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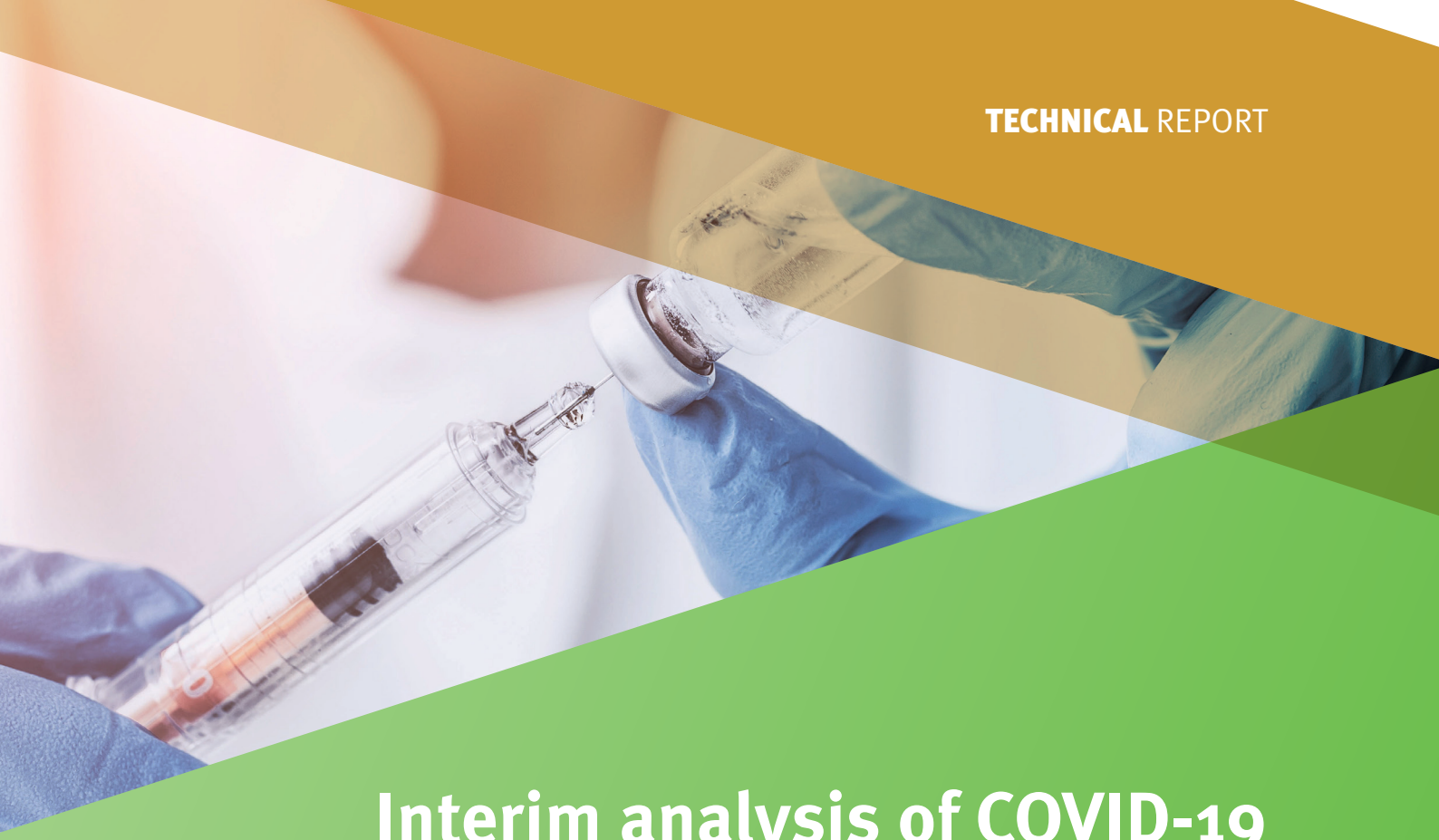
TECHNICAL REPORT



Interim analysis of COVID-19 vaccine effectiveness against hospitalisation and death using electronic health records in six European countries

April 2022 to March 2023

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ECDC TECHNICAL REPORT

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Abbreviations

EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
EHR	Electronic Health Records
EU	European Union
VE	Vaccine Effectiveness
VMP	Vaccine monitoring platform
rVE	Relative Vaccine Effectiveness
VEBIS	Vaccine Effectiveness Burden and Impact Studies

Executive summary

This report presents pooled COVID-19 vaccine effectiveness (VE) estimates for the first, second and third booster doses, against hospitalisation due to COVID-19 and COVID-19 related deaths in resident populations ≥50 years of age, living in the community, in six European countries: Belgium, Denmark, Luxembourg, Navarre (Spain), Norway, and Portugal. This study was undertaken within the Vaccine Effectiveness Burden and Impact Studies (VEBIS) project.

A retrospective cohort was constructed from linked electronic health records (EHR) in each country. Country-specific (level) relative VE (rVE) was estimated on a monthly basis, using a study period covering an eight-week follow-up period. Each month the study period was shifted forward to the following month. Country estimates were then pooled together. The study period covered in this report is April 2022 to March 2023. The rVE of first, second and third booster doses was estimated and compared to the VE of complete primary vaccination received at least 24 weeks ago (≥24 weeks).

Between April 2022 and March 2023, the number of individuals included in the analysis in each study period varied between 0.5 million and 1.3 million individuals with complete primary vaccination series ≥24 weeks ago but without a booster, between 3.1 million and 13.2 million individuals completely vaccinated with a first booster, between no individuals and 6.8 million individuals completely vaccinated with a second booster and between no individuals and 0.7 million completely vaccinated with a third booster. About 31 900 hospitalisations due to COVID-19 and 13 100 COVID-19-related deaths were recorded across the different sites throughout the study period.

The highest number of person-months contributing to the analysis was observed for Belgium and Portugal, followed by Norway, Denmark, Navarre (Spain), and Luxembourg. In persons aged ≥80 years, Belgium and Portugal rolled out the second booster dose over spring 2022 and the third booster dose in autumn 2022, while the administration of a second booster began in autumn 2022 in the remaining participating countries.

At the beginning of the study period, most of the study population had received a first booster dose, while the proportion of individuals completely vaccinated with primary doses without a booster was very low, especially in ≥65 years (Figure 2). A second booster dose was administrated initially in persons aged ≥80 years from July 2022 onwards in most participating countries except for Belgium and Portugal, where it started earlier in spring 2022 in those aged ≥80 followed by 50–79year olds in autumn 2022. In these two countries, the third booster dose was then deployed in ≥80-year-olds in October–November 2022.

Compared to complete primary vaccination, the **first booster** dose rVE against hospitalisation due to COVID-19 was mostly ≤50% between April 2022 and March 2023 in all age groups (with a few point estimates >50%). It waned 12 weeks after administration and dropped even lower after 24 weeks. In the most recent estimate, between February and March 2023, the first booster (mostly administered >24 weeks) showed little to no added protection: rVE estimates ranged between -13–17%, among the different age groups. VE estimates against COVID-19-related mortality were similar, although estimates had high uncertainty due to a low number of events, particularly in the groups <65 years.

Compared to complete primary vaccination, rVE of a **second booster** restored protection shortly after administration in the autumn of 2022 in ≥65-year-olds, to 76–79% against hospitalisation due to COVID-19 and to 76–85% against COVID-19 related death. Relative vaccine effectiveness also waned with time, falling to ≤50% after 24 weeks. In the most recent estimate, between February and March 2023, rVE of the second booster ranged between 33–49% against hospitalisation and 50–63% against mortality 12–24 weeks after administration and between 3.5–43% against hospitalisation and 50% against mortality (estimated only in ≥80 year olds) after 24 weeks.

Compared to complete primary vaccination, rVE of the **third booster** could only be estimated in individuals aged ≥80 years in Portugal and Belgium. Relative vaccine effectiveness against hospitalisation due to COVID-19 was 72% shortly after administration but waned rapidly, being zero beyond 12 weeks of administration. The lower rVE could possibly be related to the higher proportion of individuals with comorbidities among those with a third booster (being a population that had previously accepted a second booster in the spring of 2022). Relative vaccine effectiveness against mortality was 64% initially (<12 weeks after administration) and waned rapidly thereafter (<50% 12–24 weeks after administration with large confidence intervals). In February–March 2023, the rVE of a third booster 12–24 weeks after administration was 3% (95% CI: -26 709; 100).

Overall, results indicated that booster doses restored protection shortly after administration, but it waned in the period up to 24 weeks after administration.

During the autumn of 2022, the effectiveness of third booster doses (in Portugal and Belgium where second boosters had been administered over spring 2022) and second booster doses (in those remaining participating countries) were similar. This result suggests that the time since the last dose was more important than the total number of doses administered in the level of protection against both COVID-19 hospitalisation and death.

Scope of this document

This document reports the results of a 12-month prospective monitoring of COVID-19 VE using a multi-country approach based on established Electronic Health Record (EHR) databases in each country.

From October 2021 to March 2023, the project went through a proof-of-concept applied to EHR in four countries and then different pilot phases in up to six countries. Different outcomes and age groups were included over time (Table 1). The evolution of the COVID-19 pandemic, and changes in testing policies and vaccine recommendations required successive adaptations of the study protocol. Detailed objectives and methods can be found in the published master protocol [1].

This report contains VE estimates among individuals aged 50 years and older against hospitalisation due to COVID-19 and COVID-19-related death. Relative VE of booster doses is estimated using the individuals with complete primary vaccination ≥24 weeks ago without a booster as a reference. Since the rVE estimates presented in this report measure the additional protective effect of a vaccine dose, estimates are often lower than those of absolute VE reported elsewhere in the literature. VE estimates were calculated overall and by time since the last dose. The study period runs between April 2022 to March 2023.

Table 1. Successive steps in the implementation of the study

Project stage	Study period	Study Sites	Study outcome	Age groups	Reference
Proof of concept	Oct 21 – Mar 22	Denmark, Navarre (Spain), Norway, Portugal	Absolute and relative VE against hospitalisation, overall and by time since the booster	≥80 65–79	Pilot protocol (2)
Full pilot	Mar 22 – Apr 22	Denmark, Navarre (Spain), Norway, Portugal	Absolute and relative VE against SARS-CoV-2 infection, hospitalisation, ICU admission and mortality, overall and by time since the booster	≥80 65–79 50–64 18–49 5–17	Pilot protocol (2)
Prospective monitoring pilot I	Apr 22 – Jul 22	Denmark, Navarre (Spain), Norway, Portugal	Absolute, relative and additional VE against hospitalisation and mortality, overall and by time since the booster	≥80 65–79 50–64 18–49 5–17	Master protocol (1)
Prospective monitoring pilot II	Jul 22 – Nov 22	Belgium, Denmark, Luxembourg, Navarre (Spain), Norway, Portugal	Absolute, relative and additional VE against hospitalisation and mortality, overall and by time since the booster	≥80 65–79 50–64 18–49 5–17	Master protocol (1)
Prospective monitoring	Nov 22 – Mar 23	Belgium, Denmark, Luxembourg, Navarre (Spain), Norway, Portugal	Relative and additional VE against hospitalisation and mortality, overall and by time since the booster	≥80 65–79 50–64	Master protocol (1)

Background

In late 2019, a novel severe acute respiratory syndrome virus (SARS-CoV-2), causing COVID-19 disease, emerged. Since 31 December 2019 and as of 14 June 2023, 276 489 556 cases of COVID-19 (in accordance with the applied case definitions and testing strategies in the affected countries) have been reported in the World Health Organization (WHO) Europe Region, including 2 955 770 deaths [3].

As of July 2023, eight vaccine products were granted market authorisation in the EU/EEA by the European Medicines Agency (EMA). Seven vaccines are spike protein based: Comirnaty (BNT162b2), Spikevax (mRNA-1273), Vaxzevria (AZD1222), Jcovden (Ad26.COV 2.5,), Nuvaxovid (NVX-CoV2373), VidPrevtyn Beta (J07BX03) and Bimervax (J07BN); one, Valneva (VLA2001), is a non-spike protein-based vaccine (inactivated, adjuvanted). In addition, four adapted mRNA vaccines targeting Omicron subvariants were authorised (Comirnaty bivalent Original/Omicron BA.1, Comirnaty bivalent Original/Omicron BA.4-5, Spikevax bivalent Original/Omicron BA.1, Spikevax bivalent Original/Omicron BA.4-5). Administration of adapted vaccines started in September 2022 onwards as a second and/or third booster vaccination [4, 5].

ECDC is leading activities and studies in the scope of vaccine effectiveness (VE) as part of its now extended mandate on monitoring vaccines and vaccination programmes in the post-authorisation phase [6, 7]. Some of these activities are being implemented as part of the Vaccine Monitoring Platform, a joint initiative of ECDC and EMA for strengthening the continuous monitoring of the safety and effectiveness of vaccines. The VEBIS project is being funded as part of the activities undertaken in the vaccine monitoring platform (VMP). It encompasses various effectiveness studies implemented in different settings and populations and uses different data sources: VE of COVID-19 and influenza vaccine against severe acute respiratory diseases in hospital settings, VE of COVID-19 and influenza vaccine against mild diseases in primary care settings, VE of COVID-19 in healthcare workers (cohort study).

