Monitoring COVID-19 vaccine effectiveness against COVID-19 hospitalisation and death using electronic health registries in [?]65-years-old population in six European countries, October 2021 to November 2022

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Abstract

Background: Within the ECDC-VEBIS project, we prospectively monitored vaccine effectiveness (VE) against COVID-19 hospitalisation and COVID-19-related death, using electronic health registries (EHR), between October 2021 and November 2022, in community-dwelling residents aged 65–79 and [?]80-years in six European countries. Methods: EHR linkage was used to construct population cohorts in Belgium, Denmark, Luxembourg, Navarre (Spain), Norway and Portugal. Using a common protocol, for each outcome (hospitalisation and death), VE was estimated monthly over eight-week follow-up periods, allowing one month-lag for data consolidation. Cox proportional-hazards regression models were used to estimate adjusted hazard ratios (aHR) and VE=(1 – aHR) x100. Site-specific estimates were pooled using random-effects meta-analysis. Results: For [?]80-years, VE against COVID-19 hospitalisation decreased from 66.9% (95%CI: 60.1; 72.6) to 36.1% (95%CI: -27.3; 67.9) for the primary vaccination and from 95.6% (95%CI: 88.0; 98.4) to 67.7% (95%CI: 45.9; 80.8) for the first booster. Similar trends were observed for 65-79-years. The second booster VE against hospitalisation ranged between 82.0% (95%CI: 75.9; 87.0) and 83.9% (95%CI: 77.7; 88.4) for the [?]80-years and between 39.3% (95%CI: -3.9; 64.5) and 80.6% (95%CI: 67.2; 88.5) for 65-79-years. The first booster VE against COVID-19-related death declined over time for both age groups, while the second booster VE against death remained above 80% for the [?]80-years. Conclusions: Successive vaccine boosters played a relevant role in maintaining protection against COVID-19 hospitalisation and death, in the context of decreasing VE over time. Multi-country data from EHR facilitate robust near-real-time monitoring of VE in the EU/EEA and supports public health decision-making.

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Abstract text:

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Methods: EHR linkage was used to construct population cohorts in Belgium, Denmark, Luxembourg, Navarre (Spain), Norway and Portugal. Using a common protocol, for each outcome (hospitalisation and death), VE was estimated monthly over eight-week follow-up periods, allowing one month-lag for data consolidation. Cox proportional-hazards regression models were used to estimate adjusted hazard ratios (aHR) and VE=(1 – aHR) x100. Site-specific estimates were pooled using random-effects meta-analysis.

Results: For [?]80-years, VE against COVID-19 hospitalisation decreased from 66.9% (95%CI: 60.1; 72.6) to 36.1% (95%CI: -27.3; 67.9) for the primary vaccination and from 95.6% (95%CI: 88.0; 98.4) to 67.7% (95%CI: 45.9; 80.8) for the first booster. Similar trends were observed for 65-79-years. The second booster

VE against hospitalisation ranged between 82.0% (95%CI: 75.9; 87.0) and 83.9% (95%CI: 77.7; 88.4) for the [?]80-years and between 39.3% (95%CI: -3.9; 64.5) and 80.6% (95%CI: 67.2; 88.5) for 65-79-years. The first booster VE against COVID-19-related death declined over time for both age groups, while the second booster VE against death remained above 80% for the [?]80-years.

Conclusions: Successive vaccine boosters played a relevant role in maintaining protection against COVID-19 hospitalisation and death, in the context of decreasing VE over time. Multi-country data from EHR facilitate robust near-real-time monitoring of VE in the EU/EEA and supports public health decision-making.

Statements

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

Funding statement:

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Conflict of interest: Authors declare no support from any private organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Authors' contributions: The common protocol, including the design of the statistical analysis, was elaborated by SM, IK, BN, AS, JS, MV, AN and NN, with active contributions from all other authors. All authors from institutions other than ISCIII and Epiconcept were in charge of performing site VE estimations, while authors from ISCIII and Epiconcept were in charge of pooling site estimates. IK and SM drafted the first version of the manuscript. VEBIS-Lot 4 working group members had supporting roles in study design and data management. All authors contributed to the interpretation of results and critically reviewed and approved the content of this manuscript.

