Supplementary material

Monitoring COVID-19 vaccine effectiveness against 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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Appendix 1. Data sources used in the six study sites to extract the study variables

Type of variables	Study variable	Study site					
		Portugal	**Navarre (Spain)**	**Norway***	**Denmark**	**Luxembourg**	**Belgium**
Outcomes	**Hospital admission due to COVID-19**	National Hospital Discharge database (BIMH)	Enhanced COVID surveillance with individual revision of events	Norwegian Intensive Care and Pandemic Registry (NIPaR)	Danish National Patient Register (DNPR)	Epidemiological national surveillance platform (MSINF) to collect daily data from hospitals	Clinical Hospital Survey database
	Death due to COVID-19	National Death Registry (SICO) and National Health Service User databaset (NHSU): a Cause of death is from SICO, death status and date of death from NHSU.	Administrative database of deaths and individual revision of events	Norwegian Death Registry (DÅR)	MiBA and Danish Civil Registration system (CPR)	Idem + death certificate for death happened outside hospital or nursing home	NA
Exposures	**Vaccination status**	The National Vaccination Register (VACINAS)	Vaccination register	The National Immunisation Register (SYSVAK)	Danish Vaccination Registry (DVR)	MSVAC: National vaccination registry under the responsibility of Health Directorate	National vaccine registry (VACCINNET)
Variables for adjustment or stratification	**Age**	National Health Service User databaset (NHSU)	Administrative database	The National Population	CPR	Statutory health insurance database	The national population register

				Register (Folkeregisteret)			
	Sex	National Health Service User databaset (NHSU)	Administrative database	The National Population Register (Folkeregisteret)	CPR	Statutory health insurance database	national population register
	Health Region	Region of residence: National Health Service User databaset (NHSU)	Not applicale	County of residence at end of study period: The National Population Register (Folkeregisteret)	CPR	Statutory health insurance database	Province of residence: national population register
	Comorbidities	Primary Care Information System (SIM@SNS).	Administrative database	Risk groups / Comorbidities: Based on Norwegian Patient Registry (NPR)	DNPR	NA	Intermutualistic Agency database
	Previous infection	National Information System for Epidemiologic Surveillance (BI-SINAVE)	Previos infections are excluded, pendent of a sepatare analysis	The Surveillance System for Infectious Diseases (MSIS)	MiBA	MSINF (see above)	COVID-19 Laboratory test results database from Healthdata.be register
	Others specific to the study site	1. Number of tests for SARS-CoV-2 in 2020-2022: BI-SINAVE	1. Country of birth and high functional dependence:	1. Conditions of living – Crowding: Statistics Norway (SSB). Most recent	NA	1. Statutory health insurance database	1. Household income (according to tax records) categorized as low

		2. Conditions of living – Deprivation at municipality level: Most recent data from 2011 3. Other vaccines uptake: VACINAS	Administrative database	data from 2019 – separate level for missing data 2. *County of birth:* Folkeregisteret			(lowest 40%), mid (middle 30%), and high (highest 30%): STATBEL database

***** All data in Nowray was integrated in the emergency preparedness register for COVID-19 (Beredt C19), https://www.fhi.no/en/id/infectious-diseases/coronavirus/emergency-preparedness-register-for-covid-19/

Appendix 2. Methodological details in the different study sites

Variable	Definition, categorisation, use in the model					
	Portugal	**Navarre (Spain)**	**Norway**	**Denmark**	**Luxembourg**	**Belgium**
Age	Age at the start of study period (5-year categories)	Age at the start of study period (5-year categories)	Age at end of 2022 (birth cohorts) (For adjustment: 5-year age groups)	5-17, 18-49, 50-64, 65-79, 80+, adjusted in bins: 5-9, 10-14, 15-17, 18-24 and then 5-year bins until the final category, 90+ years	Age at the start of follow up, 5-year bins	Age in years at the end of the year in which the study period begins. For adjustment: 5-year age groups.
Comorbidities	Number of comorbidities (0, 1, 2, 3, 4, 5+) *Considered comorbidities include: anemia, asthma, cancer, cardiac disease, dementia, diabetes, hypertension, HIV, liver disease, neuromuscular disease, obesity, pulmonary disease, renal*	Immunocompromised Other major chronic conditions, High functional dependencies	High risk: - *Organ transplant* - *Immunodeficiency* - *Haematological cancer in the last five years* - *Other active cancers* - *Neurological or neuromuscular diseases that cause impaired cough or lung function (e.g., ALS and cerebral palsy)*	Immunocompromised, including: - *HIV* - *Immunological disease* - *Radiation therapy* - *Organtransplanted* Other, including: - *Diabetes* - *Obesity* - *Cancer* - *Neurological Disease* - *Kidney disease* - *Haematological cancers* - *Heart disease*	Not included	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): - *Received chemotherapy/ radiotherapy against cancer* - *Received multidisciplinary oncologic consult* - *Cardiovascular illness – general* - *Cardiovascular illness-specifically a heart disease* - *Alzheimer*

	disease, rheumatologic disease, stroke, tuberculosis		- *Chronic kidney disease, or significant renal impairment.* Medium risk: - *Chronic liver disease or significant hepatic impairment* - *Immunosuppressive therapy* - *Diabetes* - *Chronic lung disease including cystic fibrosis and severe asthma which have required the use of high dose inhaled or oral steroids within the past year* - *Obesity with a body mass index (BMI) of ≥35 kg/m2* - *Dementia*	- *Chronic respiratory disease* - *Liver disease (incl. alcohol lever)* - *Endocrine Disease* - *Hematological Disease* - *Coagulation Disease* - *Innate Diseases* - *TB* - *Missing a lung* - *Missing a kidney*		- *Asthma* - *Haemophilia* - *Disease of Crohn, Colitis Ulcerosa, Psoriatrische arthritis, Reumatoid arthritis* - *Chronic obstructive pulmonary disease* - *Diabetes with cardiovascular compilations* - *Diabetes Mellitus with insulin treatment* - *Epilepsy and neuropathic pain* - *Chronic hepatitis type B or C* - *Kidney failure* - *Cystic fibrosis* - *Exocrine pancreatic disease* - *Disease of Parkinson* - *Psoriasis* - *Psychosis occurring with people older than 70 years* - *Psychosis occurring with people of 70 year or younger.* - *Multiple sclerosis* - *Thrombosis while treated with antithrombotic medicines* - *Thyroid disorder* - *HIV*