The current study aimed to monitor VE of COVID-19 vaccines using routinely collected vaccination status and outcome data from established electronic health records (EHR) databases (current report). Using a common protocol [1], participating countries provide estimates of VE monthly, which are then pooled together using random-effects meta-analysis techniques. A proof of concept and a preliminary pilot study were carried out between October 2021 and April 2022, with the participation of Denmark, Navarre (Spain), Norway and Portugal. Between April and November 2022, a prospective monitoring pilot was implemented by the same four study sites with a later addition of Belgium and Luxembourg (since July 2022) [2]. Since November 2022 a prospective monitoring has been ongoing in the six study sites [1, 8, 9]. In this report, VE estimates still under monitoring in this reduced scope are presented. Specifically, these include estimates of VE of booster doses (relative VE compared to individuals who have not received any booster dose) against hospitalisation due to COVID-19 or COVID-19-related death in community-dwelling population 50 years of age or older.

Overall aim

The overall aim was to monitor real-time performance of COVID-19 vaccines in the resident populations living in the community in the European Union/European Economic Area (EU/EEA) in order to inform COVID-19 vaccine recommendations.

Objectives

Principal objective

To measure VE of booster doses of COVID-19 vaccine, in resident populations living in the community aged ≥50 years in EU/EEA countries, against the following outcomes:

- Hospital admission due to COVID-19
- Death related to COVID-19.

The relative VE (rVE) of first, second or third booster was estimated compared to individuals with COVID-19 primary vaccination administered ≥ 24 weeks ago without a subsequent booster.

Secondary objective

To measure COVID-19 VE by time since the first, second or third booster defined as the number of weeks between time of analysis and the date of the last booster dose administered.

Methodology

Study design

This was a retrospective cohort study using data collected routinely in EHR databases. A comparison of the risk of the severe outcomes (hospitalisation due to COVID-19 and COVID-19 related death), was done between individuals with different vaccination status.

Study setting

The study was carried out in six EU/EEA countries: Belgium, Denmark, Luxembourg, Spain (Navarre), Norway, Portugal, representing close to 14 million people ≥50 years. COVID-19 epidemiology and rollout of COVID-19 vaccines have been heterogeneous across the six countries (Table 2).

Figure 1. Countries participating in VEBIS multi-country study on EHR

Table 2. Uptake (%) of full vaccination with the primary series of COVID-19 vaccine*, first and second booster dose in participating EU/EEA countries, as of week 23 2023

Country	50–59 years	≥60 years	≥80 years
Belgium	91.5/82.1/47.4	98.2/92.6/71.0	100.0/93.5/73.3
Denmark	94.0/87.5/58.9	100.0/98.0/86.9	100.0/100.0/98.8
Luxembourg	84.8/75.4/7.3	91.2/85.4/49.5	99.3/91.5/63.5
Norway	94.3/81.7/NA**	97.5/70.6/60.9	96.1/92.8/75.1
Portugal	94.8/89.0/43.9	99.0/98.8/75.4	97.2/98.9/87.7
Spain	88.4/77.0/13.4	96.7/92.9/61.5	100.0/92.9/82.7
Median EU/EEA	**83.9/73.3/7.0**	**91.2/84.9/35.6**	**89.9/83.8/46.7**

*Source: ECDC Vaccine Tracker [8] * Full vaccination with the primary series of COVID-19 vaccine is defined according to the manufacturer's instructions for each vaccine product. ** Second booster not recommended in this age group as of week 23 2023.*

Data sources

Routinely collected data in various population health registries at national or regional level were used. Table 3 gives an overview of the data sources used in each six study sites for the identification of outcome variables and vaccination status. The full list of data sources used in the study is provided in Appendix 1.

Table 3. Information systems based on electronic health records of each participant site

Study variable	Study site					
	Portugal	Navarre (Spain)	Norway	Denmark	Luxembourg	Belgium
Hospital admission due to COVID-19	National Hospital Discharge database (BIMH)	Enhanced COVID-19 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
COVID-19 related death	National Death Registry (SICO) and National Health Service User database (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)	MSINF + death certificate for death happened outside hospital or nursing home	Not available
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)

Study period

VE estimates were produced prospectively each month between July 2022 and May 2023. Study periods covered an eight-week follow-up time to allow sufficient numbers of events for estimations, as well as to be sensitive and reactive to changes in VE over time. Each month, the eight-week follow-up time is shifted forward by one month. A minimum of one month between the end of study period and data extraction was applied for data consolidation. The study observation period presented in this report runs from April 2022 to March 2023.

Study population

The study population included individuals in the national vaccination plan and/or the reference population registries fulfilling the following criteria during each eight–week study period:

- Resident in any of the participating EU/EEA country at the beginning of each study period.
- Aged between 50 and 110 years at the beginning of each study period.
- Not living in nursing homes (if available, and according to last update of data).
- First vaccine dose received at a time when it was recommended for the corresponding age group (i.e. excluding individuals vaccinated before the start of the recommended period was in place for a target age-group or, alternatively, for those countries with no clearly defined recommended start date by age, the first 5% of persons vaccinated within each age-group –for each five-year age category- as these first vaccinees may not be representative of their corresponding age group).
- Completed primary COVID-19 vaccination series ≥24 weeks ago.
- Do not have inconsistent or missing data on vaccination (vaccination status unknown, any vaccination date is unknown, any vaccine brand is unknown, number of doses is unknown, interval between first and second dose is shorter than 19 days, interval between complete vaccination and booster dose or between booster doses is shorter than 90 days, number of doses higher than recommended, receive any vaccine brand not approved by EMA, and the combination of vaccine brands is not a recommended schedule by national public health authorities may vary by age group).

Definitions

Vaccination status

The following definitions were applied:

- Complete COVID-19 vaccination with primary series: individuals who received the primary series of COVID-19 vaccine doses defined as one dose of Ad26.COV2.S (Jcovden) vaccine or two doses of ChAdOx1-S (Oxford/Astra Zeneca), BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna), or a combination of any of the three vaccines. The two doses should be administered ≥19 days apart. Individuals become eligible for the study ≥24 weeks after complete COVID-19 vaccination with primary series.
- Complete COVID-19 vaccination with first booster dose: individuals who received an additional dose of an EMA approved vaccine at least three months (90 days) after completion of primary series (as defined above). This status is achieved 14 days after the date of administration of the booster dose (induction period).

- Complete COVID-19 vaccination with second booster dose: individuals who received an additional dose of an EMA approved vaccine at least three months (90 days) after the first booster dose (as defined above). This status is achieved 14 days after the date of administration of the booster dose (induction period).
- Complete COVID-19 vaccination with third booster dose: individuals who received an additional dose of an EMA approved vaccine at least three months (90 days) after the second booster dose (as defined above). This status is achieved 14 days after the date of administration of the booster dose (induction period).

Individuals who received a booster dose <14 days ago were analysed separately (i.e. not merged with the previous nor the subsequent vaccination status) and VE was not estimated for this group.

Time since booster dose vaccination

Assessment of time since vaccination started at the end of the induction period, i.e. day 14 after the date of administration of the last dose (time 0).

Time since vaccination was classified into three categories as follows:

- <12 weeks (Time 0 up to ≤84 days after time 0),
- ≥12 weeks and <24 weeks (85 – 168 days, after time 0),
- ≥24 weeks (≥169 days, after time 0).

Time since vaccination was calculated at each point in time by constructing a time-dependent variable.

Reference groups for VE estimation

The rVE of each first, second and third booster dose (overall and by time since vaccination) was estimated compared to receiving complete primary vaccination administered at least 24 weeks ago and without a booster.

Outcomes

Outcomes of interest are defined as:

Hospital admission due to COVID-19:

- Admission to hospital in which COVID-19 is the main diagnosis in the admission or discharge record (for example, based on International Classification of Diseases (ICD) coding or similar);

OR,

- Admission to hospital in which admission criteria are compatible with SARI (based on similar criteria as in SARI surveillance, ICD coding or similar) AND with a laboratory-confirmed SARS-CoV-2 infection ≤14 days before admission or up to 24 hours after admission.

COVID-19 related death:

- death for which COVID-19 is recorded as the cause of death;

OR, if cause of death not available,

- laboratory-confirmed SARS-CoV-2 infection with death within30 days after a positive test.

For each outcome, the censoring date of the outcome occurrence (date of the event of interest) was the earliest among the date of hospital admission or death, and the date of the laboratory diagnosis (i.e. the date of the first diagnosis of the infection episode that resulted in hospital admission or death).

Confounder

Basic models were adjusted according to age (in five-year categories) and sex, and when appropriate, to geographical division within each country. Additionally, estimates were adjusted by previous SARS-CoV-2 infection, socioeconomic variables, comorbidities and/or other covariates when available and as appropriate for each study site. Since many of the variables are pre-coded in the established database, the definition for variables and categories was heterogeneous across study sites (Appendix 2).

Previous SARS-CoV-2 infection

Previous infection was classified at the beginning of each study period into two categories:

- No previous infection: no positive SARS-CoV-2 test recorded prior to the first day of the study period.
- Previous infection: at least one positive SARS-CoV-2 test recorded prior to the first day of the study period.

Demographic and socioeconomic situation

- Age group, calculated at the beginning of each study based on date of birth. Age was categorised into five-year categories to adjust models. Alternatively, some study sites classified age based on year of birth (age at the end of the current year). For reporting stratified results by age-group, the following groups were used: 50–64, 65–79 and ≥80 years.
- Sex.
- Socioeconomic status: Income, crowded conditions or others as available in EHR.
- Area level socioeconomic condition (postal code, municipality or other): income per capita, inequality or deprivation index (10) or similar, as available in EHR.

Comorbidities and health-seeking behaviour

Different variables can be used to document comorbidities. It was recommended to include comorbidities as a three-level variable across participating sites:

- No comorbidities related to increased risk of severe outcomes of COVID-19.
- Medium risk comorbidities (for example, comorbidities that are associated to risk of COVID-19 but different from immunocompromising conditions, or other classification decided at site level).
- High risk comorbidities (for example, immunocompromising conditions, or other classification decided at site level).

Data analysis

Vaccination status was a time-changing variable defined at the beginning of the eight-week study period. Individuals for which vaccination status changed during the follow-up period were censored without an event reported in the vaccination status group they left, and were recorded as a delayed entry into the new vaccination status group, on the date their vaccination status changed.

Individuals were then followed up until the earliest date of:

- Event of interest, with date of outcome as previously defined;
- Death from any cause (on the date of death);
- Discontinuation in the administrative database (i.e. emigration);
- Administrative censoring (eight weeks after the start of the observation period).

Cox regression with calendar time as the underlying time scale was used to estimate hazard ratios (HRs) of defined outcomes among the group with the vaccine status of interest compared to the reference vaccination status group. Vaccine effectiveness was defined as VE = (1-HR) x 100. To estimate the rVE of booster doses compared to primary vaccination we used complete primary vaccination series ≥24 weeks ago without a subsequent booster as the reference group.

Cox regression models were adjusted by age, sex geographical region (if applicable to the study site), previous infection, comorbidities, socioeconomic variables or others as available and relevant at each study site (Appendix 2).

Methods for pooling estimates

Country-specific HRs and standard errors from each study site were combined in a model using meta-analysis techniques. Study sites did not report VE estimates for which the number of events in any of the categories being compared was less than five and those were not included in the pooled estimates [11]. Additionally, estimates based on less than 15 events after pooling together all participating sites were not reported. A random-effect approach using the Paule-Mantel method was used. This acknowledges the possibility that VE is different across different countries, depending on measured or unmeasured site-specific factors.

Ethical requirements

All sites conformed with national and EU ethical and data protection requirements.

Results

Population characteristics and number events

Between April 2022 and March 2023, the number of vaccinated individuals included in the analysis across each study period varied widely:

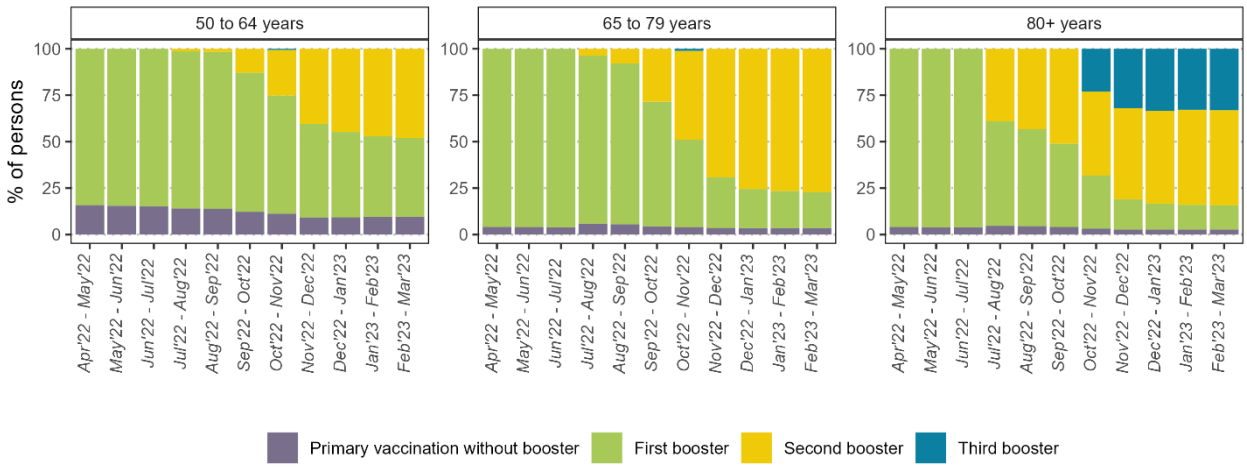
- between 0.5 to1.3 million individuals with complete primary vaccination series ≥24 weeks ago without booster;
- between 3.1 to 13.2 million individuals completely vaccinated with a first booster;
- between no individual vaccinated to 6.8 million individuals completely vaccinated with a second booster;
- between no individual vaccinated and 700 000 completely vaccinated with a third booster.