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Introduction

In December 2020, almost one year into the coronavirus disease 2019 (COVID-19) pandemic, the first vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), BNT162b2 (Comirnaty(r)), mRNA-1273 (Spikevax(r)), ChAdOx1 (Vaxzevria(r)) and Ad26.COV2-S (JCovden) received early conditional marketing authorisation from the European Medicines Agency (EMA) . These vaccines were developed against the original strain of SARS-CoV-2, used in the initial phase of the vaccination campaign and showed high vaccine effectiveness (VE, [?]95%) that, however, waned over time . The mRNA vaccines (Comirnaty(r) and Spikevax(r)) were then deployed as the first booster administered during the Autumn of 2021 and as the second booster in the Spring of 2022 in some countries, prioritising individuals of older age and those with medical underlying conditions, and further extending to other age groups. Four adapted mRNA vaccines targeting Omicron subvariants (Comirnaty(r) bivalent Original/Omicron BA.1, Comirnaty(r) bivalent Original/Omicron BA.4-5, Spikevax(r) bivalent Original/Omicron BA.1, Spikevax(r) bivalent Original/Omicron BA.4-5) were further authorised and administered from September 2022 onwards for second and third booster vaccination in the European Union/European Economic Area (EU/EEA).

Following the rollout of mass COVID-19 vaccination programmes, real-life VE monitoring started to estimate the level and duration of protection, the VE in specific populations not covered by clinical trials and VE

against new emerging genetic variants of SARS-CoV-2 . Rapid availability of this information has been of great value in guiding public health decision-makers to adapt vaccination programmes according to the public health needs. The use of population-based Electronic-Health Registries (EHR) has the advantage of large sample size and being readily available, allowing VE prospective monitoring within a short time frame and with relatively few extra resources. Because of this, EHR has become a core data source for COVID-19 VE studies in many countries .

By the end of 2021, the European Centre for Disease Prevention and Control (ECDC) established the Vaccine Effectiveness, Burden and Impact Studies of COVID-19 and Influenza (VEBIS) project to monitor the effectiveneness of vaccines in real world conditions and to inform public health actions and adaptation of vaccination programmes in the EU/EEA countries. One component of VEBIS is based on estimating VE using routinely collected vaccination and outcome data from EHR . This project is leveraging established vaccination registries and health record databases using the combination of mandatory reporting of the vaccination status into these registries and a unique personal identification number or a unique social security number across health databases as the key for individual level datalinkage, allowing to perform VE studies.

The overall aim of this component of the VEBIS project is to expand the use of electronic health registries accross Europe and to establish robust statistical methods to monitor COVID-19 VE over time as well as to improve the timeliness of reporting of VE estimates across EU/EEA. With this aim, we carried out a multi-country study based on EHR to prospectively provide monthly VE estimates of the complete primary vaccination series, the first, the second, and the third booster dose against COVID-19 hospitalisation and COVID-19-related death, in community-dwelling resident population aged 65 years and over.

Methods

Study design and setting

Using a common protocol , Belgium, Denmark, Luxembourg, Navarre (Spain), Norway and Portugal constructed population cohorts based on data collected routinely in EHR. Countries were recruited based on their assessed capability to join the study and a formal outreach performed by the ECDC. We used individual deterministic linkage to cross-match administrative population and statistical office databases with registers for COVID-19 vaccination, SARS-CoV-2 testing, hospitalisations, deaths and clinical data. Belgium was unable to include unvaccinated individuals, but followed the same protocol to compare individuals with different vaccination status to provide relative VE (rVE) estimates. A description of the EHR used by each study site to monitor COVID-19 VE is provided in the supplementary material (Supplementary material, Appendix 1).

We estimated COVID-19 VE with monthly frequency. For each month, the observation period covered eight weeks to allow sufficient events to provide precise estimates and to be sensitive to changes in VE over time. Overall, the observation period was between October 2021 and November 2022. Between October 2021 and March 2022, we piloted a common protocol for an outcome of COVID-19 hospitalisation in four study sites: Denmark, Navarre (Spain), Norway, and Portugal . From March 2022 onwards, we added the outcome of COVID-19-related death, from April 2022 onwards, we added rVE estimates and, from June 2022 onwards, we added two study sites (Belgium and Luxembourg).

