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Monovalent XBB.1.5 COVID-19 vaccine effectiveness against hospitalisations and deaths during the Omicron BA.2.86/JN.1 period among older adults in seven European countries: A VEBIS-EHR network study

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ABSTRACT

Background: We aimed to estimate XBB.1.5 vaccine effectiveness (VE) against COVID-19-related hospitalizations and deaths during BA.2.86/JN.1 predominance, among EU/EEA individuals with ≥65-years.

Research design and methods: We linked electronic health records to create historical cohorts in Belgium, Denmark, Italy, Navarre (Spain), Norway, Portugal and Sweden. We included individuals aged ≥65-years eligible for the autumnal 2023 COVID-19 vaccine. Follow-up started when ≥80% of country-specific sequenced viruses were BA.2.86/JN.1 (4/dec/23 to 08/jan/24) and ended 25 February 2024. At study site level, we estimated the vaccine confounder-adjusted hazard ratio (aHR) of COVID-19 hospitalizations and deaths between individuals with ≥14 days after vaccination versus unvaccinated in autumn 2023, overall, by time since vaccination and age groups. VE was estimated as (1-pooled aHR)x100 with a random-effects model.

Results: XBB.1.5 VE against COVID-19 hospitalizations was 50% (95%CI: 45 to 55) and 41% (95%CI: 35 to 46) in 65–79-year-olds and in ≥80-year-olds, respectively. VE against COVID19-related-death was 58% (95%CI: 42 to 69) and 48% (95%CI: 38 to 57), respectively, in both age groups. VE estimates against each outcome declined in all age groups over time.

Conclusion: Monovalent XBB.1.5 vaccine had a moderate protective effect against severe and fatal COVID-19 likely caused by BA.2.86/JN.1 during the 2023/2024 winter, among persons aged ≥65.

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COVID-19; SARS-CoV-2; vaccine effectiveness; hospitalization; cohort design; electronic health records; multi-country study

1. Introduction

In autumn 2023, COVID-19 vaccination campaigns were carried out in EU/EEA countries aiming to reduce the risk of severe disease among the most vulnerable populations. The target groups generally included those aged ≥60 or ≥65 years, persons living with comorbidities or conditions that could increase the risk of severe disease, health professionals, and caregivers. The monovalent Omicron XBB.1.5 vaccine was used in most EU/EEA countries and delivered as a booster dose or primary vaccination during autumn/winter 2023/24. In January 2024 [1], for those age ≥60 years the median vaccine coverage among EU/EEA countries was 12% (range 0.01–66.1%), and 17.1% (range 0.01%–89.3%), for those aged ≥80 years – a range which indicates variability between countries in terms of vaccine uptake. Eighty-two percent of the vaccines administered during the autumn/winter 2023/24 campaign were Comirnaty Omicron XBB.1.5 (Pfizer BioNTech) vaccine [1].

In early autumn 2023, in EU/EEA countries, the XBB.1.5 lineage was predominant. The BA.2.86 and JN.1 SARS-CoV-2 lineages rapidly increased, gaining dominance in all EU/EEA countries by mid-December [2].

Several studies reported XBB.1.5 vaccine effectiveness (VE) against severe disease in the first months of the autumn/winter season at a time of XBB.1.5 predominance [3–6], including one study conducted within the Vaccine

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Effectiveness Burden and Impact Studies project EHR network (VEBIS-EHR) [4]. These studies reported VE against COVID-19 hospitalizations among those aged ≥18 (study estimate range 62% to 74%), ≥65 (52% to 74%) and ≥80 years old (52% to 66%).

The BA.2.86 SARS-CoV-2 lineage presents more than 30 amino acid mutations compared to the XBB.1.5 lineage, and JN.1, a descendant of BA.2.86, harbors the L455S substitution at the receptor binding site. These mutations could provide immune escape capacities and reduce the effectiveness of the XBB.1.5 vaccine [7]. However, studies of XBB.1.5 VE against severe disease during periods of BA.2.86 or JN.1 predominance are still scarce [5,8]. In this context, we aimed to estimate XBB.1.5 VE against COVID-19-related hospitalizations and deaths overall and by time since vaccination during a period of BA.2.86/JN.1 predominance within a European multi-country study among older adults aged 65–79 and ≥80 years old.