About 31 900 hospitalisations due to COVID-19 and 13 100 COVID-19-related deaths were recorded across the different sites throughout the study period.

At the beginning of the study period, most of the study population had received a first booster dose, while the proportion of individuals completely vaccinated with primary doses without a booster was very low, especially in ≥65 year olds (Figure 2). A second booster was administrated initially in ≥80 year olds from July 2022 onwards in most participating countries with the exception of Belgium and Portugal, where it started earlier in spring 2022 in those aged ≥80 year olds followed by 50-79 year olds in autumn 2022. In these two countries, the third booster dose was then deployed in ≥80 year olds in October-November 2022.

The specific number of individuals (e.g. person-months contributed to the study) and number of hospitalisation events per study period, age group and vaccination status are provided in Tables 4, 5 and 6. The corresponding figures for the mortality outcome are provided in Appendix 3.

Figure 2. Vaccination status of study participants by number of booster doses received for each eight-week study period and by age-group, April 2022 to March 2023



The highest ratio of person-months contributing to the analysis was observed for Belgium and Portugal, followed by Norway, Denmark, Spain (Navarre), and Luxembourg. Because the timing of booster vaccination rollout differed across participating countries, the relative contribution of each study site differed by vaccination status (Figure 3). For example, third booster VE estimates were mainly driven by data from Belgium and Portugal.

Table 4. Number of individuals, number of hospitalisations due to COVID-19, and events per person-months across each eight-week period in ≥80 years, April 2022-March 2023

Study period	Persons aged ≥80 year olds							
	Primary vaccination ≥24 weeks ago without booster		Primary vaccination + booster 1		Primary vaccination + booster 2		Primary vaccination + booster 3	
	No.	Events/ person-month	No.	Events/ person-month	No.	Events/ person-month	No.	Events/ person-month
Apr–May 2022	58 016	177/ 95 455	1 016 780	1,762/ 1 843 384	0	<5/0	0	<5/0
May–Jun 2022	65 186	198/ 102 147	1 030 897	1,618/ 1 634 301	0	<5/0	0	<5/0
Jun–Jul 2022	63 274	167/ 100 502	882 438	1,578/ 1 275 533	341 905	123/ 425 531	0	<5/0
Jul–Aug 2022	90 479	117/ 82 641	1 173 513	2,052/ 2 018 185	866 535	584/ 1 408 781	0	<5/0
Aug–Sep 2022	89 173	98/ 158 606	1 091 489	1,178/ 1 847 555	1 252 549	454/ 1 532 594	0	<5/0
Sep–Oct 2022	86 627	89/ 145 605	983 180	833/ 1 353 738	1 542 721	478/ 1 467 698	0	<5/0
Oct–Nov 2022	76 420	93/ 132 085	718 850	522/ 852 138	1 176 467	446/ 1 510 236	607 488	168/ 862 762
Nov–Dec 2022	60 408	147/ 105 978	330 917	585/ 493 521	846 908	911/ 1 437 920	504 466	267/ 884 241
Dec–Jan 2023	58 147	114/ 104 340	259 868	457/ 450 896	832 499	990/ 1 499 730	508 961	278/ 925 416
Jan–Feb 2023	60 093	56/ 109 238	263 426	217/ 476 343	910 981	596/ 1 670 051	530 307	323/ 976 056
Feb–Mar 2023	59 564	52/ 108 072	248 399	240/ 454 009	897 335	762/ 1 650 613	527 463	486/ 969 172

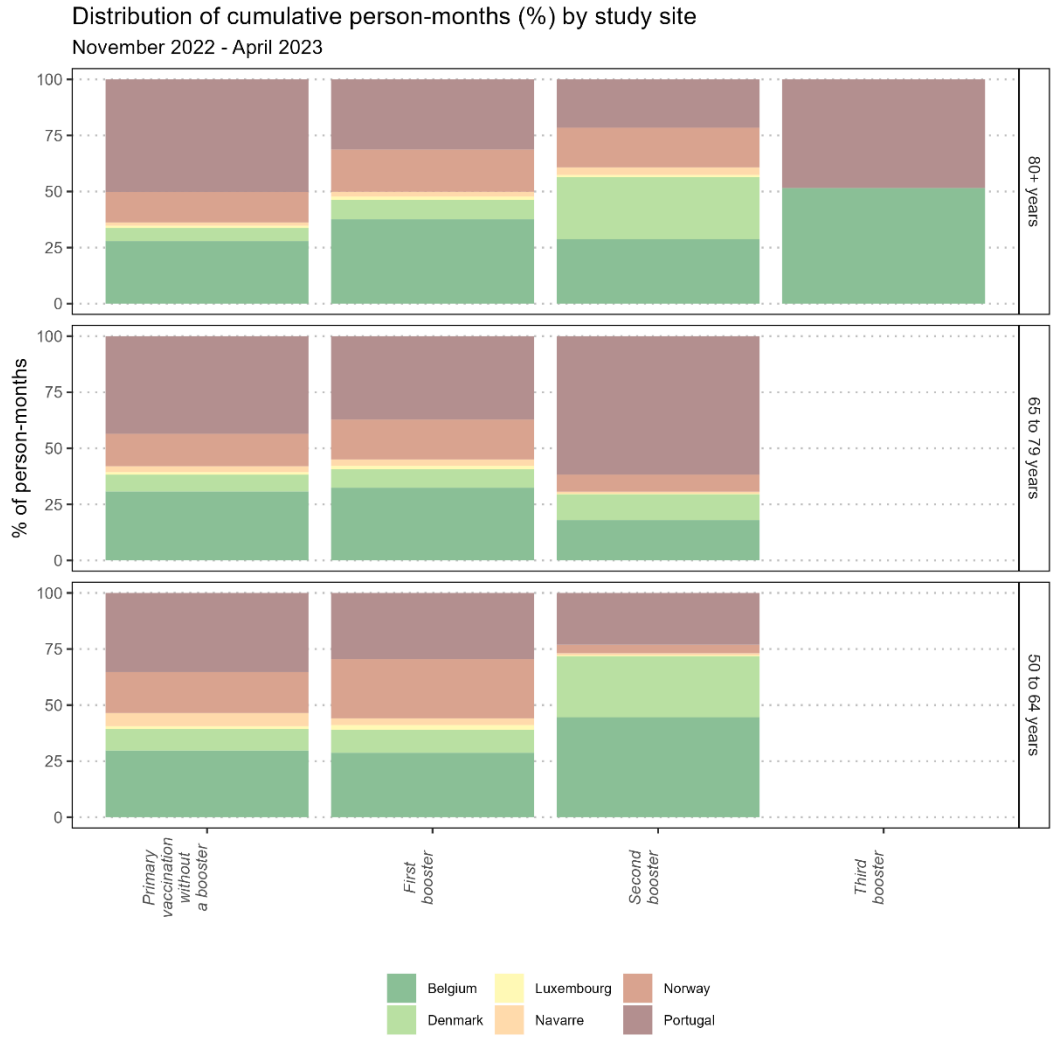
Table 5. Number of Individuals, number of hospitalisations due to COVID-19, and person-months across each eight-week period in 65–79 years, April 2022–March 2023

Study period	Persons aged 65–79 year olds					
	Primary vaccination ≥24 weeks ago without booster		Primary vaccination + booster 1		Primary vaccination + booster 2	
	N	Events/ person-month	N	Events/ person-month	N	Events/ person-month
Apr–May 2022	141 891	115/ 230 175	2 723 031	920/ 4 971 604	0	<5/0
May–Jun 2022	179 002	110/ 269 620	2 739 833	511/ 3 074 645	0	<5/0
Jun–Jul 2022	195 234	99/ 309 256	2 698 656	1 282/ 4 935 561	0	<5/0
Jul–Aug 2022	294 656	153/ 522 712	5 028 270	1 938/ 8 989 085	0	<5/0
Aug–Sep 2022	295 807	102/ 538 691	4 897 957	1 153/ 8 806 671	260 009	68/ 195 897
Sep–Oct 2022	294 073	73/ 510 312	4 701 721	919/ 6 742 351	414 516	71/ 528 062
Oct–Nov 2022	281 165	75/ 460 744	3 323 770	524/ 3 752 228	2 865 278	160/ 3 924 057
Nov–Dec 2022	211 960	142/ 354 711	1 489 407	521/ 2 037 743	3 317 916	748/ 5 609 722
Dec–Jan 2023	190 244	115/ 34 179	1 045 045	387/ 1 786 302	3 362 813	811/ 6 109 960
Jan–Feb 2023	197 128	50/ 36 061	990 443	189/ 1 781 990	3 439 983	493/ 6 325 978
Feb–Mar 2023	194 015	48/ 355 949	964 223	253/ 1 761 952	3 443 720	636/ 6 358 22

Table 6. Number of individuals, number of hospitalisations due to COVID-19 (events), and person-months in 50–64 years across each eight-week study period, April 2022–March 2023

Study period	Persons aged 50–64 year olds					
	Primary vaccination ≥24 weeks ago without booster		Primary vaccination + booster 1		Primary vaccination + booster 2	
	N	Events/ person-month	N	Events/ person-month	N	Events/ person-month
Apr–May 2022	349 395	23/602 279	2 193 694	153/4 007 754	0	<5/0
May–Jun 2022	368 291	25/626 713	2 201 324	96/4 032 618	0	<5/0
Jun–Jul 2022	384 505	35/651 450	2 207 773	246/4 038 609	0	<5/0
Jul–Aug 2022	974 768	74/1 711 719	7 072 855	480/11 352 815	0	<5/0
Aug–Sep 2022	970 151	54/1 774 164	6 156 025	312/11 180 657	0	<5/0
Sep–Oct 2022	966 106	42/1 753 990	6 159 876	276/10 516 016	0	<5/0
Oct–Nov 2022	961 917	30/1 739 865	5 563 895	189/8 485 806	2 130 793	26/2 418 882
Nov–Dec 2022	689 169	65/1 205 770	3 293 661	207/5 226 832	2 463 925	137/3 662 514
Dec–Jan 2023	657 907	53/1 161 671	2 835 375	162/4 675 556	2 595 090	133/4 459 024
Jan–Feb 2023	651 632	23/1 194 907	1 874 009	57/3 407 131	2 421 488	59/4 173 960
Feb–Mar 2023	640 070	26/1 176 840	2 446 789	96/4 490 304	2 538 848	106/4 688 738

Figure 3. Distribution of cumulative person-months (%) for each study site by age-group and by number of booster doses administrated, November 2022*–March 2023



**Information collected for all participating study sites from November 2022 onward.*

A description of the characteristics of the study population was only available from November 2022 onwards, which was the month where these descriptive data had to be reported by all participating countries. The proportion of females was higher among those ≥80 years regardless of vaccination status. Apart from those aged 50–64-years, the proportion of vaccinated males in the study population tends to increase with the number of doses administered. As the number of vaccine doses increased so did the share of individuals with medium and, especially, high-risk comorbidities, in accordance with the preferential vaccination of these groups (Appendix 4).

A series of figures in Appendix 4 show the cumulative proportion of person-months throughout the study period by vaccine products. Pfizer vaccine products were the most administered for primary vaccination doses, followed by AstraZeneca and Moderna. First booster doses were more frequently of Monovalent (Wuhan strain-based) Pfizer and Moderna vaccines, although there is a small proportion of bivalent Pfizer vaccines (both BA.1 and BA.4/5) in those with final vaccination status of first booster, showing late first booster administrations in the autumn of 2022. Various products were administered as a second booster dose including monovalent (spring 2022) and bivalent (Omicron-adapted) product (autumn 2022). Interestingly, for those contributing to the study within the third booster group (final vaccination status at the time of the study), all had been vaccinated with a monovalent vaccine as a second booster, which is consistent with second booster vaccination in the spring of 2022, before bivalent vaccines became available, and third booster vaccination in the autumn of 2022. For the group contributing to the study as second booster group, there is a mix of monovalent and bivalent products, showing the mix of individuals vaccinated in the spring and autumn campaigns, before and after the bivalent vaccines became available, respectively. Finally, third booster doses were almost exclusively bivalent vaccines, more frequently BA.1 than BA.4/5, and mostly from Pfizer.

Relative vaccine effectiveness of first, second and third booster against hospitalisation due to COVID-19

First booster

Between April 2022 to March 2023, the rVE of the first booster fluctuated around and below 50% in all age groups (Tables 7–9; Figure 4, green symbols) with the level of protection waning over time (Figure 5). The rVE of a first booster within the first 12 weeks after administration was >50%. It then dropped ≥12 weeks after its administration, and even more at ≥24 weeks. Between February–March 2023, a first booster showed little to no added protection at least 24 weeks after its administration compared to primary vaccination only, with rVE reaching 10% (95% CI: -33; 40) in ≥80 year olds, -13% (95% CI: -58; 19) in 65–79 year olds, and 17% (95% CI: -32; 49) in 50–64 year olds.