			- *Chronic heart and vascular disease (with the exception of high blood pressure) and stroke*			Immunocompromised (high risk): *if a person received a priority invitation for a COVID-19 vaccination due to being immunocompromised, then he/she was classified into a this group.*
Country of residence / country of birth / nationality	Not included	Country of birth	As registered at time of analysis (June 2022)	Not included	Country of residence = administrative address in Luxembourg (as of September 2021) Country of birth = Luxembourg / Other Nationality = Citizenship Luxembourg / Other	Not included
Deprivation index or similar	European deprivation index quintile Q1 (least deprived) to Q5 (most deprived)		Crowded conditions: if the number of rooms is lower than the number of residents or one resident lives in one room, and the number of square metres (P-area) is below 25 sq. m. per person. If the number of	Not included	Not included	Household income: low (lowest 40%)-medium (middle 30%)-high (highest 30%)

			rooms or the P-area is not specified, a household will be regarded as crowded if one of these criteria is met (incomplete and slightly outdated data)			
Geographic level	Region of residence (North, Center, Lisbon and Tagus Valey, Alentejo, Algarve)	Not included	County of residence	Adjustment for residency in the 5 geographical regions of Denmark (EU NUTS-2 regions)	Canton	Province of residence
Other vaccines uptake	Vaccination against influenza, PCV7, PCV10, PCV13 or PPV23 in the last 3 years	Not included	Not included	Not included	Not included	Not included
Number of COVID-19 tests in 2020-2022	0, 1, 2, 3, 4-9, 10+	Not included	Not included	Positive RT-PCR test for SARS-CoV-2	Not included	Not included

Appendix 3. Ethical statements for six study sites

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: We used only administrative register data 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 our 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.

Luxembourg: The planning, conduct and reporting of the study are in line with the Declaration of Helsinki. Official ethical approval and patients' consent are not required, as data collection is part of the national pandemic surveillance system set-up under the authority of the Ministry of Health.

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 122745). 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 anonymised, the need for the participants' informed consent was waived by the Ethical Committee.

Appendix 4. Age-specific rollout of the COVID-19 vaccination campaign for the 65-79 year-olds and ≥80-year-olds by vaccine dose and study site

	≥80-year-olds				65-79-year-olds			
	Primary course	1st booster	2nd booster	3rd booster	Primary course	1st booster	2nd booster	3rd booster
Belgium	2021.03.05	2021.09.22	2022.07.20	2022.09.12	2021.03.08	2021.09.22	2022.09.12	
Denmark	2020.12.28	2021.10.18	2022.09.15 (85+)		2021.03.15	2021.10.18	2022.10.01	
Luxembourg	2021.01.27	2021.07.07	2022.04.12		2021.01.27 (75+)	2021.11.08	2022.07.14	
Navarre (Spain)	2021.03.02	2021.10.25	2022.10.10		2021.04.09	2021.10.25	2022.10.10	
Norway	2021.01.31	2021.10.05	2022.06.29	n.a.	2021.03.07	2021.10.05	2022.06.29	n.a.
Portugal	2021.02.03	2021.10.11	2022.05.16	2022.09.06	2021.03.30	2021.10.11	2022.09.06	

Appendix 5. Number of events and person-months for VE estimates against hospitalisation and death due to COVID-19

Table S1. Number of hospitalizations due to COVID-19, and person-months for estimates of vaccine effectiveness (VE) against hospitalisation by vaccination status and age, in overlapping eight-week wide observation intervals from October 2021 to November 2022 in six EU/EEA countries.

Vaccination status	Age group	Follow-up period												
		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	September 1 to October 26, 2022	October 1, 2022 to November 25, 2022
Unvaccinated†	65-79-year-olds	229/ 311,465	463/ 295,571	535/ 280,857	463/ 269,006	370/ 257,793	208/ 263,817	105/ 285,486	100/ 291,490	111/ 287,689	105/ 289,087	61/ 289,785	71/ 294,033	60/ 290,185
	80+ year-olds	130/ 147,142	275/ 140,295	453/ 135,547	546/ 129,959	443/ 125,031	260/ 122,399	195/ 127,395	204/ 128,457	182/ 125,213	150/ 118,527	103/ 118,803	92/ 136,477	99/ 117,273
Complete primary vaccination	65-79-year-olds	769/ 5,430,697	1141/ 3,627,044	766/ 1,261,165	515/ 386,221	340/ 266,654	192/ 237,183	143/ 458,050	126/ 358,105	108/ 373,015)	108/ 391,304	61/ 374,079	48/ 344,104	39/ 239,640
	80+ year-olds	652/ 1,561,711	751/ 716,577	620/ 262,138	544/ 148,922	399/ 117,721	238/ 106,890	214/ 151,184	237/ 129,272	187/ 117,594	132/ 117,325	64/ 110,983	68/ 98,404	65/ 89,648)
Complete primary vaccination + first booster	65-79-year-olds	47/ 104,549	169/ 1,199,370	597/ 3,623,380	1,429/ 4,981,833	2,001/ 4,906,390	1,207/ 4,600,781	920/ 4,971,604	928/ 5,052,588	1,282/ 4,935,561	1,180/ 5,298,858	707/ 5,140,450	635/ 4,161,751	376/ 2,551,844
	80+ year-olds	38/ 308,135	181/ 1,124,695)	884/ 1,752,544	1,938/ 1,901,312	2,541/ 1,871,887	1,910/ 1,759,710	1,762/ 1,843,384	1,547/ 1,175,616	1,578/ 1,275,533	1,345/ 1,273,692	759/ 1,151,542	597/ 794,254	379/ 515,988
Complete primary vaccination + second booster	65-79-year-olds	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	68/ 195,897	71/ 528,062	56/ 1,505,538
	80+ year-olds	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	123/ 425,531	224/ 657,717	191/ 728,417	209/ 677,500	144/ 641,448

N/A = Not applicable

† Unvaccinated individuals are only captured in five countries (all except Belgium).

‡ Results up to June 1 to July 26, 2022 are limited to four sites: Denmark, Navarre (Spain), Norway and Portugal

Table S2. Number of COVID-19 related deaths, and person-months for estimates of vaccine effectiveness (VE) against COVID-19 related death by vaccination status and age, in overlapping eight-week wide observation intervals from October 2021 to November 2022 in five[†] EU/EEA countries