Selection criteria and definitions

We included individuals aged between 65 and 110 years (inclusive). We excluded residents in long-term-care facilities (using the last available information) and early vaccinees (defined as either being vaccinated before recommended for their age group or the first 5% vaccinated of each 5-year age band) to exclude vulnerable groups with different probabilities of vaccination and developing severe COVID-19. In addition, we excluded those with inconsistent data on vaccination (two-dose primary vaccination with <19 days apart, or those vaccinated with a booster <90 days after the last primary or booster dose, or a combination of brands other than recommended in the EU/EAA). Individuals with a previously recorded positive SARS-CoV-2 test (previous infection) were excluded until April 2022, but not thereafter.

Outcomes of interest were: 1) hospitalisation due to COVID-19, defined as admission to a hospital with a SARS-CoV-2 infection laboratory-confirmed from 14 days before to one day after admission, in which admission criteria are compatible with a severe acute respiratory infection , or in which COVID-19 is the main diagnosis in the discharge record, and 2) COVID-19-related death, defined as death for which COVID-19 is recorded as the cause of death or, if the cause of death is not available, laboratory-confirmed SARS-CoV-2 infection with death in the 30 days after the positive test or symptom onset.

For each outcome, we assumed the date of the positive test result (i.e. the date of the first SARS-CoV-2 positive test of the infection episode that resulted in hospital admission or death) as the date of the outcome.

The vaccination status was defined as a time-varying variable within each observation period and classified as: 1) unvaccinated (no record of COVID-19 vaccine administration); 2) complete primary vaccination, if received one dose of Jcovden(r) or two doses of any combination of Comirnaty(r), Spikevax(r) or Vaxzevria(r); 3) vaccination with the first booster, if received an additional dose of Comirnaty(r), Spikevax(r) (monovalent or bivalent) at least 90 days after the complete primary vaccination; 4) vaccination with the second booster, if received a first booster and an additional dose of Comirnaty(r), Spikevax(r) (monovalent or bivalent) at least 90 days later; 5) vaccination with the third booster, defined in the same way as the second booster.

Analytical methods for site-specific vaccine effectiveness

estimates

We used a survival analysis framework with calendar time as the underlying time scale, assigning time zero to the first day of each observation period. We excluded person-time at-risk from the date of receipt of a vaccine dose until 13 days after. Follow-up started at the beginning of the observation period and ended at the earliest occurrence of any of the following event: 1) date for the outcome of interest, 2) death of any cause, 3) date of discontinuation in the administrative database (e.g., emigration), or 4) administrative censoring (eight weeks after time zero).

We estimated adjusted hazard ratios (aHR) of each outcome and 95% confidence intervals (CI) with Cox proportional hazards models. The adjustment variables included sex, age group (in 5-year age bands), previous SARS-CoV-2 infection, comorbities (with the exception of Luxembourg) and other variables relevant at each study site (Supplementary material, Appendix 2). We computed VE as: VE = (1-aHR) x 100%, using the unvaccinated as the reference group in the primary analysis. To estimate the rVE of booster doses, we considered those with complete primary vaccination [?]169 days ago as well as those with first booster [?]90 days ago as a reference. All estimates were stratified by age group (65-79 or [?]80- years old).

For data protection reasons, sites reported aHR estimates only when at least 5 events per vaccination status category were observed. All sites fulfilled ethical and data protection requirements according to their national legislation (Supplementary material, Appendix 3).

Analytical methods for pooled vaccine effectiveness stimates

We used a random-effects meta-analysis (Paule-Mandel method) to pool site-specific aHRs, accounting from within and between sites variability in the estimates. The number of sites contributing to the pooled analysis for the different vaccination statuses at each follow-up period varied due to differences in the national COVID-19 vaccination campaign rollout (Supplementary material, Appendix 4). Only sites with general recommendations of respective doses in 65–79-years and [?]80-year-old were included in each eight-week observation period. Pooled VE estimates obtained with fewer than 15 events were not reported.