Second booster

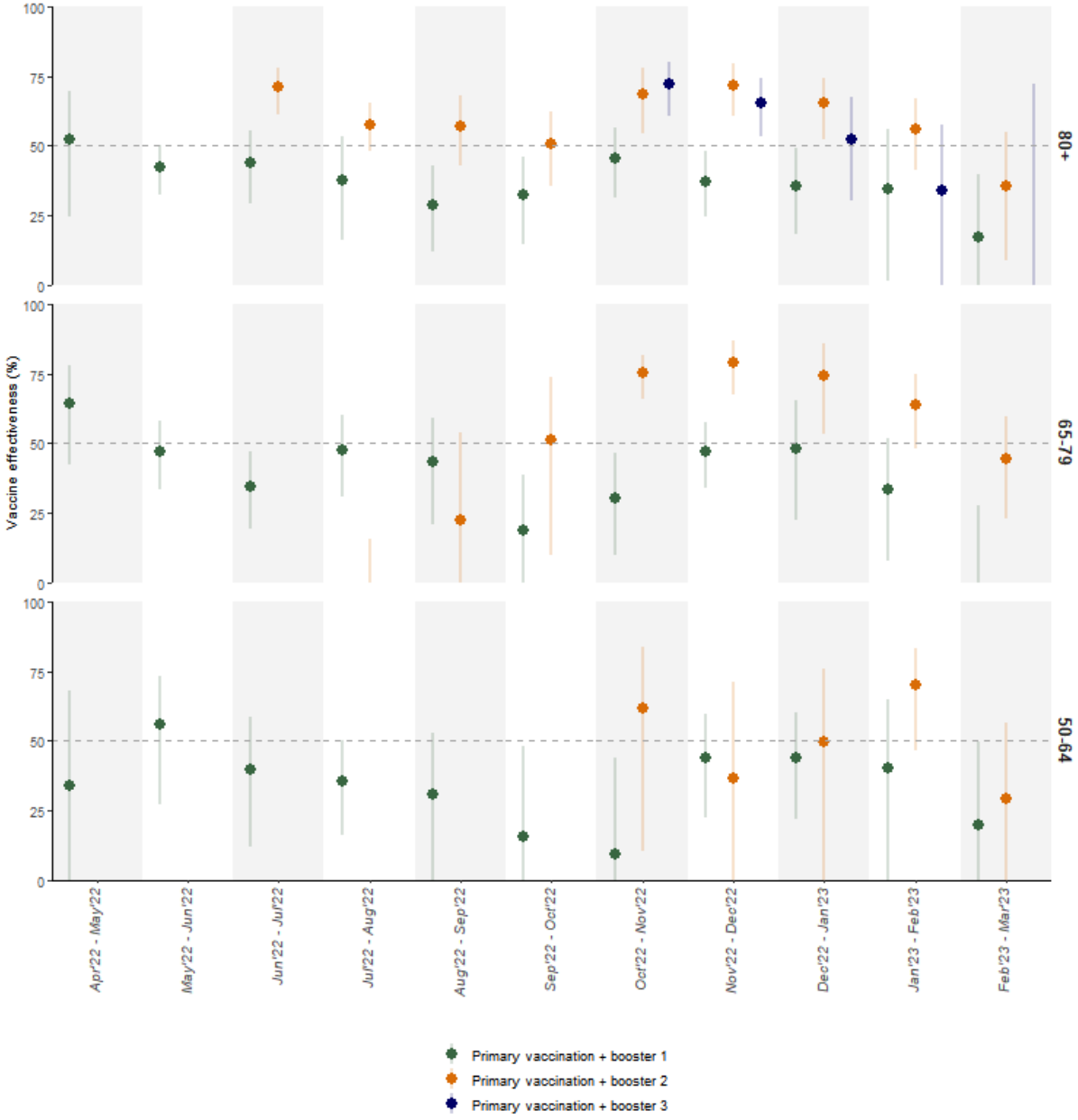
The rVE of a second booster dose was high shortly after administration, reaching 76% (95% CI: 70; 81) in ≥80 year olds and 81% (95% CI: -65; 89) in 65–79 year-olds, in November–December 2022 and 71.7% (95% CI: -53; 83) in 50–64 year olds in January–February 2023. In ≥80 year olds, the highest rVE estimates were observed in spring 2022 and autumn 2022 corresponding to a more extensive deployment of the vaccine in Belgium and Portugal (spring 2022 campaign) than in other participating countries (autumn 2022 campaign). The rVE declined with time since booster vaccination (Figure 5), with rVE estimates of <50% at ≥24 weeks after administration. In the last period available (February–March 2023), the rVE of the second booster administered 12–24 weeks ago was 49% (95% CI: 27; 65) in ≥80 year olds, 43% (95% CI: 18; 60) in 65–79 year olds, and 33% (95% CI: -125; 80) in 50–64 year olds. In February–March 2023, the rVE of the second booster administered at least 24 weeks ago was 3.5% (95% CI: -88; 51) in ≥80 year olds and 43% (95% CI: -8; 70) in 65–79 year olds.

Third booster

The rVE of a third booster dose administered during autumn 2022 (to the same risk groups who received the second booster vaccination during the spring 2022 campaign in Portugal and Belgium), could only be estimated in ≥80 year olds.

The rVE of the third booster in October–November 2022 reached 72% (95% CI: 61; 80), compared to complete primary vaccination only, similar to the rVE of a second booster, administered simultaneously in the remaining study sites during the autumn 2022 campaign (Figure 4). The rVE of third boosters waned rapidly, being null beyond 12 weeks of administration (-12% (95% CI: -319; 70) at 12–24 weeks after its administration (estimates from February–March 2023)).

Figure 4. Relative vaccine effectiveness against hospitalisation due to COVID-19 of first, second and third booster dose, compared to complete primary vaccination series without booster administered ≥24 weeks ago, for each eight-week overlapping study period between April 2022 and March 2023



VE=Vaccine effectiveness; adjusted by sex, age (5-year bins), region and comorbidities and socioeconomic variables (as available in each study site)
(Based on estimates from: Belgium, Denmark, Luxembourg, Navarra, Norway, Portugal)

Figure 5. Relative vaccine effectiveness against hospitalisation due to COVID-19 of the first, second and third booster dose, compared to complete primary vaccination without booster administered ≥24 weeks ago, by time since the booster, for each eight-week overlapping study period between April 2022 and March 2023

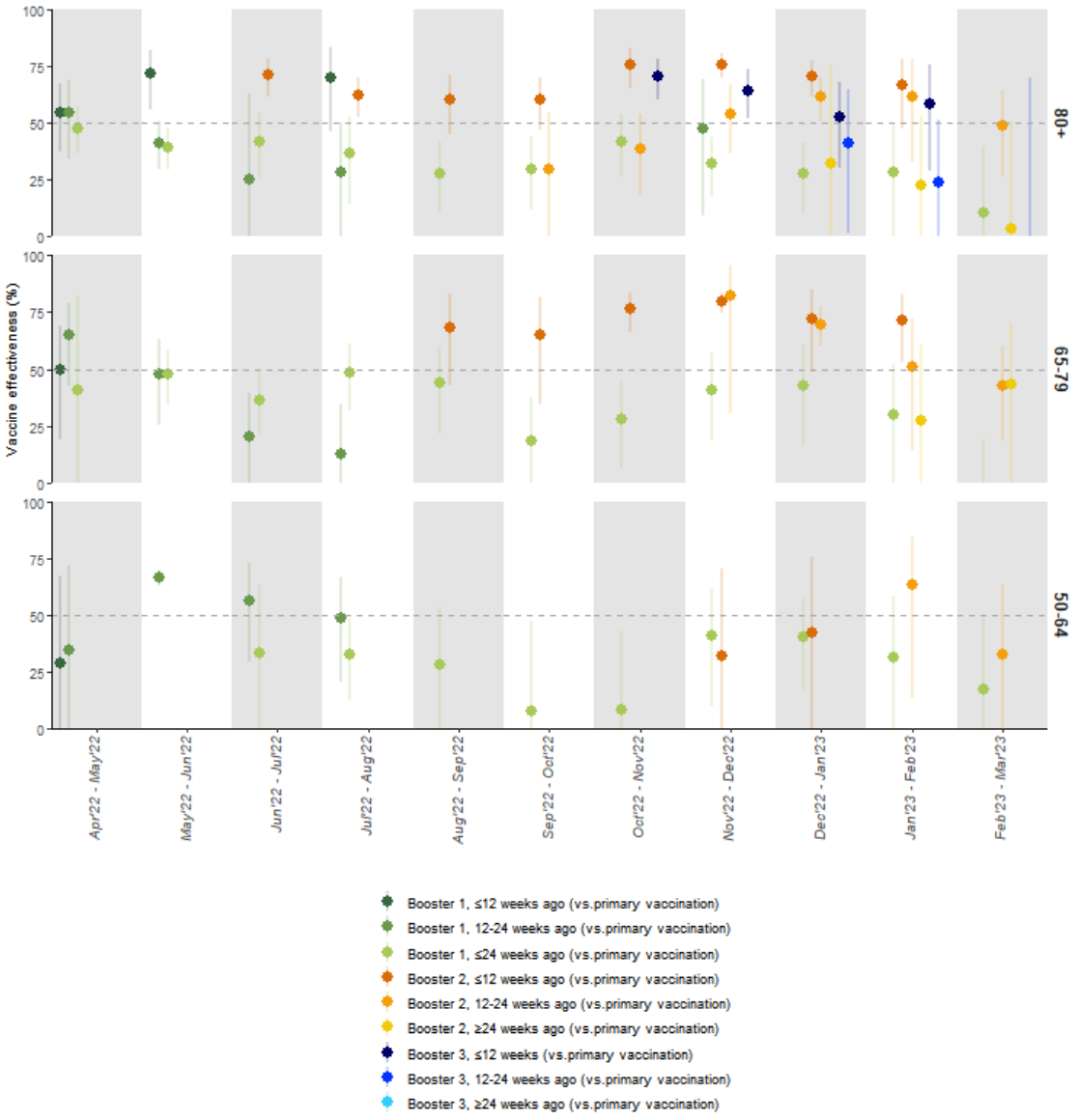


Table 7. Relative vaccine effectiveness (95% Confidence Intervals) in ≥80 years against hospitalisation due to COVID-19 of the first, second and third booster dose, compared to complete primary vaccination without booster administered ≥24 weeks ago, for each eight-week overlapping study period between April 2022 and March 2023

Study period	Complete primary vaccination + first booster dose				Complete primary vaccination + two booster doses				Complete primary vaccination + three booster doses		
	Overall	<12 weeks	12–24 weeks	>24 weeks	Overall	<12 weeks	12–24 weeks	>24 weeks	Overall	<12 weeks	12–24 weeks
April 1 to May 26, 2022	52.2% (24.7; 69.6)	54.7% (37.2; 67.3)	54.6% (34.4; 68.5)	47.8% (36.8; 56.9)	-	-	-	-	-	-	-
May 1 to June 25, 2022	42.2% (32.6; 50.5)	72.0% (55.7; 82.3)	41.4% (29.9; 51.1)	39.3% (29.4; 47.8)	-	-	-	-	-	-	-
June 1 to July 26, 2022	44.1% (29.4; 55.7)	-	24.9% (-53.2; 63.1)	41.8% (25.2; 54.7)	71.0% (61.4; 78.2)	71.0% (61.4; 78.2)	-	-	-	-	-
July 1 to August 25, 2022	37.5% (16; 53.5)	70.0% (46.5; 83.2)	28.3% (-2.9; 50.1)	36.5% (14.6; 52.8)	57.8% (48.2; 65.6)	62.5% (52.7; 70.2)	-	-	-	-	-
August 1 to September 25, 2022	28.9% (11.8; 42.7)	-	-	27.8% (10.4; 41.9)	57.2% (43.1; 67.9)	60.2% (45; 71.3)		-	-	-	-
September 1 to October 26, 2022	32.2% (14.9; 46)	-	-	29.9% (11.7; 44.3)	50.7% (35.8; 62. 2)	60.2% (46.9; 70.2)	30.0% (-7.4; 54.3)	-	-	-	-
October 1 to November 25, 2022	45.5% (31.4; 56.7)	-	-	41.8% (26.6; 53.9)	68.4% (54.5; 78.1)	75.6% (65.5; 82.8)	38.7% (17.9; 54.2)	-	72.1% (60.6; 80.2)	70.8% (60.2; 78.6)	-
November 1 to December 26, 2022	37.3% (24.4; 47.9)	-	47.2% (8.9; 69.4)	31.9% (17.7; 43.6)	71.6% (60.7; 79.4)	76.0% (69.8; 80.9)	54.0% (36.5; 66.7)	-	65.2% (53.1; 74.2)	64.3% (51.9; 73.5)	-
December 1, 2022 to January 25, 2023	35.6% (18.2; 49.3)	-	-	27.5% (10.4; 41.4)	65.2% (52.3; 74.6)	70.8% (61.4; 77.9)	61.6% (50.5; 70.1)	32.3% (-86.1; 75.4)	52.3% (30.4; 67.4)	52.8% (30.5; 68)	41.0% (1.3; 64.7)
January 1 to Feb. 25,2023	34.4% (1.7; 56.2)	-	-	28.2% (-2.1; 49.5)	56.0% (41.3; 67.1)	66.4% (47.8; 78.4)	61.6% (32.6; 78.1)	22.6% (-29; 53.6)	33.8% (-2.9; 57.4)	58.6% (28.9; 75.9)	23.9% (-18.6; 51.2)
February 1 to March 28, 2023	17.2% (-13.5; 39.6)	-	-	10.4% (-33.3; 39.7)	35.7% (8.7;54.8)	-	49.0% (26.7; 64.5)	3.5% (-88.2; 50.6)	-7.9% (-321.1; 72.3)	-	-12.1% (-319.2; 70)