Vaccination status	Age group	Follow-up period												
		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	September 1 to October 26, 2022	October 1, 2022 to November 25, 2022
Unvaccinated	65-79-year-olds	N/A	N/A	N/A	N/A	N/A	85/ 263,853	57/ 278,851	52/ 284,851	51/ 281,009	30/ 282,408	30/ 282,976	32/ 278,937	21/ 282,612
	80+ year-olds	N/A	N/A	N/A	N/A	N/A	225/ 122,428	164/ 127,799	211/ 128,885	188/ 125,635	93/ 118,958	76/ 119,255	88/ 136,915	77/ 117,730
Complete primary vaccination	65-79-year-olds	N/A	N/A	N/A	N/A	N/A	102/ 232,313	100/ 382,715	96/ 352,210	68/ 367,132	44/ 379,412	26/ 375,545	15/ 251,195	20/ 210,453
	80+ year-olds	N/A	N/A	N/A	N/A	N/A	212/ 105,385	241/ 151,996	276/ 131,997	204/ 118,401	102/ 116,330	61/ 111,688	56/ 99,027	47/ 73,714
Complete primary vaccination + first booster	65-79-year-olds	N/A	N/A	N/A	N/A	N/A	421/ 4,467,690)	451/ 4,831,083	499/ 4,913,682	412/ 4,797,355	323/ 5,091,730	244/ 4,941,744	243/ 3,968,103	174/ 2,438,372
	80+ year-olds	N/A	N/A	N/A	N/A	N/A	1,258/ 1,759,883	1,437/ 1,845,307	1,480/ 1,636,612	923/ 1,277,984	600/ 1,276,266	313/ 1,093,178	268/ 785,472	228/ 464,819
Complete primary vaccination + second booster	65-79-year-olds	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	37/ 768,103
	80+ year-olds	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	247/ 425,607	227/ 658,215	190/ 729,420	174/ 660,644	153/ 388,747

N/A = Not applicable

[†] Belgium did not provide estimates on COVID-19 related death and did not participate in this analysis.

[‡] Results up to June 1 to July 26, 2022 are limited to four sites: Denmark, Navarre (Spain), Norway and Portugal

Appendix 6. Detailed results of vaccine effectiveness against hospitalisation due to COVID-19

Figure S1. Pooled booster dose(s) relative vaccine effectiveness (vs. primary vaccination≥169 days ago) against COVID-19 hospitalisation by age group, in overlapping eight-week wide observation intervals from April 2022 to November 2022, in six EU/EEA countries. Random effects meta-analysis.

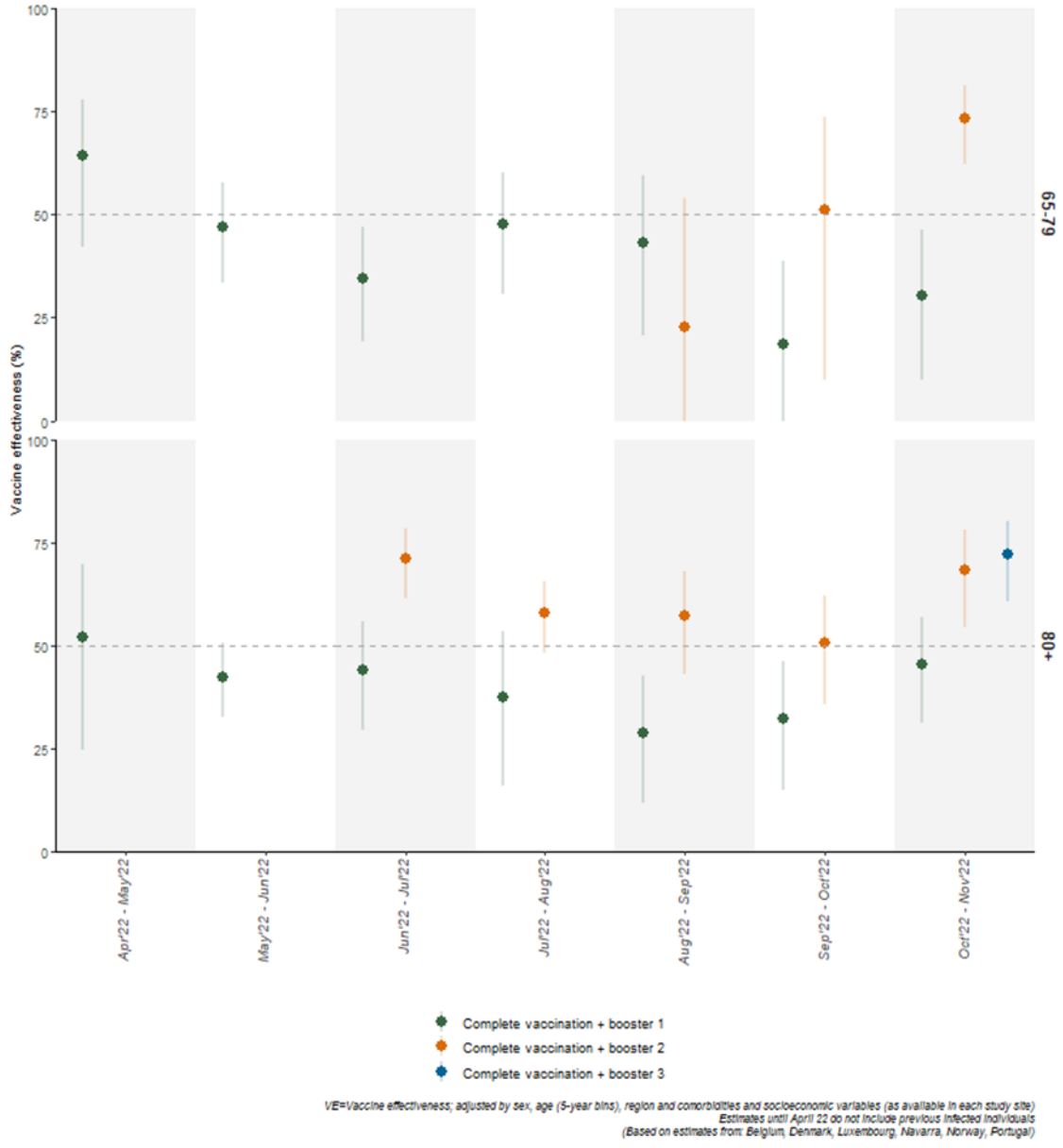
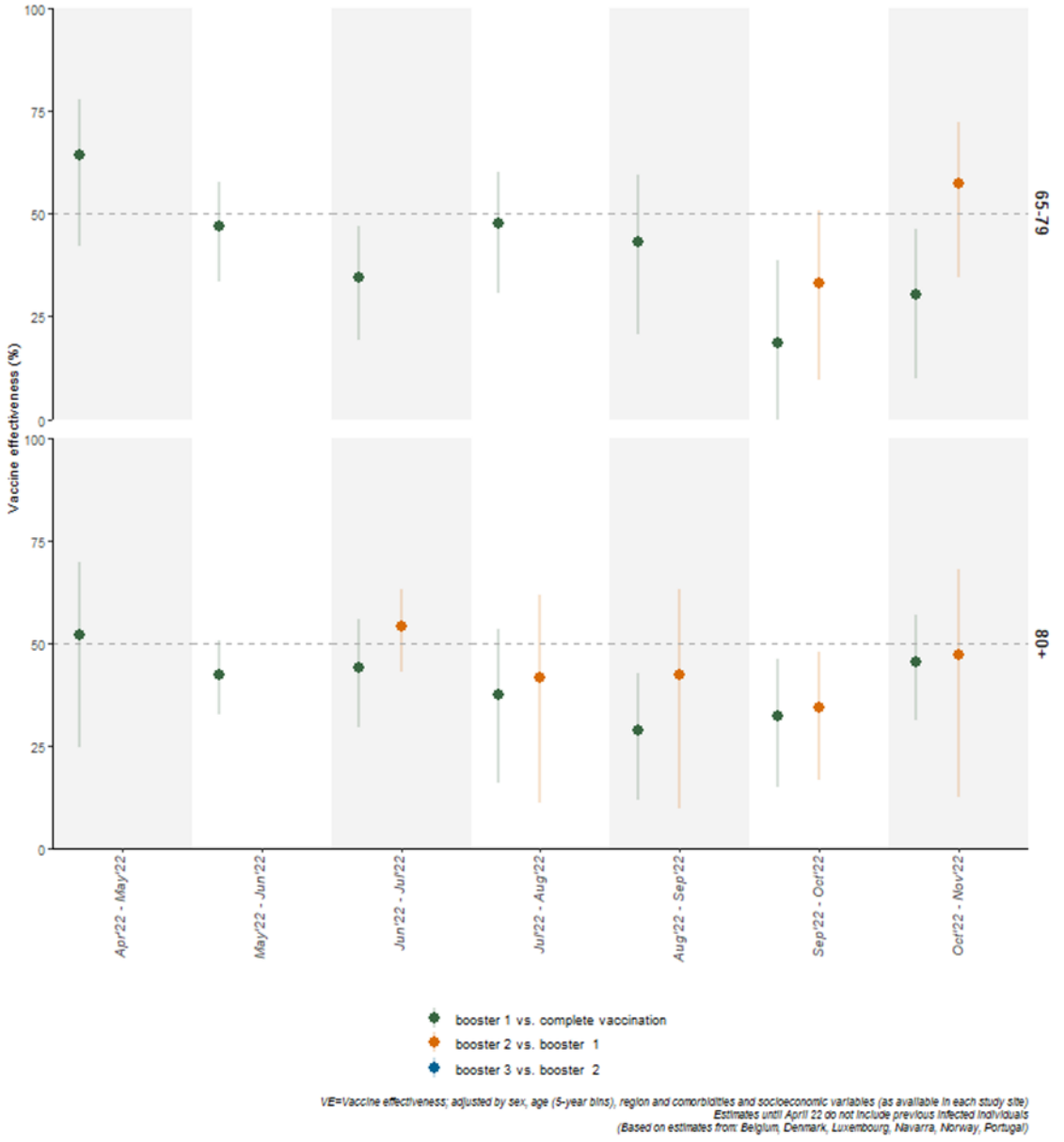