2. Methods

This study was developed under the VEBIS-EHR network. The VEBIS project, funded by the European Centre for Prevention and Disease Control (ECDC), aims to monitor COVID-19 VE using linkage of electronic health records (EHR) within an EU/EEA multi-country setting (Table S2). As of April 2024, seven countries participate in the VEBIS-EHR network: Belgium, Denmark, Italy, Spain (Navarre), Norway, Portugal, and Sweden.

Detailed methods and the results of VEBIS-EHR studies have been published previously [9–11]. Briefly, using a common protocol [12] we developed a historical cohort study by reconstructing the study site cohorts of individuals aged 65 years or older resident in the and eligible to receive the autumnal 2023 vaccine dose at the start of the country-specific vaccination campaign (Table S1). Further, the eligible population consisted of those with primary vaccination series completed at least 180 days ago and who, in the last 90 days, had no vaccine dose administered nor documented SARS-CoV-2 infection or COVID-19 hospitalization. Detailed information on the eligibility criteria is presented in the Supplementary material, Annex 2. Vaccination status, baseline characteristics, and outcome occurrence were obtained by linking national/regional EHR. We defined BA.2.86/JN.1 lineage predominance period at the study-site level, designating the period of predominance to have started by the date on which 80% of sequenced samples were attributable to BA.2.86/JN.1 based on data extracted from the ECDC European Respiratory Virus Surveillance Summary (ERVISS) [13] database and subset to the countries of interest (Figure S1).

If the number of the weekly sequenced viruses was low, BA.2.86 frequency data from neighboring countries were used as a proxy. In Table S1 we present details on the start of BA.2.86 predominance period by study site. The end of the study period was 25 February in all study sites, approximately two months before data extraction (April 2024) to ensure EHR were sufficiently updated.

Among those identified as eligible at the start of the vaccination campaign (Supplementary material, Annex 2), we excluded all individuals hospitalized due to COVID-19 between the start of the vaccination campaign and the country-specific starting date of the study. Individual follow-up started at the beginning of the country-specific study period and ceased at the date of either the outcome, death for any cause, or the end of the study period – whichever was earliest. Vaccination status was treated as a time-dependent exposure, excluding the time-interval 1–13 days post-vaccination from the analysis.

Hospitalisation due to COVID-19 was defined as a hospital admission due to a severe acute respiratory infection with a SARS-CoV-2 positive test from 14 days before to one day after admission, or with COVID-19 as the primary diagnosis in admission on discharge records. A COVID-19-related death was defined as a death with COVID-19 coded as cause, or death for any cause with a SARS-CoV-2 positive test in the 30 days preceding death.

We undertook a two-stage pooling of estimates calculated at the study-site level. In the first stage, site-specific estimates of confounder-adjusted vaccine hazard ratios (aHR) and 95% confidence intervals (95%CI) were calculated using Cox regression with calendar time as the underlying scale adjusted by 5-year age groups, sex, region in the country, comorbidities, number of vaccine booster doses received prior to the current vaccination campaign, and nationality and socioeconomic status in some of the study sites (Table S3 & S4). In the second stage, study site-specific aHR estimates and standard errors were pooled using a random-effects meta-analysis using Paule-Mantel method. Pooled VE was estimated as (1-pooled aHR)x100. To assess heterogeneity, we used the I^2 index [14]. A fixed-effects model was used as a secondary analysis.

3. Results

At the end of the individual observation period, we included 13,729,181 unvaccinated and 6,454,441 vaccinated persons across both age groups. Among the vaccinated cohorts, at the end of the observation period, the distribution of the participants by time since vaccination was 2,526,206 (39.1%) with 14–89 days since vaccination, and 3,928,235 (60.9%) within the 90 to 179 day since vaccination category.

The proportion of individuals with high-risk comorbidities (7.4% vs 2.4%) and with a greater number of previous booster doses (≥2 boosters: 92.4% vs 33.4%) was higher among vaccinated than unvaccinated. Further, but to a lesser extent, vaccinated persons with a longer time since vaccination (90–179 days) also had a greater frequency of high-risk comorbidities (9.0% vs 4.8%) and a greater number of previous booster doses (≥2 boosters: 94.3% vs 89.4%) compared to those vaccinated with less time since vaccination (14–90 days) (Table 1).