Table 8. Relative vaccine effectiveness (95% Confidence Intervals) in 65-79 years against hospitalisation due to COVID-19 of the first, second and third booster dose, compared to complete primary vaccination without booster ≥24 weeks ago for each eight-week overlapping study period between April 2022 and March 2023

Study period	Complete primary vaccination + first booster dose				Complete primary vaccination + two booster doses			
	Overall	<12 weeks	12–24 weeks	>24 weeks	Overall	<12 weeks	12–24 weeks	>24 weeks
April 1 to May 26, 2022	64.2% (42.2; 77.8)	49.7% (18.7; 68.8)	65.2% (42.7; 78.9)	40.7% (-98.3; 82.3)	-	-	-	-
May 1 to June 25, 2022	47.1% (33.6; 57.8)	-	47.7% (25.5; 63.3)	47.6% (34.1; 58.4)	-	-	-	-
June 1 to July 26, 2022	34.6% (19.2; 47)	-	20.5% (-4.5; 39.6)	36.0% (20.9; 48.3)	-	-	-	-
July 1 to August 25, 2022	47.5% (30.6; 60.3)	-	12.9% -16.1; 34.6)	48.5% (31.6; 61.3)	-	-	-	-
August 1 to September 25, 2022	43.2% (20.6; 59.3)	-	-	43.9% (21.3; 59.9)	22.7% (-29.6; 53.9)	68.4% (42.5; 82.6)	-	-
September 1 to October 26, 2022	18.6% (-8.1; 38.7)	-	-	18.4% (-7.2; 37.8)	51.2% (9.9; 73.6)	65.1% (34.3; 81.5)	-	-
October 1 to November 25, 2022	30.4% (9.8; 46.3)	-	-	27.8% (6.3; 44.4)	73.4% (62.2; 81.3)	76.6% (66.5; 83.6)	-	-
November 1 to December 26, 2022	47.0% (33.7; 57.7)	-	-	40.9% (18.7; 57.1)	79.1% (67.4; 86.7)	79.6% (74.4; 83.7)	82.5% (30.4; 95.6)	-
December 1, 2022 to January 25, 2023	48.1% (22.5; 65.3)	-	-	42.5% (16.2; 60.5)	74.5% (53.5; 86)	72.0% (48.6; 84.7)	69.8% (60.1; 77.2)	-
January 1 to Feb. 25,2023	33.2% (7.9; 51.6)	-	-	29.6% (-3.2; 52)	63.9% (48.3; 74.7)	71.7% (53; 83)	50.8% (13.9; 71.9)	27.4% (-33.2; 60.4)
February 1 to March 28, 2023	-0.9% (-40.3; 27.5)	-	-	-13.4% (-58.3; 18.7)	44.2% (23.1; 59.6)	-	42.9% (18.1; 60.1)	43.1% (-7.9; 70)

Table 9. Relative vaccine effectiveness (95% Confidence Intervals) in 50-64 years against hospitalisation due to COVID-19 of the first, second and third booster dose, compared to complete primary vaccination only without booster ≥24 weeks ago for each eight-week overlapping study period between April 2022 and March 2023

Study period	Complete primary vaccination + first booster dose				Complete primary vaccination + two booster doses			
	Overall	<12 weeks	12–24 weeks	>24 weeks	Overall	<12 weeks	12–24 weeks	>24 weeks
April 1 to May 26, 2022	33.8% (-36.6; 67.9)	28.6% (-55.9; 67.3)	34.2% (-54.1; 71.9)	-	-	-	-	-
May 1 to June 25, 2022	55.6% (27; 73)	-	66.6% (62.9; 69.9)	-	-	-	-	-
June 1 to July 26, 2022	39.5% (11.8; 58.5)	-	56.0% (29.2; 72.7)	33.3% (-21.3; 63.4)	-	-	-	-
July 1 to August 25, 2022	35.4% (16.2; 50.2)	-	48.6% (20.6; 66.7)	32.8% (12.5; 48.4)	-	-	-	-
August 1 to September 25, 2022	31.0% (-0.8; 52.7)	-	-	28.1% (-10.1; 53)	-	-	-	-
September 1 to October 26, 2022	15.6% (-37.5; 48.2)	-	-	7.4% (-62.7; 47.3)	-	-	-	-
October 1 to November 25, 2022	9.4% (-46.9; 44.1)	-	-	8.1% (-47.3; 42.6)	-	-	-	-
November 1 to December 26, 2022	34.1% (0.9; 56.2)	-	-	32.0% (-17.3; 60.6)	45.8% (-44.2; 79.7)	33.4% (-125.4; 80.3)	-	-
December 1, 2022 to January 25, 2023	40.6% (7.6; 61.8)	-	-	34.7% (-2.3; 58.3)	65.7% (35.1; 81.9)	57.0% (-24.2; 85.1)	-	-
January 1 to Feb. 25,2023	40.4% (-0.5; 64.6)	-	-	31.2% (-13.3; 58.2)	70.0% (46.6; 83.1)	-	63.5% (13.6; 84.6)	-
February 1 to March 28, 2023	19.6% (-28.7; 49.8)	-	-	17.5% (-32.4; 48.6)	29.3% (-15; 56.5)	-	32.5% (-25.2; 63.6)	-

Vaccine effectiveness against COVID-19-related mortality

First booster

Between April 2022 and March 2023, the overall rVE of the first booster dose against COVID-19 related mortality showed a similar range and trend to that of rVE against hospitalisation due to COVID-19, although estimates had high uncertainty, particularly in the groups <65 years (Tables 10, 11 12).

Second booster

The second booster dose substantially restored protection (Figure 7), in November–December 2022 the rVE (compared to complete primary vaccination only) reached 77% (95% CI: 38; 92) in ≥80 year olds and 85% (95% CI: 62; 94) in 65–79 year olds, but only 34% (95% CI: -74; 76) in 50–64 year olds (only estimate produced in that age group).

In February–March 2023, the rVE of the second booster administered 12–24 weeks ago was 59% (95% CI: 34; 75) in ≥80-year-olds and 15% (95% CI: -72; 58) in 65–79 year olds. The rVE of the second booster administered ≥24 weeks ago was 50% (95% CI: -91; 87) in ≥80-year-olds. The observed trend was similar to the one shown against hospitalisation.

Third booster

The rVE of the third booster dose administered in autumn 2022 in the population who had received the second booster vaccination during spring 2022, could only be consistently estimated in ≥80-year-olds based on data provided by Portugal and Belgium. The rVE of the third booster in October–November 2022, administered less than <12 weeks after administration, was 64% (95% CI: 48; 75) similar to rVE estimates for the second booster administered simultaneously in other study sites (Figure 7). The rVE of third boosters waned rapidly thereafter. In February–March 2023, the rVE of a third booster administered 12–24 weeks ago was 3% (95% CI: -26 709; 100).

Figure 6. Relative vaccine effectiveness against COVID-19-related mortality of the first, second and third booster dose, compared to complete primary vaccination administered ≥24 weeks ago without booster, for each eight-week overlapping study period, April 2022 and March 2023

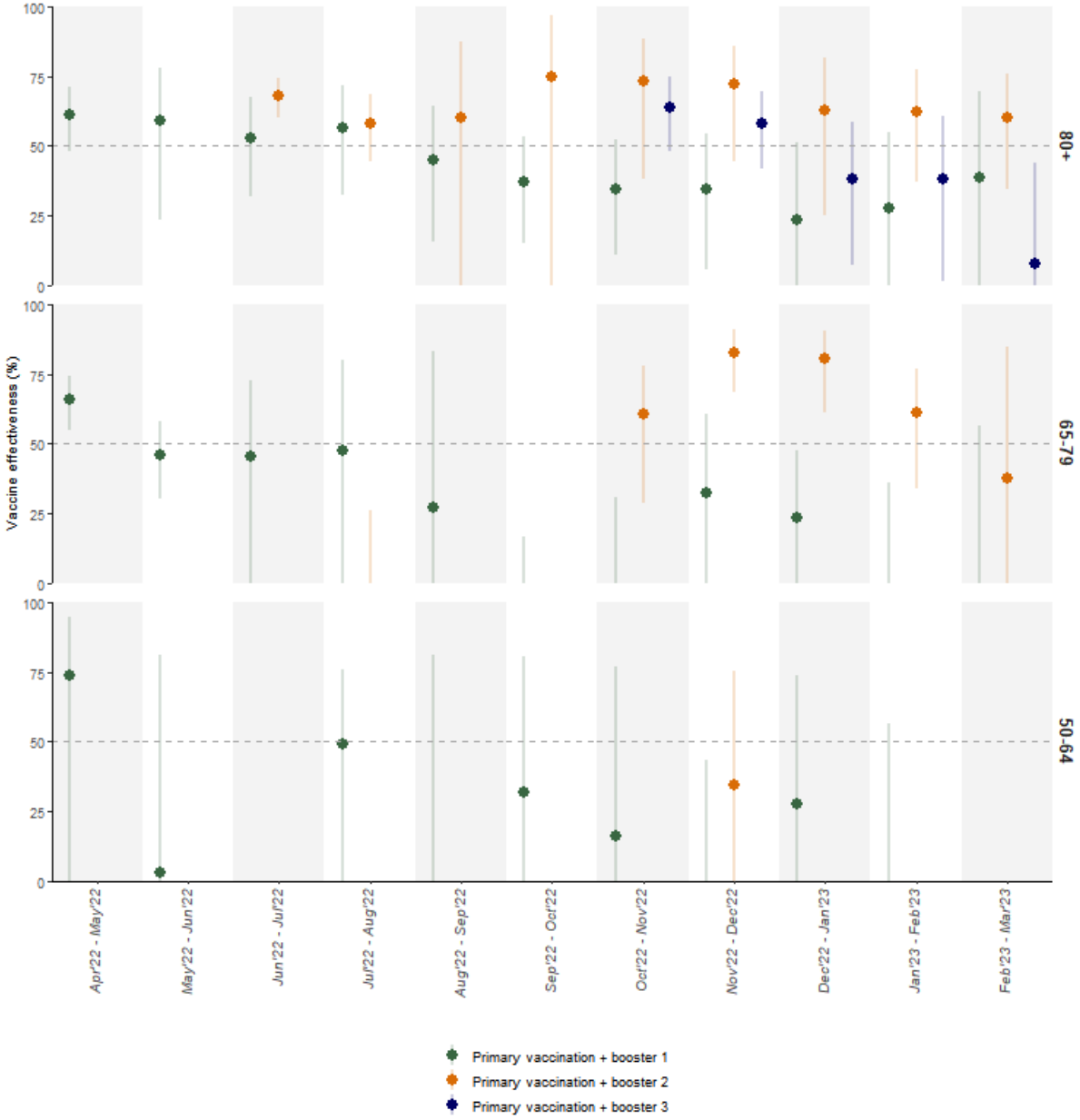


Figure 7. Relative vaccine effectiveness against COVID-19 related mortality of the first, second and third booster dose, compared to complete primary vaccination administered ≥24 weeks ago without booster, by time since the booster, for each eight-week overlapping study period, April 2022 and March 2023

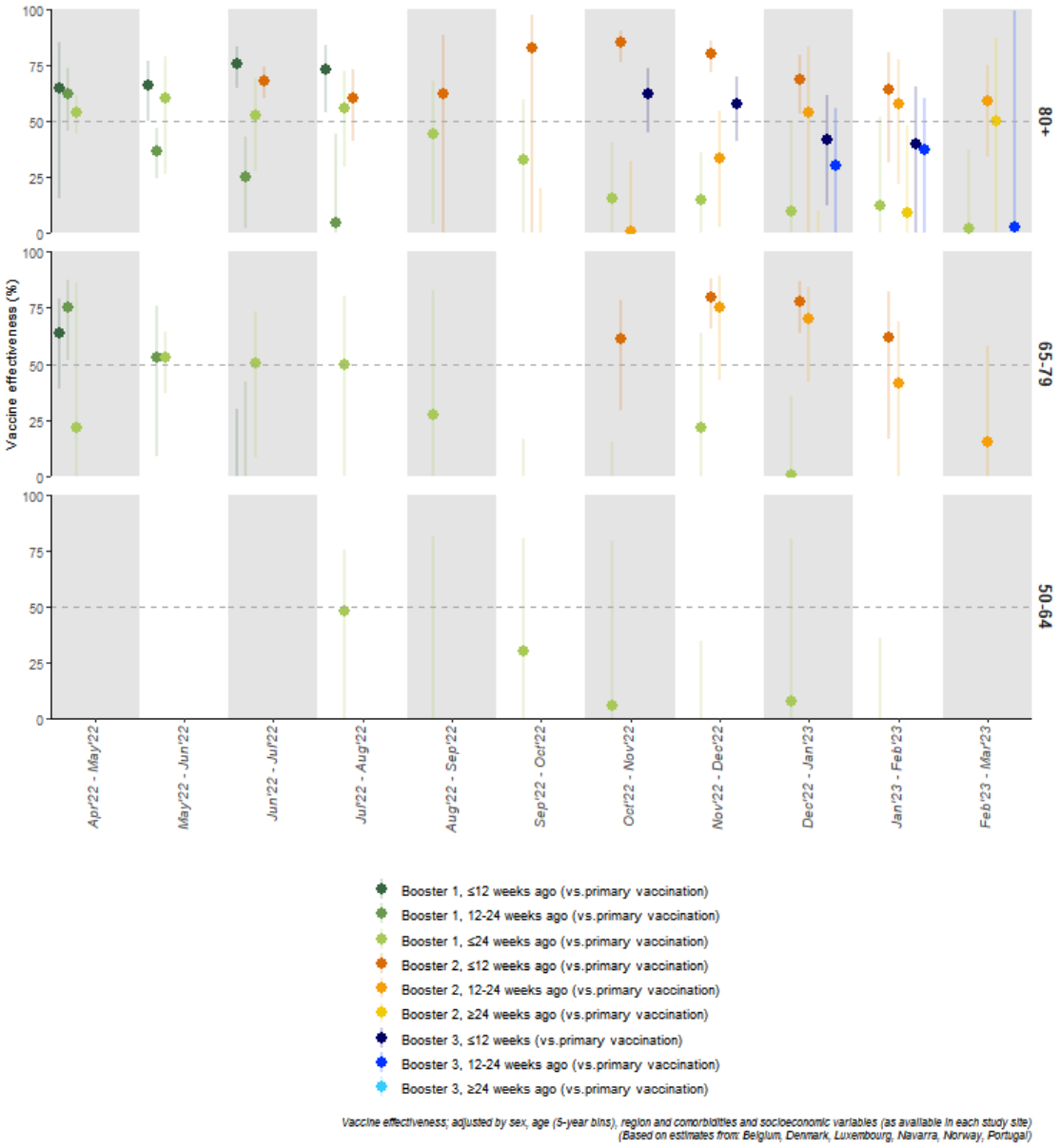


Table 10. Relative vaccine effectiveness (95% confidence intervals) in ≥80 years against COVID-19 related mortality of the first, second and third booster dose, compared to complete primary vaccination administered ≥24 weeks ago without booster for each eight-week study period, April 2022 and March 2023