Figure S2. Pooled booster dose(s) relative VE (vs. one less dose) against COVID-19 hospitalisation by age group, in overlapping eight-week wide observation intervals from April 2022 to November 2022, in six EU/EEA countries. Random effects meta-analysis.



Appendix 7. Detailed results of vaccine effectiveness against death due to COVID-19

Figure S3. Pooled booster dose(s) relative VE (vs. complete vaccination≥169 days ago) against COVID-19 death by age group, in overlapping eight-week wide observation intervals from April 2022 to November 2022, in five EU/EEA countries. Random effects meta-analysis.

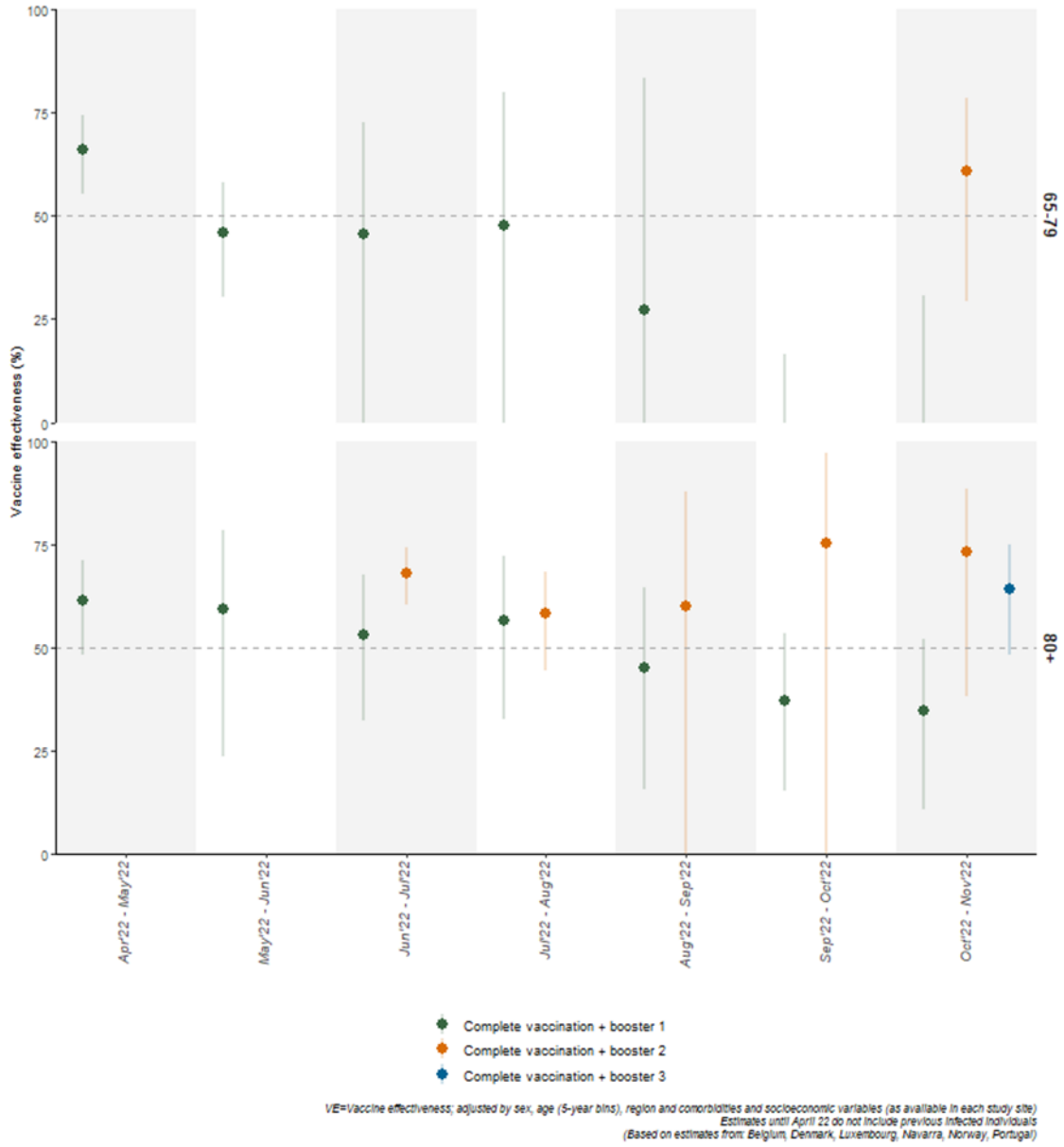
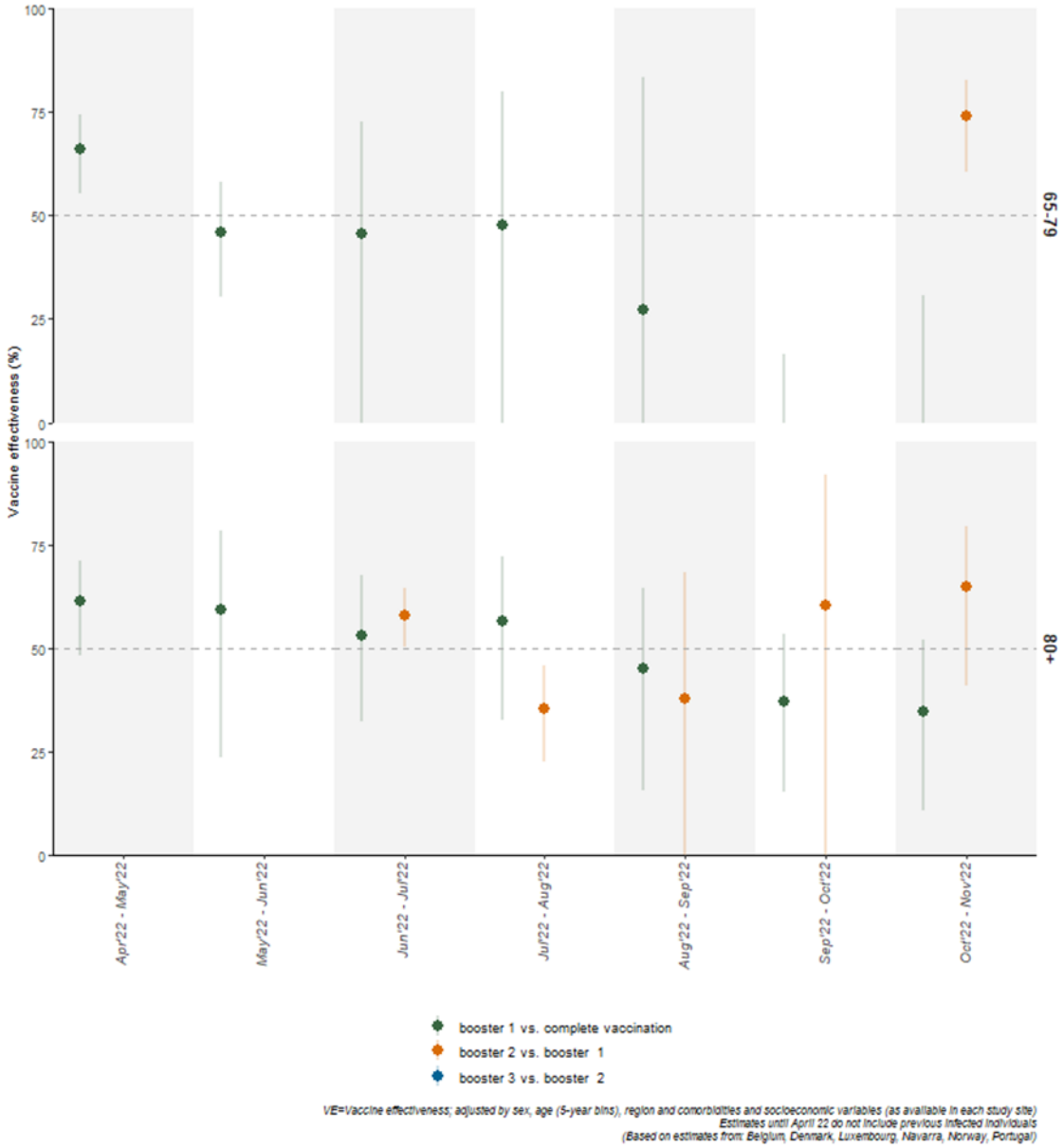


Figure S4. Pooled booster dose(s) relative VE (vs. one less dose) against COVID-19 death by age group, in overlapping eight-week wide observation intervals from April 2022 to November 2022, in five EU/EEA countries. Random effects meta-analysis.



VE=Vaccine effectiveness; adjusted by sex, age (5-year bins), region and comorbidities and socioeconomic variables (as available in each study site)
Estimates until April 22 do not include previous infected individuals
(Based on estimates from: Belgium, Denmark, Luxembourg, Navarra, Norway, Portugal)