Results

Characteristics of the study population

Pooling together the data from the six participating study-sites, the distribution of study participants by vaccination status in each observation period is shown in Figure 1. Throughout the study, the proportion of unvaccinated individuals remained low, at 3–5% of 65–79-years and 1–2% of [?]80-years. The proportion

of vaccinated with the first booster increased progressively in both age groups until the respective second booster recommendation and declined afterwards. In the last observation period (October-November 2022), 25% of [?] 80-years had been vaccinated with the third booster.

The number of observed COVID-19 hospitalisations ranged between 816 in the first observation period (October-November 2021) and 471 in the last observation period (October-November 2022) among 65–79-years, and between 690 and 665 among [?]80-years. The number of COVID-19-related deaths registered among 65–79-years ranged between 523 in March-April 2022 and 231 in October-November 2022 and between 1470 and 549 among the [?]80-years.

Vaccine effectiveness against COVID-19 hospitalisation (vs un vaccinated*)*

For the [?]80-years, VE of complete primary vaccination against COVID-19 hospitalisation decreased from 66.9% (95%CI: 60.1; 72.6) in October-November 2021 to 36.1% (95%CI: -27.3; 67.9) by October–November 2022 (Table 1, Figure 2). A similar trend was observed in 65-79 years with corresponding estimates of 86.8% (95%CI: 84.5; 88.8) and 31.5% (95%CI: -7.1; 56.2).

VE of the first booster for the [?]80-years peaked at 95.6% (95%CI: 88.0; 98.4) in October–November 2021 declining to 54.6% (95%CI: 29.6; 70.7) by May 2022 with little variation afterwards (Table 2). For the 65–79-years, the first booster VE declined progressively from 95.4% (95%CI: 92.9; 97) in November-December 2021 to 52.1% (95%CI: 20.2; 71.2) in October–November 2022.

The second booster VE for the [?]80-years started at 82.0% (95%CI: 75.9; 87.0) in June–July 2022 and was 83.9% (95%CI: 77.7; 88.4) in October–November 2022. For 65–79-years, VE was 39.3% (95%CI: -3.9; 64.5) in August–September 2022 but increased to 80.6% (95%CI: 67.2; 88.5) in October–November 2022 (Table 3).

The third booster VE estimate against COVID-19 hospitalisation was 82.0% (95%CI: 71.8; 88.5) but was only available for [?]80-years in October–November 2022 in Portugal.

Relative vaccine effectiveness (rVE) against COVID-19 hospitalisation

Relative to complete primary vaccination [?]169 days ago, the first booster rVE for [?]80-years ranged between 52.2% (95%CI: 24.7; 69.6) in April–May 2022 and 45.5% (95%CI: 31.4; 56.7) in October–November 2022. The corresponding estimates for the 65–79-years were 64.2% (95%CI: 42.2; 77.8) and 30.4% (95%CI: 9.8; 46.3), respectively. (Table 2, Figure S1).

Relative to the first booster vaccination [?]90 days ago, the incremental protection conferred by the second booster ranged for the [?]80-years between 54.0% (95%CI: 42.9; 62.9) in June-July 2022 and 34.2% (95%CI: 16.8; 47.9) in September-October 2022 and, for the 65–79-years, from -39.9% (95%CI: -89.3; 3.4) in August-September 2022 to 57.4% (95%CI: 34.6; 72.2) in October-November 2022 (Table 3, Figure S2).

Vaccine effectiveness against COVID-19-related death (vs unvaccinated)

For the [?]80-years, complete primary vaccination VE against COVID-19-related death varied between 41.4% (95%CI: 26.0; 53.6) in March–April 2022 and 45.1% (95%CI: -29.2; 76.6) in October–November 2022. The corresponding figures for the 65–79-years were 21.3% (95%CI: -19.8; 48.2) and 45.0% (95%CI: -28.0; 76.4) (Table S1, Figure 3).