Study period	Complete primary vaccination + first booster dose				Complete primary vaccination + two booster doses				Complete primary vaccination + three booster doses		
	Overall	<12 weeks	12–24 weeks	>24 weeks	Overall	<12 weeks	12–24 weeks	>24 weeks	Overall	<12 weeks	12–24 weeks
April 1 to 26 May 2022	61.3% (48.3; 71)	65.0% (15.6; 85.5)	62.2% (45.9; 73.6)	53.7% (44.4; 61.5)	-	-	-	-	-	-	-
May 1 to 25 June 2022	59.2% (23.6; 78.2)	66.0% (50.4; 76.7)	36.5% (24.4; 46.6)	60.3% (26.3; 78.6)	-	-	-	-	-	-	-
June 1 to 26 July 2022	53.1% (32.2; 67.5)	76.0% (65.1; 83.5)	25.2% (2.2; 42.8)	52.9% (27.6; 69.3)	68.0% (60.3; 74.2)	68.0% (60; 74.4)	-	-	-	-	-
July 1 to 25 August 2022	56.5% (32.7; 72)	73.0% (54.2; 84.1)	5.0% (-63; 44.6)	55.8% (29.7; 72.3)	58.1% (44.5; 68.3)	60.3% (41.4; 73.1)	-	-	-	-	-
August 1 to 25 September 2022	45.2% (15.5; 64.5)	-	-	44.6% (3.9; 68.1)	59.9% (-29.6; 87.6)	62.1% (-25.7; 88.6)	-	-	-	-	-
September 1 to 26 October 2022	37.1% (15.2; 53.4)	-	-	33.0% (-11.7; 59.8)	75.1% (-109.4; 97)	82.7% (-14.9; 97.4)	-18.0% (-74; 20)	-	-	-	-
October 1 to 25 November 2022	34.6% (10.7; 52.1)	-	-	15.9% (-18.8; 40.4)	73.3% (38.2; 88.4)	85.0% (76; 90.6)	1.0% (-44.1; 32)	-	64.0% (48.1; 75)	62.0% (44.7; 73.9)	-
November 1 to 26 December 2022	44.2% (24.3; 58.8)	-	-	22.2% (-15.6; 47.7)	77.0% (37.9; 91.5)	80.0% (70.7; 86.3)	24.0% (-12.6; 48.7)	-	58.0% (41.6; 69.8)	58.0% (41.1; 70.1)	-
December 1 2022 to 25 January 2023	38.8% (13.7; 56.6)	-	-	26.8% (-33.5; 59.8)	71.2% (38.3; 86.6)	68.0% (49.4; 79.8)	72.0% (52; 83.7)	-42.0% (-124; 10)	38.0% (7.1; 58.6)	42.0% (12.2; 61.7)	30.0% (-10.7; 55.7)
January 1 to 25 Feb. 2023	27.9% (-14.7; 54.7)	-	-	12.5% (-58.6; 51.7)	62.5% (37.2; 77.7)	64.0% (31.4; 81.1)	58.0% (22.1; 77.3)	9.2% (-59.1; 48.2)	38.0% (1.7; 60.9)	40.0% (-3.9; 65.4)	37.0% (0.4; 60.2)
February 1 to 28 March 2023	38.7% (-23.5; 69.6)	-	-	2.0% (-52.9; 37.2)	60.2% (34.7; 75.7)	-	59.3% (33.9; 74.9)	50.0% (-91.3; 86.9)	8.0% (-51.6; 44.2)	-	3.0% (-26709.2; 99.6)

Table 11. Relative vaccine effectiveness (95% confidence intervals) in 65-79 years against COVID-19 related mortality of the first, second and third booster dose, compared to complete primary vaccination administered ≥24 weeks ago without booster for each eight-week overlapping study period, April 2022 and March 2023

Study period	Complete primary vaccination + first booster dose				Complete primary vaccination + two booster doses			
	Overall	<12 weeks	12–24 weeks	>24 weeks	Overall	<12 weeks	12–24 weeks	>24 weeks
April 1 to 26 May 2022	66.0% (55.2; 74.3)	64.0% (38.6; 78.9)	75.4% (51.8; 87.5)	21.5% (-355.5; 86.5)	-	-	-	-
May 1 to 25 June 2022	45.8% (30.3; 57.9)	-	52.9% (9; 75.6)	52.7% (36.7; 64.6)	-	-	-	-
June 1 to 26 July 2022	45.7% (-7.3; 72.5)	-25.0% (-123.1; 30)	-6.7% (-96; 41. 9)	50.4% (8.4; 73.1)	-	-	-	-
July 1 to 25 August 2022	47.5% (-37.9; 80)	-	-110.0% (-282.7; -15.2)	49.8% (-26.6; 80.1)	-	-	-	-
August 1 to 25 September 2022	27.2% (-215.3; 83.2)	-	-	27.3% (-206.3; 82.8)	-	-	-	-
September 1 to 26 October 2022	-33.0% (-111.8; 16.5)	-	-	-34.0% (-114; 16.1)	-	-	-	-
October 1 to 25 November 2022	-8.5% (-69.6; 30.6)	-	-	-34.2% (-112.6; 15.3)	61.0% (29.3; 78.5)	61.0% (29.3; 78.5)	-	-
November 1 to 26 December 2022	40.2% (-48.8; 76)	-	-	28.7% (-166.4; 80.9)	85.3% (61.6; 94.4)	76.0% (60.8; 85.3)	-	-
December 1 2022 to 25 January 2023	33.0% (-1.7; 55.9)	-	-	12.4% (-61.6; 52.5)	85.1% (73.4; 91.7)	80.0% (64.3; 88.8)	-	-
January 1 to 25 Feb 2023	-7.5% (-80; 35.8)	-	-	-88.6% (-219.4; -11.4)	61.2% (34.1; 77.2)	61.7% (16.7; 82.4)	41.5% (-9; 68.7)	-
February 1 to 28 March 2023	-82.6% (-661.9; 56.2)	-	-	-159.0% (-388; -37.4)	37.4% (-155.5; 84.7)	-	15.0% (-72.5; 58.1)	-

Table 12. Relative vaccine effectiveness (95% confidence intervals) in 50–64 years against COVID-19 related mortality of the first, second and third booster dose, compared to complete primary vaccination administered ≥24 weeks ago without booster in 50–64 years for each eight-week overlapping study period, April 2022 and March 2023

Study period	Complete primary vaccination + first booster dose				Complete primary vaccination + two booster doses			
	Overall	<12 weeks	12–24 weeks	>24 weeks	Overall	<12 weeks	12–24 weeks	>24 weeks
April 1 to 26 May 2022	73.8% (-31.6; 94.8)	-	-	-	-	-	-	-
May 1 to 25 June 2022	3.2% (-387.9; 80.8)	-	-	-	-	-	-	-
June 1 to 26 July 2022	-	-	-	-	-	-	-	-
July 1 to 25 August 2022	48.8% (-7.9; 75.7)	-	-	48.0% (-11.2; 75.7)	-	-	-	-
August 1 to 25 September 2022	-14.8% (-588.8; 80.9)	-	-	-17.6% (-637.1; 81.2)	-	-	-	-
September 1 to 26 October 2022	31.8% (-137.1; 80.4)	-	-	30.0% (-153.4; 80.7)	-	-	-	-
October 1 to 25 November 2022	16.0% (-206; 76.9)	-	-	5.6% (-324.4; 79)	-	-	-	-
November 1 to 26 December 2022	-12.0% (-148.9; 49.6)	-	-	-32.9% (-245.3; 48.8)	34.6% (-74; 75.5)	-	-	-
December 1, 2022 to 25 January 2023	27.5% (-100.7; 73.8)	-	-	7.4% (-325.7; 79.9)	-	-	-	-
January 1 to 25 Feb. 2023	-9.2% (-173.6; 56.4)	-	-	-73.1% (-368.8; 36.1)	-	-	-	-
February 1 to28 March 2023	-	-	-	-	-	-	-	-

Challenges, limitations and interpretations

The multi-country approach for VE monitoring using data routinely collected in EHR and according to a common protocol, offers multiple advantages. The increased sample size allows the possibility to monitor less frequent events by pooling results from several countries, while also achieving good comparability across participating sites. Nonetheless, the number of events was sometimes too low to provide estimates with precision, especially for VE against mortality related to COVID-19 in younger age groups or, when using as reference, group individuals with complete primary vaccination only, which summed up to very few individuals among ≥80 years. The rapid availability of data in EHR allows a near-real-time monitoring to support decision-making, which is only delayed by the time needed for severe outcomes to occur after SARS-CoV-2 infection and by the time needed for data consolidation. In our study, we allowed a minimum of one month between the end of the study period and the data extraction, thus allowing an analysis of the observation period of the two to three months before the time of data analysis.

However, using EHR also presents some challenges. Data are not collected for epidemiological study purposes but rather for patient clinical management or resources assessment. Data extraction and coding by intermediate institutions imply some heterogeneity in the way variables are defined across sites (e.g. comorbidity variables were usually pre-coded at country level). This means adjustment may not be equally accurate or comparable across sites. On the other hand, because these pre-coded categories were often the ones used to target vulnerable groups for vaccination, allowing that they vary from site to site may provide better internal validity. The multisite approach implies that the relative contribution of the study sites is different for the different vaccination statuses, which can make interpretation complex. However, it is also an opportunity to compare vaccine doses across countries with different vaccines rollout calendars (i.e. second and third booster campaigns deployed simultaneously in different countries)

Additionally, EHR are less flexible to include new variables than primary data collection, and some relevant aspects are missing such as the infecting SARS-CoV-2 variant, comorbidities (in one study site), previous SARS-CoV-2 infections or corresponding data (such as date of infection) or socioeconomic variables, among others.

Another limitation of using EHR for VE estimations is the misclassification of hospitalisations not due to COVID-19 as events of interest. To minimise this, outcomes of interest were restricted to hospital admissions in which the main cause was COVID-19 or SARI with positive SARS-CoV-2 test. Because the cause of death was not available in a timely manner in most countries, it is likely that deaths in which SARS-CoV-2 was detected, but was not the cause of death, have been incorrectly included as events in the study. Regarding case ascertainment, it is also relevant to consider that, with the evolution of the pandemic and the reduction in systematic use of SARS-CoV-2 tests in the hospital setting, the probability of misclassification of events may increase.

Finally, despite the adjustment by comorbidities and limiting the estimates to the population eligible for an additional booster dose at each point in time, it is possible that people who received an additional vaccine dose were different from those who did not receive it regarding the risk of severe COVID-19 outcomes, in ways not adjusted for in this study. This can be more relevant with the higher number of doses, when vaccination coverage decreases and/or vaccination campaigns are limited to the more vulnerable groups. Further, it is likely that people who received successive vaccinations close in time did not have any mild SARS-CoV-2 infection in the meantime. This could partially explain the lower and more rapid waning of effectiveness of the third booster dose, which was only administered to populations who opted for a second booster in the spring and a third dose later in the autumn in Portugal and Belgium.

The different rollout of COVID-19 vaccine boosters in the different participating countries needs to be considered in this multi-country collaboration. For example, the rVE of the second and the third boosters during the autumn 2022 was very similar, which could be misinterpreted as no additional benefit of the third booster dose. However, the third booster was only administered to people with a second booster during the previous Spring vaccination campaign in the countries that implemented it, thus they represent different populations. What these results suggest is that recent administration of a vaccine in autumn 2022 was equally effective, regardless of the number of previous doses (if it was the second or the third booster dose), and that probably the time since vaccination is more relevant to protection than the number of doses.

Changing in SARS-CoV-2 testing recommendations and the increase in the use of self-tests that are not captured in EHR is likely to have resulted in any adjustment by previous infection probably being highly misclassified.