Table S3. Estimated vaccine effectiveness (VE) for primary vaccination (vs. unvaccinated) against COVID-19 death by age group, in overlapping eight-week wide observation intervals from March 2022 to November 2022, in five[†] EU/EEA countries. Random effects meta-analysis.

Age group	VE (95% CI) vs.unvaccinated												
	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	September 1 to October 26, 2022	October 1, 2022 to November 25, 2022
65-79-year-olds	N/A	N/A	N/A	N/A	N/A	21.3% (-19.8; 48.2) [§]	48.4% (1.3; 73) [§]	56.8% (37.1; 70.3) [§]	55.3% (33.9; 69.9) [§]	46.1% (-12.4; 74.1) [§¶]	66.2% (-21.5; 90.6) [§¶]	75.0% (48.0; 88.0) [§¶#◊]	45.0% (-28; 76.4) [§¶#◊]
80+ year-olds	N/A	N/A	N/A	N/A	N/A	41.4% (26; 53.6) [§]	45.1% (-16.5; 74.2) [§]	17.6% (-281.6; 82.2) [§]	32.5% (-14.6; 60.2)	28.7% (-71.9; 70.4) [§¶]	61.9% (45.6; 73.3) [§¶]	54.3% (23.9; 72.6) [§¶]	45.1% (-29.2; 76.6) [§¶◊]

VE = Vaccine effectiveness; CI = confidence interval; N/A: Not applicable: In the first six months of the study VE estimates were not available for death outcome

[†] Unless otherwise indicated, results are based on pooling VE estimates from Denmark, Luxembourg, Navarre (Spain), Norway and Portugal. (Belgium did not provide estimates of VE against COVID-10 death).