In the 65–79 years age group there were 1,752 hospitalization events among 17.5 million person-months at risk in unvaccinated, and 908 COVID-19 hospitalizations events among 9.9 million person-months at risk in vaccinated persons (Table 2). XBB.1.5 COVID-19 VE against COVID-19 hospitalizations was 50% (95%CI: 45 to 55) overall, 51% (95%CI: 45 to 56)

Table 1. Descriptive characteristics of the study population ($N = 20,183,622$) by vaccination status and time since vaccination at the end of the study period*, within the seven study sites (Belgium, Denmark, Italy, Navarre-Spain, Norway, Portugal, and Sweden) during BA.2.86/JN.1 predominant period (from 4 December 2023 until 25 February 2024): VEBIS-EHR network.

Variable	Not vaccinated n (%)	Vaccinated ≥14 days n (%)	Vaccinated 14–89 days n (%)	Vaccinated 90–179 days n (%)
Total (row % over total =20,183,622)	13,729,181 (68.0)	6,454,441 (32.0)	2,526,206 (12.5)	3,928,235 (19.5)
Study site				
Belgium	936,583 (6.8)	1,065,561 (16.5)	75,731 (3.0)	989,830 (25.2)
Denmark	219,481 (1.6)	894,411 (13.9)	100,989 (4.0)	793,422 (20.2)
Italy	10,750,561 (78.3)	1,296,464 (20.1)	984,379 (39.0)	312,085 (7.9)
Navarre	43,442 (0.3)	80,225 (1.2)	5.891 (0.2)	74,334 (1.9)
Norway	397,240 (2.9)	525,048 (8.1)	160,684 (6.4)	364,364 (9.3)
Portugal	924,227 (6.7)	1,246,193 (19.3)	321,791 (12.7)	924,402 (23.5)
Sweden	457,647 (3.3)	1,346,539 (20.9)	876,741 (34.7)	469,798 (12)
Age group (years)				
65-79	9,726,723 (70.8)	4,508,062 (69.8)	1,745,539 (69.1)	2,762,523 (70.3)
≥80	4,002,458 (29.2)	1,946,379 (30.2)	780,667 (30.9)	1,165,712 (29.7)
Sex				
Male	7,657,292 (55.8)	3,391,289 (52.5)	1,308,246 (51.8)	2,083,043 (53)
Female	6,071,867 (44.2)	3,063,151 (47.5)	1,217,960 (48.2)	1,845,191 (47)
Missing	22 (0)	-	-	-
Comorbidities**				
High risk comorbidities	334,606 (2.4)	475,966 (7.4)	122,656 (4.8)	354,450 (9.0)
Medium/low risk comorbidities	4,879,671 (35.5)	3,209,401 (49.7)	1,154,983 (45.7)	2,054,418 (52.3)
No comorbidities	8,488,930 (61.8)	2,754,247 (42.7)	1,277,701 (49.4)	1,506,546 (38.4)
Missing	25,974 (0.2)	14,827 (0.2)	2,006 (0.1)	12,821 (0.3)
Number of previous booster doses				
0	1,428,006 (10.4)	31,220 (0.5)	16,104 (0.6)	15,116 (0.4)
1	7,709,948 (56.2)	460,459 (7.1)	252,856 (10)	207,603 (5.3)
2	4,029,079 (29.3)	4,159,638 (64.4)	1,374,745 (55.4)	2,784,893 (70.9)
3	545,174 (4)	1,505,152 (23.3)	720,151 (28.5)	785,001 (20)
4	16,925 (0.1)	296,458 (4.5)	161,663 (6.4)	134,795 (3.4)
5	44 (0)	1,514 (0)	687 (0)	827 (0)
Missing	5 (0)	0 (0)	0 (0)	0 (0)
Vaccine product				
BNT162b2 (original strain))		75,915 (1.2)	13,953 (0.5)	61,962 (1.6)
mRNA-1273 (original strain)		143 (0)	79 (0)	64 (0)
BNT162b2 (bivalent original/BA.1)		4,695 (0.1)	676 (0)	4,019 (0.1)
mRNA-1273 (bivalent original/BA.1)		11 (0)	-	10 (0)
BNT162b2 (bivalent original/BA.4/BA.5)		24,963 (0.4)	2,561 (0.1)	22,402 (0.6)
mRNA-1273 (bivalent original/BA.4/BA.5)		98 (0)	5 (0)	93 (0)
BNT162b2 (XBB.1.5)		6,294,059 (97.5)	2,503,875 (99.1)	3,790,184 (96.5)
mRNA-1273 (XBB.1.5)		49,597 (0.8)	99 (0)	49,498 (1.3)
NVX-CoV2601		4,950 (0.1)	4,950 (0.2)	0 (0)
Others		-	-	-
Missing		7 (0)	5 (0)	-

*Vaccination status and time since vaccination were assessed at the end of the individual observation period

**High risk comorbidities: immunocompromised conditions with COVID-19 vaccine recommendation; Medium/low risk: non-immunocompromised conditions with COVID-19 vaccine recommendation; No comorbidities: persons without any of the risk comorbidities. (Details are presented in Table S3).

and 47% (95%CI: 32 to 59) among those who received the vaccine respectively between 14 to 89 days and 90 to 179 days (Figure S2).