We observed a decrease in the first booster VE estimates between March-April 2022 and October-November 2022 from 83.5% (95%CI: 73.2; 89.8) to 64.4% (95%CI: 51.8; 73.7) for the [?]80-years and from 85.4% (95%CI: 79.3; 89.8) to 43.1% (95%CI: 4.9; 66.0) for the 65–79-years (Table S2, Figure 2).

The second booster VE for [?]80-years remained above 80% between June-July 2022 and October-November 2022, showing no evident trends (Table S3, Figure 2). For the 65–79-years second booster VE was 77.0% (95%CI: 47.6; 89.9) in the last observation period (October-November 2022).

Relative vaccine effectiveness (rVE) against COVID-19-related death

rVE estimates showed that additional protection against COVID-19-related death achieved with the first booster decreased over time in both age groups (Table S2, Figure S3), specifically from 61.3% (95%CI: 48.3; 71.0) in April-May 2022 to 34.6% (95%CI: 10.7; 52.1) in October-November 2022 for the [?]80-years and from 66.0% (95%CI: 55.2;74.3) in April-May 2022 to -8.5% (95%CI: -69.6; 30.6) in October-November 2022 for the 65–79-years.

Considering first booster vaccination [?]90 days ago as a reference group, the second booster rVE against COVID-19-related death varied between 58.0% (95%CI: 50.3; 64.5) in June-July 2022 and 65.0% (95%CI: 40.9; 79.3) in October-November 2022 for the [?]80-years. For the 65–79-years the first available estimate of second booster rVE was 74.0% (95%CI: 60.6; 82.8) in October-November 2022 (Table S3, Figure S4).

Discussion

The prospective production of VE estimates using population-based EHR with short time lag between data consolidation and data analysis is an added value to provide necessary evidence to adapt vaccine policies in the different target groups in a timely way In this study, timely, rapid and robust estimates have been calculated using a common protocol applied to population registries for complete primary vaccination, first, second and third booster doses. The harmonization of the outcome and exposure definitions, and the application of common analytical methods enhanced comparability and allowed for joint estimates. These methodological approaches are of high added value especially when the incidence of COVID-19 decreases and fewer events are reported. Results are based on a multi-country collaboration and estimates reflect on the performance of the vaccines in the population across several countries. In addition, the overall study period covered the predominance of the Delta SARS-COV-2 variant, the emergence of the Omicron and its subvariants, as well as the successive administration of first, second and third vaccine boosters which is another key strength of this analysis. Nonetheless, the production of real time VE estimates depends on access approvals to different EHR by the public health instititutes. While such access have been relatively easily granted in exceptional circumstances during pandemic time, the sustainability of such process may be difficult moving forward.

Our results showed a decrease in complete primary vaccination VE against hospitalisation in both agre groups (65–79 and [**?**] 80-years) from 87–67% in October–November 2021 to 32–36% in October–November 2022. While the first booster initially restored immunity to similar levels to the ones observed at the beginning of the vaccination programme ([?]95% by the end of 2021), its VE also decreased to approximately 50–68% by May 2022, around 6-7 months after first booster vaccination campaign and after the emergence of Omicron and its subvariants. VE estimates against COVID-19-related deaths of the first booster available since March–April 2022 showed a similar trend, although less pronounced among [?]80-years, compared to 65–79-years.

The significant decline in VE following the emergence of SARS-CoV-2 Omicron in December 2021 is in line with neutralisation studies indicating vaccine escape by Omicron . It is also highly consistent with reports from the USA, Canada, South Africa and Europe on lower VE against severe disease during the Omicron subvariants predominance, in particular BA.2 and BA.4/BA.5. Rapid waning of first booster VE against hospitalisation during Omicron predominant period has also been reported in the literature (VE of 29–58% 3–6 months after uptake) . This decline in VE motivated the recommendation for an additional booster dose in vulnerable population subgroups, but also the development of adapted vaccines to closely match circulating variants.

Other factors could also contribute to the observed decrease in VE. The Omicron BA.1 wave in early 2022 resulted in the highest SARS-CoV-2 incidence observed throughout the pandemic in Europe, with estimated 48% of the European population infected . This could have enhanced the immunity at a different rate for vaccinated and unvaccinated population, leading to an underestimation of VE .