[‡] Unless otherwise indicated, results up to June 1 to July 26, 2022 are limited to four sites: Denmark, Navarre (Spain), Norway and Portugal

[§] Navarre (Spain) did not reach 5 events or this dose was still not recommended at this site and did not contribute to the estimate

[¶] Luxembourg did not reach 5 events or this dose was still not recommended at this site and did not contribute to the estimate

[#] Denmark did not reach 5 events or this dose was still not recommended at this site and did not contribute to the estimate

[◊] Norway did not reach 5 events or this dose was still not recommended at this site and did not contribute to the estimate

Table S4. Estimated vaccine effectiveness (VE) and relative vaccine effectiveness (rVE) for the first booster dose against COVID-19 death by age group, in overlapping eight-week wide observation intervals from October 2021 to November 2022, in five[†] 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	September 1 to October 26, 2022	October 1, 2022 to November 25, 2022
	VE (95% CI) vs unvaccinated												
65-79-year-olds	N/A	N/A	N/A	N/A	N/A	85.4% (79.3; 89.8) [§]	76.9% (69.1; 82.8) [§]	66.3% (53.3; 75.7) [§]	65.7% (52.8; 75) [§]	71.6% (57.6; 80.9) [§¶]	74.1% (58.1; 83.9) [§¶]	65.3% (48.1; 76.8) [§¶]	43.1% (4.9; 66.0) [§]
80+ year-olds	N/A	N/A	N/A	N/A	N/A	83.5% (73.2; 89.8)	75.5% (66.1; 82.3)	68.3% (58.3; 75.9)	64.9% (42.4; 78.7)	69.2% (55.6; 78.6)	77.7% (68.5; 84.3) [§¶]	71.1% (62.2; 78) [§¶]	64.4% (51.8; 73.7) [§¶]
	rVE (95% CI) vs complete primary vaccination ≥169 days ago												
65-79-year-olds	N/A	N/A	N/A	N/A	N/A	N/A	66.0% (55.2;74.3) [§]	45.8% (30.3;57.9) [§]	45.7% (-7.3; 72.5) [§]	47.5% (-37.9; 80) [§¶]	27.2% (-215.3; 83.2) [§¶#]	-33.0% (-111.8; 16.5) [§¶]	-8.5% (-69.6; 30.6) [§¶◊]
80+ year-olds	N/A	N/A	N/A	N/A	N/A	N/A	61.3% (48.3; 71.0)	59.2% (23.6; 78.2)	53.1% (32.2; 67.5)	56.5% (32.7; 72.0)	45.2% (15.5; 64.5) [¶]	37.1% (15.2; 53.4) [§¶]	34.6% (10.7; 52.1) [§¶]

VE = Vaccine effectiveness; CI = Confidence interval; N/A: Not applicable: In the first six months of the study VE and rVE estimates were not available for death outcome

[†] Unless otherwise indicated, results are based on pooling VE estimates from Denmark, Luxembourg, Navarre (Spain), Norway and Portugal. (Belgium did not provide estimates of VE against COVID-10 death).

‡ Unless otherwise indicated, results up to June 1 to July 26, 2022 are limited to four sites: Denmark, Navarre (Spain), Norway and Portugal

[§]Navarre (Spain) did not reach 5 events or this dose was still not recommended at this site and did not contribute to the estimate

[¶] Luxembourg did not reach 5 events or this dose was still not recommended at this site and did not contribute to the estimate

[#] Denmark did not reach 5 events or this dose was still not recommended at this site and did not contribute to the estimate

[◊] Norway did not reach 5 events or this dose was still not recommended at this site and did not contribute to the estimate

Table S5. Estimated vaccine effectiveness (VE) and relative vaccine effectiveness (rVE) for the second booster dose against COVID-19 death 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 five† 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				
65-79-year-olds	N/A	N/A	§¶#◊˜	§¶#◊˜	77.0% (47.6; 89.9) §¶#◊
80+ year-olds	80.0% (75; 84) §#◊	81.6% (56.2; 92.3) §¶#	85.7% (44.6; 96.3) §¶#	88.6% (42.1; 97.7) §¶#◊	82.9% (76; 87.9) §#◊
	rVE (95% CI) vs complete primary vaccination ≥169 days ago				
65-79-year-olds	N/A	N/A	§¶#◊˜	§¶#◊˜	61.0% (29.3; 78.5) §¶◊#
80+ year-olds	68.0% (60.3; 74.2) §¶◊#	58.1% (44.5; 68.3) §¶#	59.9% (-29.6; 87.6) §¶#	75.1% (-109.4; 97) §¶◊#	73.3% (38.2; 88.4) §¶◊
	rVE (95% CI) vs the first booster ≥90 days ago				
65-79-year-olds	N/A	N/A	§¶#◊˜	§¶#◊˜	74.0% (60.6; 82.8) §¶◊#
80+ year-olds	58.0% (50.3; 64.5) §¶◊#	35.2% (22.7; 45.7) §¶#	37.8% (-21.3; 68.1) §¶#	60.4% (-90.6; 91.8) §¶#	65.0% (40.9; 79.3) §¶◊

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

† Unless otherwise indicated, results are based on pooling VE estimates from Denmark, Luxembourg, Navarre (Spain), Norway and Portugal. Belgium did not provide estimates of VE against COVID-10 death).

‡ Results up to June 1 to July 26, 2022 are limited to four sites: Denmark, Navarre (Spain), Norway and Portugal

§ Navarre (Spain) did not reach 5 events or this dose was still not recommended at this site and did not contribute to the estimate

¶ Luxembourg did not reach 5 events or this dose was still not recommended at this site and did not contribute to the estimate

Denmark did not reach 5 events or this dose was still not recommended at this site and did not contribute to the estimate

◊ Norway did not reach 5 events or this dose was still not recommended at this site and did not contribute to the estimate

˜ Portugal did not reach 5 events or this dose was still not recommended at this site and did not contribute to the estimate

Appendix 8. Measures of heterogeneity from the random-effects meta-analysis pooling site-specific estimates from six EU/EEA countries

Table S6. Measures of heterogeneity in the estimation of 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 five[†] EU/EEA countries (corresponding to estimates in Table 1).

Age group	VE (95% CI) vs unvaccinated												
	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	September 1 to October 26, 2022	October 1, 2022 to November 25, 2022
65–79 year-olds	I^2=0% ; tau^2=0 ; p=0.53	I^2=88% ; tau^2=0.12 ; p<0.01	I^2=93% ; tau^2=0.22 ; p<0.01	I^2=94%; tau^2=0.32; p<0.01	I^2=82% ; tau^2=0.13 ; p<0.01	I^2=0% ; tau^2=0; p=0.67	I^2=64% ; tau^2=0.16 ; p=0.01	I^2=83% ; tau^2=0.57 ; p<0.01	I^2=81% ; tau^2=0.39 ; p<0.01	I^2=83% ; tau^2=0.56 ; p<0.01	I^2=0% ; tau^2=0 ; p=0.64	I^2=7% ; tau^2=0.01 ; p=0.34	I^2=0% ; tau^2=0 ; p=0.36
≥80-year-olds	I^2=0% ; tau^2=0 ; p=0.76	I^2= 54%; tau^2= 0.03; p= 0.09	I^2=89%; tau^2=0.17; p<0.01	I^2=56%; tau^2=0.03; p=0.05	I^2=62% ; tau^2=0.03 ; p=0.09	I^2=0% ; tau^2=0 ; p=0.91	I^2=85% ; tau^2=0.27 ; p<0.01	I^2=86% ; tau^2=0.26 ; p=0.01	I^2=34% ; tau^2=0.30 ; p=0.02	I^2=0% ; tau^2=0 ; p=0.54	I^2=0% ; tau^2=0 ; p=0.67	I^2=73% ; tau^2=0.24 ; p=0.03	I^2=73% ; tau^2=0.26 ; p=0.03

VE: Vaccine effectiveness; CI: confidence interval

[†] Results are based on pooling VE estimates from Denmark, Luxembourg, Navarre (Spain), Norway and Portugal (Belgium did not provide estimates of VE against unvaccinated), unless indicated in equivalent categories in Table 1.