In ≥80 years age-group, there were 2,117 COVID-19 hospitalization events among 6.9 million person-months at risk in unvaccinated, and 1,306 among 4.1 million person-months at risk in vaccinated persons. VE was 41% (95%CI: 35 to 46) overall and 42% (95%CI: 36 to 47) and 39% (95% CI: 17% to 54%) by time since vaccination among those who received the vaccine between 14 and 89 days and 90–179 days, respectively (Figure S3).

In the 65–79-year age-group there were 247 COVID-19 related deaths among 15.6 million person-months at risk in unvaccinated, and 151 among 7.8 million person-months at risk in vaccinated individuals. XBB.1.5 COVID-19 VE estimates against COVID-19-related deaths was 58% (95%CI: 42 to 69) overall, 59% (95%CI: 41 to 72) among those with 14–89 days since vaccination and 54% (95%CI: −16 to 82) among those who received the vaccine between 90 and 179 days ago (Figure S4).

In the ≥ 80-year age-group, there were 547 COVID-19 related deaths event among 6.5 million person-months at risk in unvaccinated, and 389 among 3.4 million person-months at risk in the vaccinated. The XBB.1.5 COVID-19 VE was 48% (95%CI: 38 to 57) overall, 51% (95%CI: 42 to 59) among those with 14–89 days since vaccination and 9% (95%CI: −86% to 56%) among those who received the vaccine between 90 and 179 days ago (Figure S5).

There was low to moderate heterogeneity between study site aHR estimates ($I^2 = 0\%$ to 77%). High heterogeneity ($I^2 = 77\%$) was observed in the VE estimate against death within 90–179 days since vaccination for the 80+ cohort, leading to a very wide 95% confidence interval for this estimate. Fixed effects pooled estimates were similar to the random effect estimates presented in the primary analysis (Figures S2–4).

Table 2. Number of events (COVID-19 hospitalisations or COVID-19 related deaths), person months at risk by vaccine status, and vaccine effectiveness overall and by time since vaccination for individuals aged 65–79 and ≥80 years old, within the seven study sites (Belgium, Denmark, Italy, Navarre-Spain, Norway, Portugal, and Sweden), during BA.2.86/JN.1 predominance period up to 25 February 2024, VEBIS-EHR network.

	Events	Person-month	VE (95%CI)	Heterogeneity I^2 (min-max study level VE estimates)
Age group 65–79				
Hospitalisations				
Not yet vaccinated	1752	17,500,532		
Overall vaccinated (≥14 days)	908	9,957,896	50.2% (44.6; 55.2)	0% (45.3%, NV to 60%, BE)
Vaccinated (14–89 days)	813	6,472,961	50.9% (45.1; 56)	0% (48%, NO to 62%, BE)
Vaccinated (90–179 days)	91	2,708,455	47.3% (32; 59.1)	0% (−30.1%, NV to 67%, SE)
Deaths				
Not yet vaccinated	247	15,614,443		
Overall vaccinated (≥14 days)	151	7,823,133	57.5% (41.5; 69.1)	23.2% (17%, SE to 68.1%, DK)
Vaccinated (14–89 days)	130	4,553,478	59.2% (41.3; 71.7)	32.9% (25%, SE to 68%, PT)
Vaccinated (90–179 days)	7	777,627	54.0% (−16.3; 81.8)	0% (54%, PT to 54%, PT)
Age group ≥80 years				
Hospitalisations				
Not yet vaccinated	2117	6,886,612		
Overall vaccinated (≥14 days)	1306	4,107,972	40.7% (35.1; 45.9)	0% (29%, BE to 48%, DK)
Vaccinated (14–89 days)	1167	2,661,954	42.1% (36.4; 47.2)	0% (25%, BE to 48.2%, NV)
Vaccinated (90–179 days)	139	1,446,776	38.6% (17.4; 54.3)	39.1% (−1%, IT to 68.5%, DK)
Deaths				
Not yet vaccinated	547	6,451,715		
Overall vaccinated (≥14 days)	389	3,432,184	48.4% (38.2; 56.9)	9.9% (36%, NO to 70%, SE)
Vaccinated (14–89 days)	330	2,404,345	51.2% (41.9; 59)	0% (43%, NO to 71%, SE)
Vaccinated (90–179 days)	55	855,733	9.4% (−85.5; 55.8)	77.2% (−159%, IT to 51%, PT)