The administration of a second booster for the [?]80-years and other vulnerable population groups in the Spring of 2022 (only in Portugal and Belgium among the participating study sites) raised VE to around 80% for both hospitalisation and death, and it remained stable between June–July and October–November 2022. However, relative VE did decrease with time since the Spring vaccination campaign and only increased again

in October-November 2022, likely reflecting the second booster vaccination rollout in the remaining participating study sites (Supplementary material, appendix 4). Specifically, second booster was recommended in Summer 2022 (Norway, Belgium) and in Autumn 2022 (Navarre, Spain), and Portugal and Belgium introduced the third booster for the [?]80-years in Autumn 2022, resulting in second and third boosters administered simultaneously in different study sites. The observed similar VE estimates for the second and third boosters in our study suggest that the time since the last dose might be more relevant than the total number of doses received.

In addition, adapted bivalent vaccines were introduced and used as booster (first, second, third) from September 2022 onwards , with countries rapidly discontinuing the use of monovalent vaccines. This affects the comparability of the most recent VE estimates with the ones obtained before September 2022, and may have led to the underestimation of the relative benefit of the most recent booster dose. Studies have suggested different effectiveness of monovalent and bivalent vaccines and that bivalent vaccines with BA.4/5 component could provide more protection than those with BA.1 .

There are several limitations to be flagged. Even though all the sites followed a common protocol, there were some differences in the information available at each site and the outcomes definitions allow a small degree of flexibility. Also, because variables for adjustment collected by study sites were limited by the information available within the respective EHR, there might be some residual confounding in the estimates. The VE monitoring system was implemented in highly vaccinated populations, and by October 2021 the primary series vaccination coverage was already >90% in all participating study sites and continued to increase , resulting in a small group of unvaccinated individuals that made VE estimation at the study site level challenging. In particular, at the end of the observation period, this extreme distribution of vaccination led to considerable statistical uncertainty. Henceforth, we envisage that monitoring relative VE, that quantify the additional benefit of each booster dose, will provide more robust results and will be more informative. Up to March–April 2022, we excluded individuals with previous infections. Systematic testing for SARS-CoV-2 was discontinued in most countries during the Omicron wave at the beginning of 2022, self-tests were readily available in the community and the results were not reported in EHR. In this context, the risk of misclassification of previous infection is high, and after April 2022 this exclusion criterion was no longer applied. While most of the vaccines administered as first, second and third boosters were mRNA vaccines in the EU/EEA, it would be of importance to get brand specific estimates. Unfortunatly, there was not sufficient information in some registries to provide vaccine brand specific estimates. Last but not least, the project aims to expand to additional countries in order to have a better geographical representativeness across the EU/EEA.

In conclusion, according to our results, successive COVID-19 vaccine booster doses have been key to maintaining protection against severe disease over time. Despite the reduction in VE, booster vaccination continues to substantially reduce the risk of hospitalisation and death due to COVID-19 in older individuals. Overall, this study demonstrated the feasibility of real-world prospective monitoring of COVID-19 VE in real time using EHR with application of a common protocol across six EU/EEA countries. Although it comes with some methodological challenges, the use of population-based EHR across several sites provide robust estimate at EU level and should be maintained to continue with near-real-time VE estimates in a changing landscape of COVID-19 vaccine recommendations.

References

Table 1 . Estimated vaccine effectiveness (VE) for complete primary vaccination (vs. unvaccinated) against COVID-19 hospitalization by age group, in overlapping eight-week wide observation intervals from October 2021 to November 2022 in six EU/EEA countries. Random effects meta-analysis.