In addition, adjustment by post-vaccination infection may bring additional methodological challenges [12-143]. All the above limitations could result in the underestimation of VE. Despite these limitations, it is also plausible that a drop in VE in the most recent study period is caused by a higher circulation in Europe of XBB (and XBB1.5), which is associated with a higher immune escape [14].

Conclusions

Overall, estimates of rVE generated in this study indicate that booster doses were effective in restoring protection against both hospitalisation due to COVID-19 and COVID-19 related mortality [15-16]. However, rVE point estimates declined over time, particularly for the third booster dose, which was only administered to the ≥80 years age group in Belgium and Portugal. Although there is uncertainty about the timing and the magnitude of waning immunity, due to a possible underestimation of the rVE, these results clearly support the policy of providing additional boosters periodically to maintain protection, especially to those ≥80 years.

After the first booster vaccination campaign that took place in most countries in the autumn of 2021, the additional protection conferred by that first booster compared to the level of protection seen among those who had only completed primary vaccination (at least 24 weeks earlier) with no subsequent booster had decreased to below 50% and showed little or no additional protection as of March 2023. The second and third boosters each increased rVE to >70% compared to only primary vaccination, but their effect also waned rapidly. Vaccine effectiveness against COVID-19-related mortality was more preserved, with rVE generally >50% for both second and third boosters as of March 2023. In contrast, little protection offered by the third booster compared to only primary vaccination was observed against hospitalisation due to COVID-19 during 2023 in ≥80 years, which could be explained by the low number of countries contributing to the estimates (Portugal and Belgium), the higher proportion of individuals with comorbidities among those with a third booster, and because some individuals in the comparison group (complete primary vaccination) were vaccinated during the autumn 2022 campaign. The effectiveness for doses administered in autumn 2022 (when bivalent vaccines were used, both BA.1 and BA.4/5), was similar, regardless of booster dose number (third booster dose administered in Portugal and Belgium, or second booster doses in other countries). This suggests that the time since the last dose could be more important than the total number of doses administered in the protection against both COVID-19 hospitalisation and death. Thus, further analyses focusing on the additional VE regardless of number of doses should be considered.

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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	Not applicable
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 Register (Folkeregisteret)	CPR	Statutory health insurance database	The national population register
	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).	Primary Care Information System	Risk groups / Comorbidities: Based on Norwegian Patient Registry (NPR)	DNPR	Not applicable	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 2. Conditions of living – Deprivation at municipality level: Most recent data from 2011 3. Other vaccines uptake: VACINAS	1. Country of birth and high functional dependence: Administrative database	1. Conditions of living – Crowding: Statistics Norway (SSB). Most recent data from 2019 – separate level for missing data 2. *County of birth:* Folkeregisteret	Not applicable	1. Statutory health insurance database	1. Household income (according to tax records) categorized as low (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 categories: 5-9, 10-14, 15-17, 18-24 and then 5-year categories until the final category, 90+ years	Age at the start of follow up, 5-year categories	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 disease, rheumatologic disease, stroke, tuberculosis*	Immunocompromised Other major chronic conditions - *Diabetes* - *Severe Obesity* - *Cancer* - *Ictus* - *Dementia* - *Kidney disease* - *Haematological cancers* - *Heart disease* - *Chronic respiratory disease* - *Liver disease* - *Rheumatic arthritis*	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)* - *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 heart and vascular disease (with the exception of high*	Immunocompromised, including: - *HIV* - *Immunological disease* - *Radiation therapy* - *Organtransplanted* Other, including: - *Diabetes* - *Obesity* - *Cancer* - *Neurological Disease* - *Kidney disease* - *Haematological cancers* - *Heart disease* - *Chronic respiratory disease* - *Liver disease (incl. alcohol lever)* - *Endocrine Disease* - *Hematological Disease* - *Coagulation Disease* - *Innate Diseases* - *TB* - *Missing a lung* - *Missing a kidney*	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* - *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*

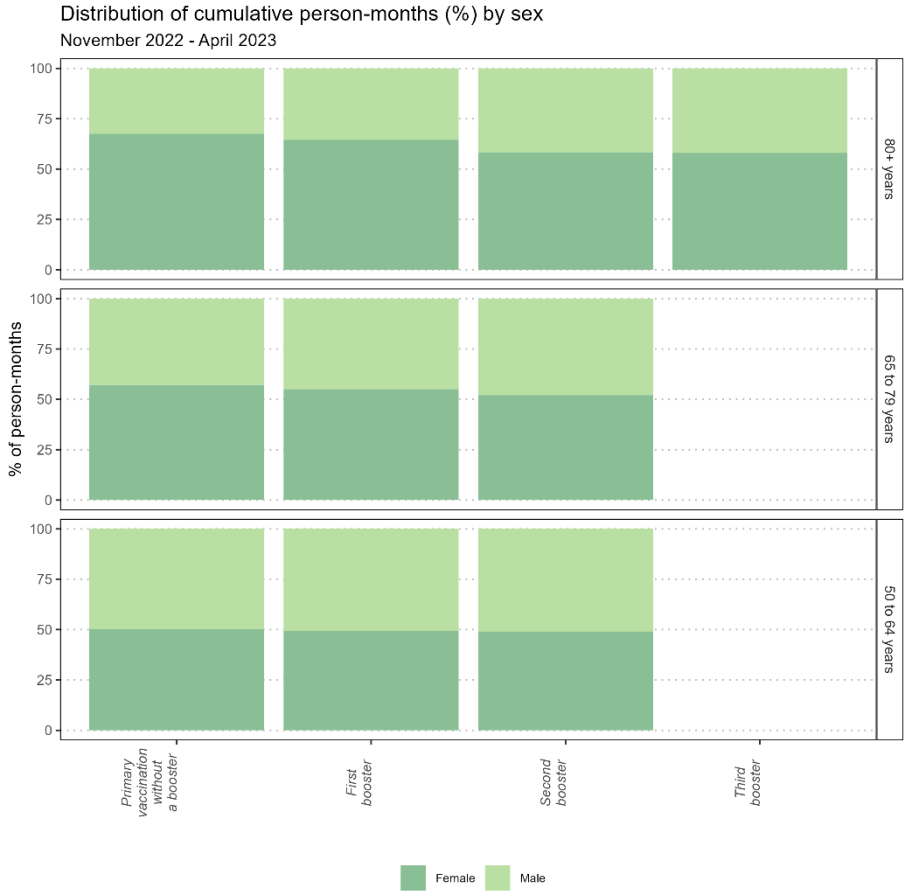
Variable	Definition, categorisation, use in the model					
	Portugal	Navarre (Spain)	Norway	Denmark	Luxembourg	Belgium
			blood pressure) and stroke			Immunocompromised (high risk): *if a person received a priority invitation for a COVID-19 vaccination due to being immunocompromised, then he/she was 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)	High functional dependence	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 rooms or the P-area is not specified, a household was regarded as crowded if one of these criteria is met (incomplete and slightly outdated data)	Not included	Not included	Household income: low (lowest 40%)-medium (middle 30%)-high (highest 30%)
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

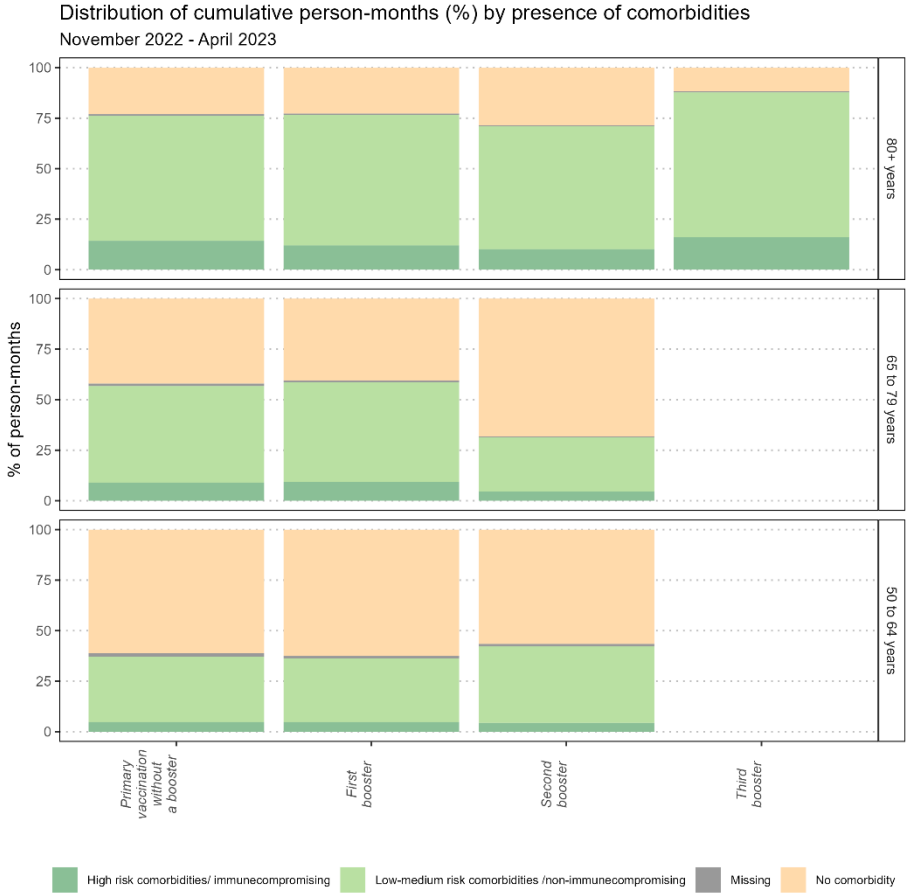
Appendix 3. Individuals, number of COVID-19 related deaths and person-month by 8-week period, between April 2022-March 2023, by age group

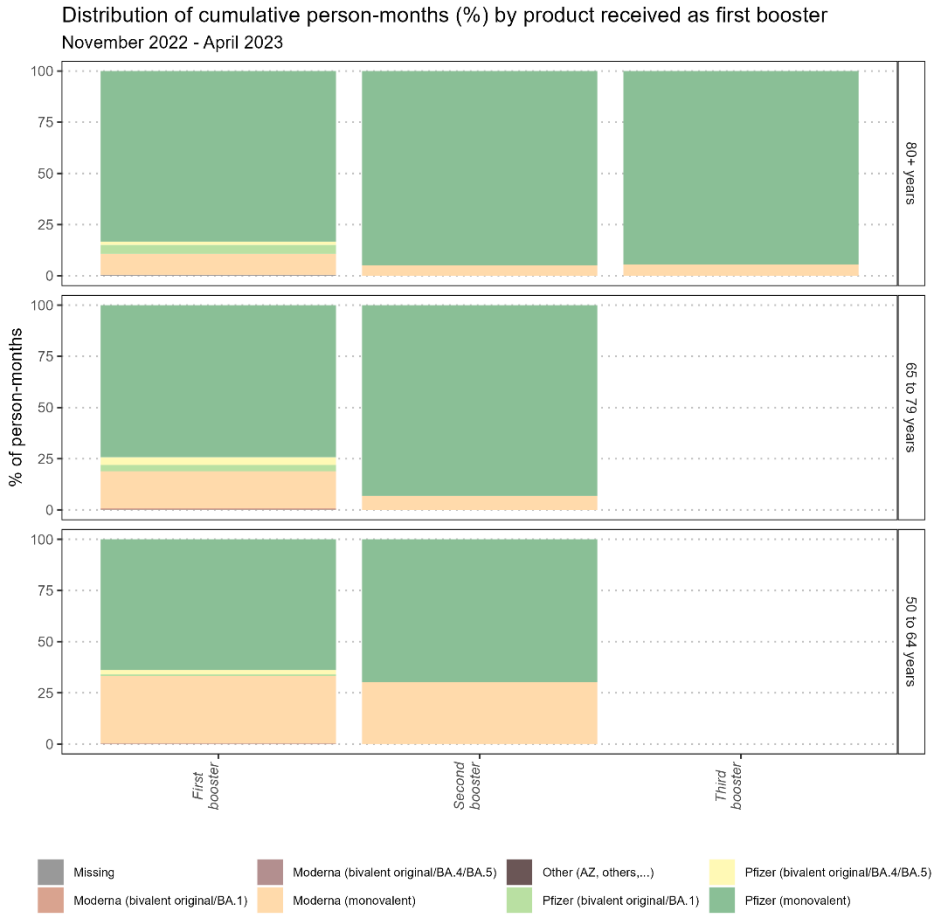
Age group	Study period	Primary vaccination without booster ≥24 weeks		Complete vaccination + booster 1		Complete vaccination + booster 2		Complete vaccination + booster 3	
		N	Events/ person-month	N	Events/ person-month	N	Events/ person-month	N	Events/ person-month
≥ 80	Apr–May 2022	58,361	175/ 96 037	1 017 584	1397/ 1 848 699	0	<5/0	0	<5/0
	May–Jun 2022	65 577	222/ 102 836	1 031 854	1480/ 1 636 612	0	<5/0	0	<5/0
	Jun–Jul 2022	63 671	177/ 101 232	883 489	923/ 1 277 984	341 905	247/ 425 607	0	<5/0
	Jul–Aug 2022	63 625	96/ 109 291	740 744	600/ 1 276 266	408 209	227/ 658 215	0	<5/0
	Aug–Sep 2022	62 265	59/ 108 984	696 778	320/ 1 153 938	488 519	190/ 729 420	0	<5/0
	Sep–Oct 2022	60 265	55/ 98 519	607 410	268/ 785 472	579 689	174/ 660 644	0	<5/0
	Oct–Nov 2022	52 839	51/ 90 233	452 513	228/ 464 819	501 043	179/ 610 239	259 940	121/ 391 152
	Nov–Dec 2022	60 673	71/ 106 489	214 422	234/ 311 223	609 353	361/ 1 024 948	271 444	189/ 466 658
	Dec–Jan 2023	45 237	56/ 80 635	173 649	215/ 296 415	616 554	407/ 1 105 306	274 649	194/ 491 982
	Jan–Feb 2023	44 358	38/ 80 031	157 107	120/ 280 495	634 207	244/ 1 154 609	275 085	157/ 498 276
	Feb–Mar 2023	43 763	28/ 78 768	153 944	101/ 278 936	605 338	201/ 1 108 911	273 851	186/ 497 952
65–79	Apr–May 2022	138 587	70/ 224 508	1 841 200	377/ 3 357 694	0	<5/0	0	<5/0
	May–Jun 2022	175 656	76/ 263 982	2 660 119	499/ 4 913 682	0	<5/0	0	<5/0
	Jun–Jul 2022	191 889	59/ 303 450	2 619 538	173/ 2 910 279	0	<5/0	0	<5/0
	Jul–Aug 2022	204 930	41/ 356 594	2 773 095	323/ 5 091 730	0	<5/0	0	<5/0
	Aug–Sep 2022	205 096	25/ 370 298	2 765 211	244/ 4 941 744	260 763	12/ 196 709	0	<5/0
	Sep–Oct 2022	202 968	23/ 345 006	2 699 610	243/ 3 968 103	0	<5/0	0	<5/0
	Oct–Nov 2022	191 550	25/ 298 826	2 035 729	169/ 1 922 702	1 541 106	60/ 1 443 320	0	<5/0
	Nov–Dec 2022	204 585	45/	1 069 168	166/	2 180 996	132/	0	<5/0