VE: vaccine effectiveness, CI: Confidence Interval, BE: Belgium, DK: Denmark, IT: Italy; NO: Norway, NV: Navarre, PT: Portugal, SE: Sweden
VE = one minus the pooled confounder-adjusted hazard ratio at study level using a Cox regression time dependent model (confounder variables used in each study site are available in Annex 3 and 4 of the Supplementary material.

4. Discussion

Our results indicate that in the population aged 65 years and older, the 2023 autumnal monovalent XBB.1.5 booster conferred protection against severe COVID-19 outcomes during the period in which COVID-19 cases were likely to be caused by the Omicron BA.2.86 or JN.1 lineages. These estimates of protection represent a reduction in risk that ranged from 42% to 51% for COVID-19 hospitalization and from 51% to 59% for COVID-19 deaths for those who received the vaccine in the last 3 months, and were consistently lower among those aged ≥80 years. For those vaccinated, but with more time since vaccination (three or more months) during the BA.2.86/JN.1 predominance period, XBB.1.5 vaccine presented lower levels of protection against COVID-19 hospitalizations, ranging from 39% to 47%, and against COVID-19 related deaths ranging from 9% to 54% though, as discussed earlier, the latter estimates against COVID-19-related deaths had low precision.

Our results suggest a lower VE among those who received a vaccine between 14 and 89 days in the BA.2.86/JN.1 predominant period, compared to the XBB predominant period estimates obtained in the VEBIS-EHR network [4]. Specifically, among those 65–79-years-old XBB.1.5 VE against hospitalizations decreased from 64% (95%CI 55 to 72) in the XXB period to 51% (95%CI 45 to 56) in the BA 2.86/JN1 period and for those ≥80 years from 65% (95%CI 56 to 71) to 42% (95%CI 36 to 47). The XBB.1.5 VE against COVID-19-related deaths declined in those aged 65–79 years from 67% (95%CI: 43 to 81) to 59% (95%CI 41 to 72) and in those ≥80 years from 67% (95%CI: 41 to 81) to 51% (95%CI: 42 to 59). These differences could be due to higher natural immunity in the comparison group due to recent SARS-CoV-2 infection, although other studies employing different study designs have also found evidence of reduced vaccine effectiveness against BA.2.86/JN.1 relative to XBB.1.5 [15].

Our results are concordant with results from other studies that estimated COVID-19 VE against severe outcomes potentially due to XBB sub-lineages or JN.1 SARS-CoV-2 lineages. A test-negative design study conducted in England [8] in the population aged 65 years or more showed a decrease in VE against hospitalizations among the 2–4 weeks since vaccination group, from 74% (95%CI: 62% to 82%) against XBB sub-lineages to 37% (95%CI: −20 to 66) against JN.1. Similar results were also observed in two studies conducted in the United States [5,6] that aimed to estimate XBB.1.5 VE against hospitalizations likely due to XBB sub-lineages versus JN.1 among individuals aged ≥18 years. In both studies, a reduction in the protection of XBB.1.5 vaccine against COVID-19 hospitalizations was observed within the first 60 days after vaccination, respectively from 62% (95%CI: 44% to 74%) to 32% (95%CI: 3% to 52%) [5], and from 74% (95%CI: 49% to 87%) to 50% (95%CI: 15% to 71%) [6].

The results presented here should be interpreted cautiously, considering the potential presence of confounding bias, given its observational nature, and the possible misclassification of the vaccine status and outcome once we used an EHR-based multicentre study. The vaccine status hazard ratios were adjusted for several potential confounding factors at the study site level. Although this adjustment was made, we cannot exclude the presence of confounding residual bias from our analysis. Considering misclassification of the exposure, vaccination information was extracted from national vaccination registries and measured prior to, and independently of, the outcome. Estimates of 2023 autumnal COVID-19 vaccine coverage observed within our EHR-based study population were very close to the officially reported

equivalents produced by the ECDC (Table S5). We considered our VE estimate representative of XBB.1.5 vaccine performance given that 98.3% (Table 1) of the vaccines received during the study period were the monovalent XBB.1.5. Among these, 99% were the BNT162b2 XBB1.5-adapted vaccine, which indicates that our VE estimates represent the effectiveness of this vaccine product in general.

