic arthritis*	*Considered comorbidities include: anemia, asthma, cancer, cardiac disease, dementia, diabetes, hypertension, HIV, liver disease, neuromuscular disease, obesity, pulmonary disease, renal disease, rheumatologic disease, stroke, tuberculosis*	*Vaccine priority groups:* *LISA Healthcare worker (status per October 2018)* *SOL Nursing home resident (status per December 31, 2020).* *Comorbidity groups: (binary)* *Any records with ICD-10 codes as primary/secondary diagnosis from inpatient stay or outpatient contact in hospital or from privatepracticing specialists, January 1, 2017 – December 27, 2020)* *Chronic pulmonary disease NPR J41 J42 J43 J44 J45 J46 J47 J84 J98 E84* *Cardiovascular conditions and diabetes* *NPR, SPDR I05 I06 I07 I08 I09 I110 I2 I34 I35 I36 I37 I39 I42 I43 I46 I48 I49 I50 E10-E14* *ATC: A10 (at least*

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Table 4 (*continued*)

Variable	Definitions of common covariates					
	Belgium	Denmark	Italy	Navarre (Spain)	Portugal	Sweden
	- *Thrombosis while treated with antithrombotic medicines* - *Thyroid disorder* - *HIV* Immunocompromised (high risk): if a person has one of the following comorbidities associated with immunodeficiency: - *Disease of Crohn, Colitis Ulcerosa, Psoriatrische arthritis, Reumatoid arthritis* - *Kidney failure* - *Cystic fibrosis* - *Psoriasis* - *Multiple sclerosis* - *Organ transplantation* - *Received chemotherapy/ radiotherapy against cancer* - *Received multidisciplinary oncologic consult*		- *Advanced heart failure (Classes III-IV NYHA) and post cardiogenic shock patients* - *Amyotrophic lateral sclerosis and other motor neuron disorders, multiple sclerosis, muscular dystrophy, infantile cerebral palsy, myasthenia gravis, dysimmune neuropathies* - *Type 1 diabetes, Type 2 diabetes with complications or requiring combination therapy (with at least two anti-diabetes drugs)* - *Addison's disease* - *Panhypopituitarism* - *Cystic fibrosis* - *-Cirrhosis of the liver* - *Intracerebral ischemic or hemorrhagic event that has led to impaired neurological and cognitive autonomy* - *Individuals who have had a stroke on 2020 or later ranked as level 3 or higher* - *Thalassemia major* - *Sickle cell anemia* - *Other severe anemias* - *Down syndrome* - *Body Mass Index > 35* - *Severely disabled persons pursuant to law 104/1992 art. 3 paragraph 3* - *Chronic Alcohol Misuse* - *Functional or anatomic asplenia* - *COPD* - *Chemotherapy or Radiotherapy* - *Coagulopathies* - *Diabetes Mellitus and other endocrinopathies* - *Patients in hemodialysis or with chronic kidney diseases expected to start dialysis* - *Hemoglobinopathy such as sickle cell anemia or thalassemia* - *Chronic Liver Disease* - *Cochlear implant* - *Chronic Kidney Disease* - *Chronic eczema or psoriasis* - *Diseases associated with a high risk of aspiration pneumonia* - *Chronic Cardiovascular Disease* - *Chronic Respiratory Disease* - *Motor neuron diseases* - *Chronic inflammatory diseases and malabsorption syndromes* - *Blood cancers (leukemia, lymphoma and myeloma)* - *Solid tumors*			*two filled prescriptions during 2020, before December 27, 2020)* *Autoimmunity-related conditions* *NPR D86 G35 K50 K51 L40 M05 M06 M07 M08 M09 M13 M14 M45* *Malignancy NPR, CAN C0 C1 C2 C3 C4 C5 C6 C7 C8 C9 D45 D46 D47 (CAN from 2017 to 2019, NPR for 2020)* *Moderate to severe renal disease* *NPR I12 I13 N00 N01 N02 N03 N04 N05 N07 N11 N14 N17 N18 N19 Q61*

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Table 4 (*continued*)

Variable	Definitions of common covariates					
	Belgium	Denmark	Italy	Navarre (Spain)	Portugal	Sweden
			- *Obesity (Body Mass Index 30–35)* - *Bone marrow transplant* - *Drug Misuse* - *Solid organ transplant* - *Patients with CSF leak from trauma or intervention* - *Patients going to start immunosuppressive treatment* - *Metabolic diseases* - *Hematopoietic diseases* - *Pathologies that require important surgical interventions* - *Neurological diseases* - *Cerebrovascular diseases* - *Down Syndrome* - *Disabilities (physical, sensorial, learning or psychic)*			
Country of residence / country of birth / nationality	Not included	Not included	Country of birth: born in Italy; born in other countries	Country of birth	Not included	Country of birth. Sweden, Nordic, Eu, Other
Deprivation index or similar socioeconomic status indicator	Household income: low (lowest 40 %)-medium (middle 30 %)-high (highest 30 %)	Not included	Not included	High functional dependence	European deprivation index quintile Q1 (least deprived) to Q5 (most deprived)	Individual education, marital status
Geographic level	Province of residence	Adjustment for residency in the 5 geographical regions of Denmark (EU NUTS-2 regions)	19 regions and 2 autonomous provinces of Italy where vaccination took place	Not included	Health region of residence (North, Center, Lisbon and Tagus Valley, Alentejo, Algarve)	Categories of rural/urban/ metropolitan areas

Data availability

The authors do not have permission to share data.

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