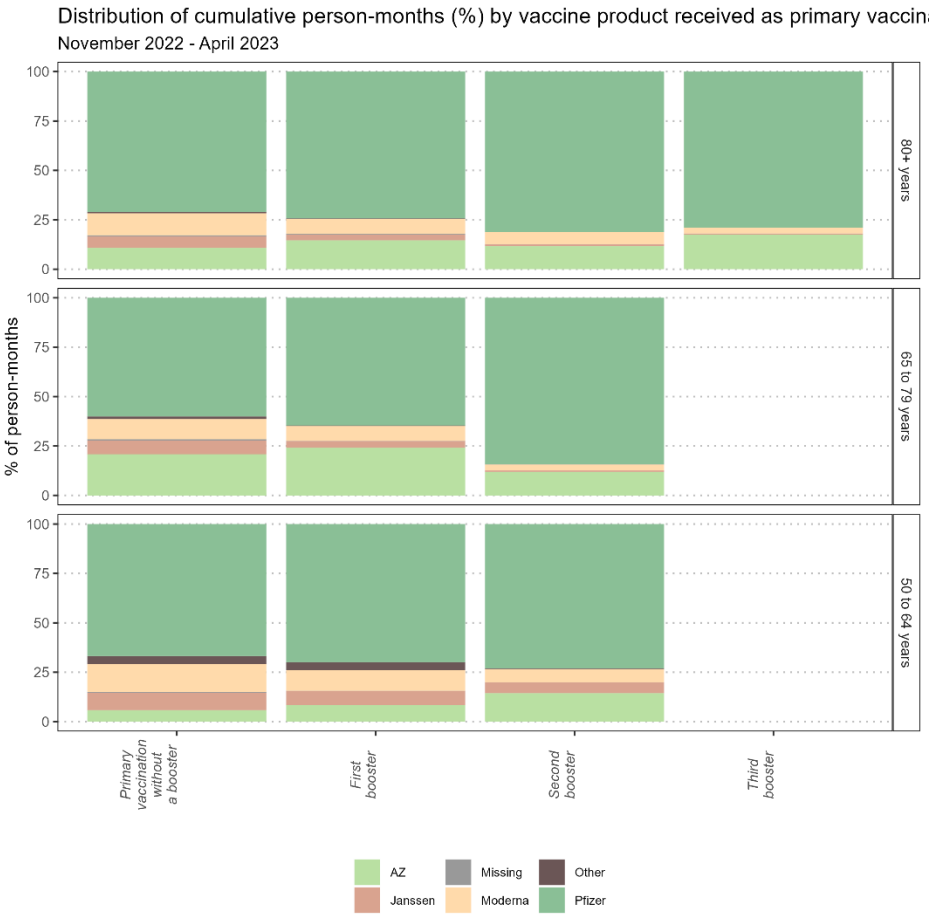
Age group	Study period	Primary vaccination without booster ≥24 weeks		Complete vaccination + booster 1		Complete vaccination + booster 2		Complete vaccination + booster 3	
		N	Events/ person-month	N	Events/ person-month	N	Events/ person-month	N	Events/ person-month
			344 948		1 344 492		3 563 394		
	Dec–Jan 2023	133 866	37/ 238 631	691 136	141/ 1 151 654	2 220 645	146/ 4 003 248	0	<5/0
	Jan–Feb 2023	135 655	20/ 246 031	629 352	89/ 1 119 866	2 239 174	117/ 4 097 215	0	<5/0
	Feb–Mar 2023	132 140	18/ 240 651	612 194	75/ 1 111 962	2 243 426	119/ 4 124 350	0	<5/0
50–64	Apr–May 2022	327 750	8/ 565 383	2 098 543	19/ 3 838 848	0	<5/0	0	<5/0
	May–Jun 2022	344 451	8/ 584 101	2 104 957	15/ 3 864 131	0	<5/0	0	<5/0
	Jun–Jul 2022	358 093	4/ 610 379	906 491	13/ 1 672 935	0	<5/0	0	<5/0
	Jul–Aug 2022	669 900	12/ 1 151 030	2 247 438	34/ 4 157 885	0	<5/0	0	<5/0
	Aug–Sep 2022	664 092	12/ 1 206 551	2 251 885	30/ 4 171 008	0	<5/0	0	<5/0
	Sep–Oct 2022	659 605	15/ 1 187 926	2 251 285	34/ 3 847 105	0	<5/0	0	<5/0
	Oct–Nov 2022	652 814	8/ 1 172 401	2 223 597	26/ 3 194 991	0	<5/0	0	<5/0
	Nov–Dec 2022	653 950	14/ 1 144 119	2 422 428	40/ 3 658 08	1 230 727	16/ 1 514 380	0	<5/0
	Dec–Jan 2023	442 413	9/ 762 314	1 280 902	21/ 1 874 517	651 283	12/ 1 186 664	0	<5/0
	Jan–Feb 2023	414 110	9/ 753 878	1 008 597	22/ 1 798 689	1 359 441	12/ 2 466 746	0	<5/0
	Feb–Mar 2022	401 625	8/ 734 269	722 184	11/ 1 303 684	711 253	8/ 1 288 753	0	<5/0

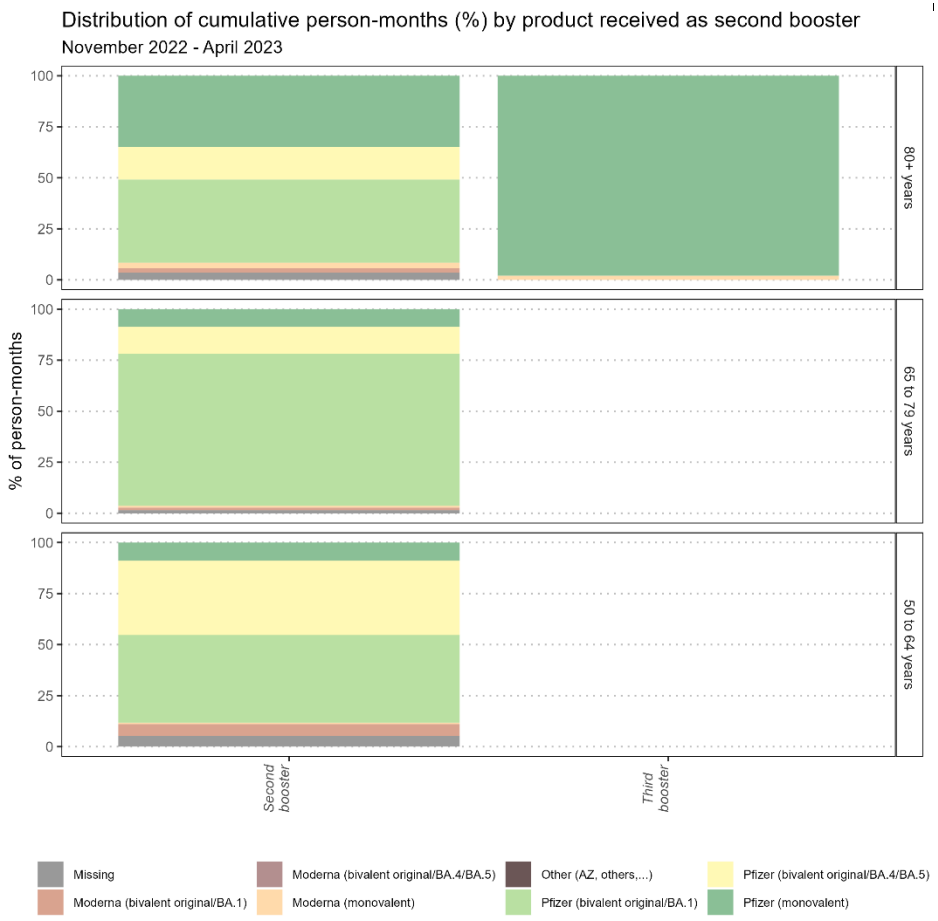
Appendix 4. Distribution of person-months in the study by covariates, from November 2022* to March 2023

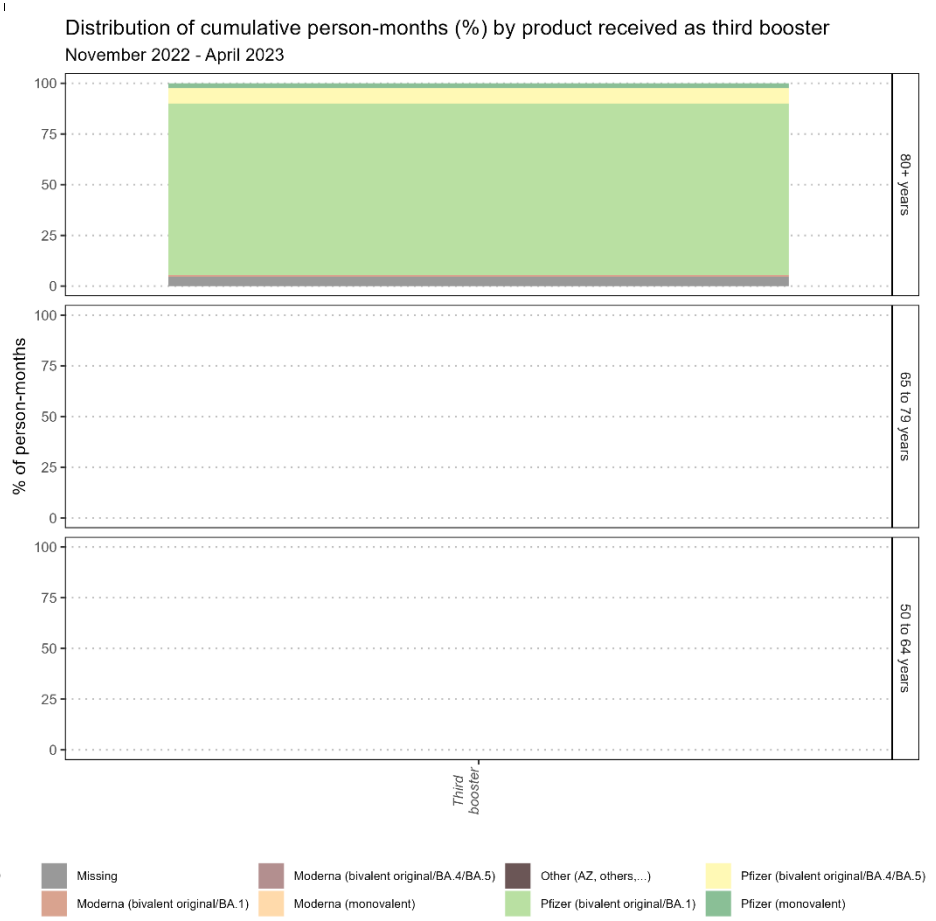





Distribution of cumulative person-months (%) by product received as first booster
November 2022 - April 2023
% of person-months
100
75
50
25
0
80+ years
65 to 79 years
50 to 64 years
First booster
Second booster
Third booster
Missing
Moderna (bivalent original/BA.1)
Moderna (bivalent original/BA.4/BA.5)
Moderna (monovalent)
Other (AZ, others,...)
Pfizer (bivalent original/BA.1)
Pfizer (bivalent original/BA.4/BA.5)
Pfizer (monovalent)


Distribution of cumulative person-months (%) by vaccine product received as primary vaccin
November 2022 - April 2023
% of person-months
100
75
50
25
0
80+ years
65 to 79 years
50 to 64 years
Primary vaccination without a booster
First booster
Second booster
Third booster
AZ
Janssen
Missing
Moderna
Other
Pfizer





**Information collected for all participating study sites from November 2022 onward.*

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