Additionally, we cannot rule out the presence of misclassification or underreporting of COVID-19 hospitalizations and deaths, even using national hospitalizations, death and laboratory registries given the lag between event and full recording of such events in the relevant EHRs, and also due the reduction in SARS-CoV-2 testing that would underestimate COVID-19 related deaths identification. To reduce the effect of misclassification bias due to unextracted events, or otherwise due to extraction of incomplete records, a two-month delay between the end of the study period (i.e. the last possible event) and extraction of data from source EHRs has been implemented. For the purpose of this analysis, no EHR extractions were undertaken until at least April 2024. Nevertheless, we do not expect that misclassification of the outcome could be differential by the vaccine status. If underreporting of events is present in our data, we do not expect a bias to arise from it, only a loss in the number of events and statistical power. On the other hand, if non-COVID-19 hospitalization are classified as COVID-19 event, we expect that our estimates would be biased to the null effect [16].

Another issue to be addressed, will be the high diffusion of self-diagnosis through at-home testing and the possible under-ascertainment of asymptomatic and mild cases, it is likely that some SARS-CoV-2 infections were not reported, thus leading to a possible overestimation of the eligible individuals at the start of the vaccination campaigns. This was likely more frequent in those who did not receive the seasonal booster, possibly causing an underestimation of VE.

The comparison of VE by time since XBB.1.5 administration among different epidemic phases, like XXB vs BA.2.86 predominance periods, should be interpreted with caution because of the possible different unmeasured characteristics among persons who received the seasonal booster at different times. For example, those who received the booster dose later might be generally less prone to adopt preventive measures and therefore have had a higher exposure to risky behaviors than those who received it earlier. Additionally, the number of individuals with a recent infection will be higher among unvaccinated persons during BA.2.86/JN.1 period. Both these situations could have resulted in an underestimation of VE during the BA.2.86/JN.1 predominance period, and a slight overestimation of VE in the XBB predominance period.

Despite the limitations described above, our study also has several strengths. As we employed mostly national registries, large sample sizes and a large number of events were reported by study sites, leading to a high precision around VE estimates and allowing stratified VE estimates. Additionally, the fact that the study was conducted in seven different EU/EEA countries using a common scientific protocol published ahead of the study development [12], and the low to moderate heterogeneity observed between study-level VE estimates, reinforce the consistency and reproducibility of the results in the participating study sites.

5. Conclusions

Our XBB.1.5 VE estimates against severe COVID-19, likely caused by BA.2.86/JN.1, were lower than those observed during the XBB.1.5 lineage predominance period. Nevertheless, the results of our study indicate that the XBB.1.5 vaccine offered moderate protection (≥40%) for up to six months after vaccination against severe COVID-19, likely caused by BA.2.86/JN.1, during the 2023/2024 winter in older (≥65 years old) populations. These findings indicate the importance of protection provided by COVID-19 vaccines.

Disclosure statement

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or material discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or mending, or royalties.

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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 hospitalized patients by the Committee for Medical Ethics from the Ghent University Hospital (reference number BC-07507) and authorization 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 hospitalized 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 authorization 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.

Norway: Ethical approval was granted by Regional Committees for Medical and Health Research Ethics (REC) Southeast (reference number 122,745). The Norwegian Institute of Public Health has performed a Data Protection Impact Assessment (DPIA) for Beredt C19.

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 anonymized, 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 authorized 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 Authorization 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.

Data availability statement

Authors cannot share the data used for this study, which should be requested to the data owner institutions following their respective procedures.

Author contribution

S Bacci, N Nicolay, B Nunes, J Humphreys and S Monge conceived the study and B Nunes, J Humphreys, N Nicolay and S Monge conceited the methods. All authors from Public Health institutions at each study site were responsible for the data management and analysis at the site level. JH was in charge of pooling site estimates, with the help of S Monge. B Nunes drafted the first version of the manuscript, with the help of J Humphreys and S Monge, A Nardone, and E Kissling. All the authors contributed to the interpretation of the results and critically reviewed the manuscript. All the authors approved the final version of this manuscript. All the authors within the VEBIS-EHR working group made a substantial contribution to the conception or design of the work, critically revised the manuscript, provided their final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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