[‡] Results up to June 1 to July 26, 2022 are limited to four sites: Denmark, Navarre (Spain), Norway and Portugal.

Table S7. Measures of heterogeneity in the estimation of 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 (corresponding to estimates in Table 2).

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	September 1 to October 26, 2022	October 1, 2022 to November 25, 2022
	VE (95% CI) vs unvaccinated												
65–79 year-olds	I^2=0% ; tau^2=0; p=0.47	I^2= 74% ; tau^2=0.14 ; p<0.01	I^2=79% ; tau^2= 0.07; p=0.01	I^2=95% tau^2=0.22; p<0.01	I^2=94% ; tau^2=0.26 ; p<0.01	I^2=79% ; tau^2=0.11 ; p<0.01	I^2=12% ; tau^2=0.01 ; p=0.32	I^2=67% ; tau^2=0.20 ; p=0.01	I^2=73% ; tau^2=0.13 ; p=0.01	I^2=56% ; tau^2=0.08 ; p=0.12	I^2=0% ; tau^2=0 ; p=0.91	I^2=35% ; tau^2=0.06 ; p=0.26	I^2=50% ; tau^2=0.15 ; p=0.15
≥80-year-olds	I^2=86% ; tau^2=0.85 ; p=0.01	I^2= 88% ; tau^2=0.40 ; p<0.01	I^2=93% ; tau^2= 0.24; p<0.01	I^2=81% tau^2= 0.05; p=0.02	I^2=55% tau^2=0.02 ; p=0.07	I^2=0% ; tau^2=0 ; p=0.47	I^2=20% ; tau^2=0.01 ; p=0.30	I^2=69% ; tau^2=0.10 ; p=0.05	I^2=77% ; tau^2=0.11 ; p=0.08	I^2=41% ; tau^2=0.03 ; p=0.23	I^2=67% ; tau^2=0.13 ; p=0.08	I^2=72% ; tau^2=0.17 ; p<0.01	I^2=71! ; tau^2=0.22 ; p<0.01
	rVE (95% CI) vs complete primary vaccination ≥169 days ago												
65–79 year-olds	N/A	N/A	N/A	N/A	N/A	N/A	I^2=74% ; tau^2=0.17 ; p=0.01	I^2=4% ; tau^2=0 ; p=0.38	I^2=0% ; tau^2=0 ; p=0.65	I^2=55% ; tau^2=0.06 ; p=0.05	I^2=48% ; tau^2=0.08 ; p=0.13	I^2=17% ; tau^2=0 .02; p=0.27	I^2=0% ; tau^2=0 ; p=0.62
≥80-year-olds	N/A	N/A	N/A	N/A	N/A	N/A	I^2=77% ; tau^2=0.15 ; p=0.07	I^2=0% ; tau^2=0 ; p=0.76	I^2=39% ; tau^2=0.02 ; p=0.26	I^2=62% ; tau^2=0.07 ; p=0.01	I^2=0% ; tau^2=0 ; p=0.76	I^2=0% ; tau^2=0; p=0.92	I^2=0% ; tau^2=0 ; p=0.94

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

[†]Results are based on pooling VE estimates from Belgium, Denmark, Luxembourg, Navarre (Spain), Norway and Portugal, except absolute VE estimates (using the unvaccinated as a reference) which do not include Belgium, unless indicated in equivalent categories in Table 2.

[‡] Results up to June 1 to July 26, 2022 are limited to four sites: Denmark, Navarre (Spain), Norway and Portugal

Table S8. Measures of heterogeneity in the estimation 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 (corresponding to estimates in Table 3).

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				
65–79 year-olds	N/A	N/A	I^2=0% ; tau^2=0 ; p=1.00	I^2=16% ; tau^2=0.04 ; p=0.28	I^2=0% ; tau^2=0 ; p=0.42
≥80-year-olds	I^2=0% ; tau^2=0 ; p=1.00	I^2=0% ; tau^2=0 ; p=.041	I^2=51% ; tau^2=0.05 ; p=0.15	I^2=70% ; tau^2=0.19 ; p=0.01	I^2=0% ; tau^2=0 ; p=0.53
	rVE (95% CI) vs complete primary vaccination ≥169 days ago				
65–79 year-olds	N/A	N/A	I^2=0% ; tau^2=0 ; p=1.00	I^2=0% ; tau^2=0 ; p=0.59	I^2=0% ; tau^2=0 ; p=0.62
≥80-year-olds	I^2=0% ; tau^2=0 ; p=1.00	I^2=0% ; tau^2=0 ; p=0.79	I^2=26% ; tau^2=0.02 ; p=0.25	I^2=0% ; tau^2=0; p=0.78	I^2=47% ; tau^2=0.08 ; p=0.09
	rVE (95% CI) vs the first booster≥90 days ago				
65–79 year-olds	N/A	N/A	I^2=0% ; tau^2=0 ; p=1.00	I^2=0% ; tau^2=0 ; p=0.86	I^2=48% ; tau^2=0.09 ; p=0.24
≥80-year-olds	I^2=0% ; tau^2=0 ; p=1.00	I^2=91% ; tau^2=0.12; p<0.01	I^2=90% ; tau^2=0.14 ; p<0.01	I^2=54% ; tau^2=0.03 ; p=0.12	I^2=90% ; tau^2=0.28 ; p<0.01

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

[†] Results are based on pooling VE estimates from Belgium, Denmark, Luxembourg, Navarre (Spain), Norway and Portugal, except absolute VE estimates (using the unvaccinated as a reference) which do not include Belgium, unless indicated in equivalent categories in Table 3.

[‡] Results up to June 1 to July 26, 2022 are limited to four sites: Denmark, Navarre (Spain), Norway and Portugal

Table S9. Measures of heterogeneity in the estimation of vaccine effectiveness (VE) for primary vaccination (vs. unvaccinated) against COVID-19 death by age group, in overlapping eight-week wide observation intervals from March 2022 to November 2022, in five[†] EU/EEA countries (corresponding to estimates in Table S1).