Age group	VE (95% CI) vs unvaccinated	VE (95% CI) vs unvaccinated	VE (95% CI) vs unvaccinated	VE (95% CI) vs unvaccinated	VE (95% CI) vs unvaccinated	VE (95% CI) vs unvaccinated	VE (95% CI) vs unvaccinated	VE (95% CI) vs unvaccinated	VE (95% CI) vs unvaccinated	VE (95% CI) vs unvaccinated	VE (95% CI) vs unvaccinated	V (C v u v c r
	October 1 to November 25, 2021	November 1 to December 26, 2021	December 1, 2021 to January 25, 2022	January 1 to February 25, 2022	February 1 to March 28, 2022	March 1 to April 25, 2022	April 1 to May 26, 2022	May 1 to June 25, 2022	June 1 to July 26, 2022	July 1 to August 25, 2022	August 1 to September 25, 2022	S 1 C t 2 2
[?]80-year-olds	66.9% (60.1; 72.6)	60.3% (49.7; 68.7)	52.4% (26.5; 69.1)	46.2% (33.4; 56.6)	37.6% (21.7; 50.3)	36.8% (24.4; 47.2)	43.5% (-8.0; 70.5)	47.6% (-11.6;75.4)	34.3% (12.9; 50.3)	34.9% (17.0;48.9)	54.5% (37.1;67.0)	3 (1
65–79 year-olds	86.8% (84.5; 88.8)	85.4% (78.8; 89.9)	77.8% (64.2; 86.3)	55.3% (19.7; 75.1)	44.3% (15.7; 63.1)	32.4% (17.3; 44.7)	38.6% (-2.3; 63.2)	35.2% (-72.4;75.6)	40.9% (-19; 70.7)	10.0% (-91.7; 57.8)	31.6% (-0.2; 53.2)	5 (6

VE: Vaccine effectiveness; CI: confidence interval

Table 2 . Vaccine effectiveness and relative vaccine effectiveness (rVE) for the first booster dose against COVID-19 hospitalisation by age group, in overlapping eight-week wide observation intervals from October 2021 to November 2022 in six EU/EEA countries. Random effects meta-analysis.

Age group	October 1 to November 25, 2021	November 1 to December 26, 2021	December 1, 2021 to January 25, 2022	January 1 to February 25, 2022	February 1 to March 28, 2022	March 1 to April 25, 2022	April 1 to May 26, 2022	May 1 to June 25, 2022	June 1 to July 26, 2022	July 1 to August 25, 2022	August 1 to September 25, 2022	S 1 C t 2 2
	VE (95% CI) vs unvaccinated	**VE (95% CI) vs unvaccinated**	**VE (95% CI) vs unvaccinated**	**VE (95% CI) vs unvaccinated**	**VE (95% CI) vs unvaccinated**	**VE (95% CI) vs unvaccinated**	**VE (95% CI) vs unvaccinated**	**VE (95% CI) vs unvaccinated**	**VE (95% CI) vs unvaccinated**	**VE (95% CI) vs unvaccinated**	**VE (95% CI) vs unvaccinated**	**V (C v u v c r**
[?]80-year-olds	95.6% (88.0; 98.4)	95.2% (90.6; 97.5)	93.3% (88.9; 95.9)	87.8% (84.4; 90.4)	82.0% (78.6; 84.9)	75.9% (72.4;78.9)	66.4% (59.0;72.5)	54.6% (29.6;70.7)	56.9% (37.1;70.5)	61.8% (50.8;70.3)	62.1% (40.4; 75.9)	5 (7

Age group	October 1 to November 25, 2021	November 1 to December 26, 2021	December 1, 2021 to January 25, 2022	January 1 to February 25, 2022	February 1 to March 28, 2022	March 1 to April 25, 2022	April 1 to May 26, 2022	May 1 to June 25, 2022	June 1 to July 26, 2022	July 1 to August 25, 2022	August 1 to September 25, 2022
65–79 year-olds	85.0% (78.6; 89.5)	95.4% (92.9; 97)	95.3% (93.8; 96.5)	91.4% (86; 94.7)	87.6% (78.8; 92.8)	83.7% (76.0;88.9)	70.0% (61.9;76.4)	60.0% (30.1;77.1)	61.0% (40.5;74.4)	60.9% (44.2;72.7)	58.8% (46.0; 68.6)
	rVE (95% CI) vs complete primary vaccination [?]169 days ago	**rVE (95% CI) vs complete primary vaccination [?]169 days ago**	**rVE (95% CI) vs complete primary vaccination [?]169 days ago**	**rVE (95% CI) vs complete primary vaccination [?]169 days ago**	**rVE (95% CI) vs complete primary vaccination [?]169 days ago**	**rVE (95% CI) vs complete primary vaccination [?]169 days ago**	**rVE (95% CI) vs complete primary vaccination [?]169 days ago**	**rVE (95% CI) vs complete primary vaccination [?]169 days ago**	**rVE (95% CI) vs complete primary vaccination [?]169 days ago**	**rVE (95% CI) vs complete primary vaccination [?]169 days ago**	**rVE (95% CI) vs complete primary vaccination [?]169 days ago**
[?]80-year-olds	N/A*	N/A*	N/A*	N/A*	N/A*	N/A*	52.2% (24.7;69.6)	42.2% (32.6;50.5)	44.1% (29.4;55.7)	37.5% (16.0;53.5)	28.9% (11.8; 42.7)
65–79 year-olds	N/A*	N/A*	N/A*	N/A*	N/A*	N/A*	64.2% (42.2;77.8)	47.1% (33.6;57.8)	34.6% (19.2;47.0)	47.5% (30.6;60.3)	43.2% (20.6; 59.3)

VE = Vaccine effectiveness; CI –Confidence interval; * N/A: Not applicable: In the first six months of the study

Table 3 . Estimates of vaccine effectiveness (VE) and relative vaccine effectiveness (rVE) for the second booster dose against COVID-19 hospitalization by age group, in overlapping eight -week wide observation intervals from May 2021 (earliest month with available estimates for the 2nd booster) to November 2022, in six EU/EEA countries. Random effects meta-analysis.

Age group	June 1 to July 26, 2022	July 1 to August 25, 2022	August 1 to September 25, 2022	September 1 to October 26, 2022	October 1, 2022 to November 25, 2022
	VE (95% CI) vs unvaccinated	**VE (95% CI) vs unvaccinated**	**VE (95% CI) vs unvaccinated**	**VE (95% CI) vs unvaccinated**	**VE (95% CI) vs unvaccinated**
[?]80-year-olds	82.0% (75; 87)	75.0% (67.1; 81.0)	80.4% (70.1; 87.1)	80.0% (63.3; 89.0)	83.9% (77.7; 88.4)

Age group	June 1 to July 26, 2022	July 1 to August 25, 2022	August 1 to September 25, 2022	September 1 to October 26, 2022	October 1, 2022 to November 25, 2022
65–79 year-olds	N/A*	N/A*	39.3% (-3.9; 64.5)	77.2% (57.9; 87.7)	80.6% (67.2; 88.5)
	rVE (95% CI) vs complete primary vaccination [?]169 days ago	**rVE (95% CI) vs complete primary vaccination [?]169 days ago**	**rVE (95% CI) vs complete primary vaccination [?]169 days ago**	**rVE (95% CI) vs complete primary vaccination [?]169 days ago**	**rVE (95% CI) vs complete primary vaccination [?]169 days ago**
[?]80-year-olds	71.0% (61.4; 78.2)	57.8% (48.2; 65.6)	57.2% (43.1; 67.9)	50.7% (35.8; 62.2)	68.4% (54.5; 78.1)
65–79 year-olds	N/A*	N/A*	22.7% (-29.6; 53.9)	51.2% (9.9; 73.6)	73.4% (62.2; 81.3)
	rVE (95% CI) vs the first booster[?]90 days ago	**rVE (95% CI) vs the first booster[?]90 days ago**	**rVE (95% CI) vs the first booster[?]90 days ago**	**rVE (95% CI) vs the first booster[?]90 days ago**	**rVE (95% CI) vs the first booster[?]90 days ago**
[?]80-year-olds	54.0% (42.9; 62.9)	41.6% (11.1; 61.6)	42.2% (9.7; 63.0)	34.2% (16.8; 47.9)	47.0% (12.5; 67.9)
65–79 year-olds	N/A*	N/A*	-39.9% (-89.3; 3.4)	33.3% (9.5; 50.8)	57.4% (34.6; 72.2)

VE = Vaccine effectiveness; CI –Confidence interval N/A*: Not applicable before vaccine recommendation was issued

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