Age group	VE (95% CI) vs.unvaccinated												
	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	September 1 to October 26, 2022	October 1, 2022 to November 25, 2022
65-79-year-olds	N/A	N/A	N/A	N/A	N/A	I^2=44% ; tau^2=0.06 ; p=0.20	I^2=58% ; tau^2=0.19 ; p=0.11	I^2=0% ; tau^2=0 ; p=0.93	I^2=0% ; tau^2=0 ; p=0.37	I^2=52% ; tau^2=0.22 ; p=0.14	I^2=80% ; tau^2=1.02; p=0.01	I^2=0% ; tau^2=0 ; p=1.00	I^2=0% ; tau^2=0 ; p=1.00
80+ year-olds	N/A	N/A	N/A	N/A	N/A	I^2=22% ; tau^2=0.01 ; p=0.28	I^2=85% ; tau^2=0.36 ; p<0.01	I^2=93% ; tau^2=1.52 ; p=0.02	I^2=66% ; tau^2=0.17 ; p=0.13	I^2=87% ; tau^2=0.52 ; p=0.01	I^2=0% ; tau^2=0 ; p=0.63	I^2=43% ; tau^2=0.09 ; p=0.15	I^2=72% ; tau^2=0.28 ; p=0.06

VE = Vaccine effectiveness; CI = confidence interval; N/A: Not applicable: In the first six months of the study VE estimates were not available for death outcome

[†] Results are based on pooling VE estimates from Denmark, Luxembourg, Navarre (Spain), Norway and Portugal. (Belgium did not provide estimates of VE against COVID-10 death), unless indicated in equivalent categories in Table S1.

[‡] Results up to June 1 to July 26, 2022 are limited to four sites: Denmark, Navarre (Spain), Norway and Portugal

Table S10. Measures of heterogeneity in the estimation of vaccine effectiveness (VE) and relative vaccine effectiveness (rVE) for the first booster dose against COVID-19 death by age group, in overlapping eight-week wide observation intervals from October 2021 to November 2022, in five[†] EU/EEA countries (corresponding to estimates in Table S2).

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	September 1 to October 26, 2022	October 1, 2022 to November 25, 2022
	VE (95% CI) vs unvaccinated												
65-79-year-olds	N/A	N/A	N/A	N/A	N/A	I^2=50% ; tau^2=0.05 ; p=0.15	I^2=0% ; tau^2=0 ; p=0.57	I^2=3% ; tau^2=0.01 ; p=0.35	I^2=0% ; tau^2=0 ; p=0.57	I^2=0% ; tau^2=0 ; p=0.53	I^2=23% ; tau^2=0.04 ; p=0.26	I^2=0% ; tau^2=0 ; p=0.57	I^2=0% ; tau^2=0 ; p=0.95
80+ year-olds	N/A	N/A	N/A	N/A	N/A	I^2=86% ; tau^2=0.19 ; p<0.01.	I^2=49% ; tau^2=0.05 ; p=0.11	I^2=19% ; tau^2=0.02 ; p=0.29	I^2=77% ; tau^2=0.17 ; p<0.01	I^2=45% ; tau^2=0.07 ; p=0.04	I^2=38% ; tau^2=0.04 ; p=0.17	I^2=0% ; tau^2=0 ; p=0.50	I^2=6% ; tau^2=0.01 ; p=0.34
	rVE (95% CI) vs complete primary vaccination ≥169 days ago												
65-79-year-olds	N/A	N/A	N/A	N/A	N/A	N/A	I^2=0% ; tau^2=0 ; p=0.55	I^2=0% ; tau^2=0 ; p=0.40	I^2=65% ; tau^2=0.24 ; p=0.05	I^2=86% ; tau^2=0.62 ; p<0.01	I^2=91% ; tau^2=1.51 ; p<0.02	I^2=0% ; tau^2=0; p=0.41	I^2=0% ; tau^2=0 ; p=0.59
80+ year-olds	N/A	N/A	N/A	N/A	N/A	N/A	I^2=29% ; tau^2=0.03 ; p=0.18	I^2=74% ; tau^2=0.27 ; p=0.02	I^2=58% ; tau^2=0.08 ; p=0.02	I^2=62% ; tau^2=0.13 ; p=0.01	I^2=37% ; tau^2=0.07 ; p=0.19	I^2=0% ; tau^2=0; p=0.43	I^2=0% ; tau^2=0 ; p=0.81

VE = Vaccine effectiveness; CI = Confidence interval; N/A: Not applicable: In the first six months of the study VE and rVE estimates were not available for death outcome

[†]Results are based on pooling VE estimates from Denmark, Luxembourg, Navarre (Spain), Norway and Portugal (Belgium did not provide estimates of VE against COVID-10 death), unless indicated in equivalent categories in Table S2.

[‡] Results up to June 1 to July 26, 2022 are limited to four sites: Denmark, Navarre (Spain), Norway and Portugal

Table S11. Measures of heterogeneity in the estimation of vaccine effectiveness (VE) and relative vaccine effectiveness (rVE) for the second booster dose against COVID-19 death 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 five† EU/EEA countries (corresponding to estimates in Table S3).

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				
65-79-year-olds	N/A	N/A	§	§	I^2=0% ; tau^2=0 ; p=1.00
80+ year-olds	I^2=0% ; tau^2=0 ; p=1.00	I^2=85% ; tau^2=0.34 ; p=0.01	I^2=93% ; tau^2=0.89 ; p<0.01	I^2=92% ; tau^2=1.27 ; p<0.01	I^2=0% ; tau^2=0 ; p=0.92
	rVE (95% CI) vs complete primary vaccination ≥169 days ago				
65-79-year-olds	N/A	N/A	§	§	I^2=0% ; tau^2=0 ; p=1.00
80+ year-olds	I^2=0% ; tau^2=0 ; p=1.00	I^2=0% ; tau^2=0 ; p=0.34	I^2=88% ; tau^2=0.63; p<0.01	I^2=95% ; tau^2=2.24 ; p<0.01	I^2=72% ; tau^2=0.27 ; p=0.06
	rVE (95% CI) vs the first booster ≥90 days ago				
65-79-year-olds	N/A	N/A	§	§	I^2=0% ; tau^2=0 ; p=1.00
80+ year-olds	I^2=0% ; tau^2=0 ; p=1.00	I^2=0% ; tau^2=0 ; p=0.93	I^2=82% ; tau^2=0.19 ; p=0.02	I^2=94% ; tau^2=1.21 ; p<0.01	I^2=75% ; tau^2=0.11 ; p=0.05

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

† Results are based on pooling VE estimates from Denmark, Luxembourg, Navarre (Spain), Norway and Portugal (Belgium did not provide estimates of VE against COVID-10 death), unless indicated in equivalent categories in Table S3.

‡ Results up to June 1 to July 26, 2022 are limited to four sites: Denmark, Navarre (Spain), Norway and Portugal.

§ Not Possible to estimate due to low number of events (less than 15 events)