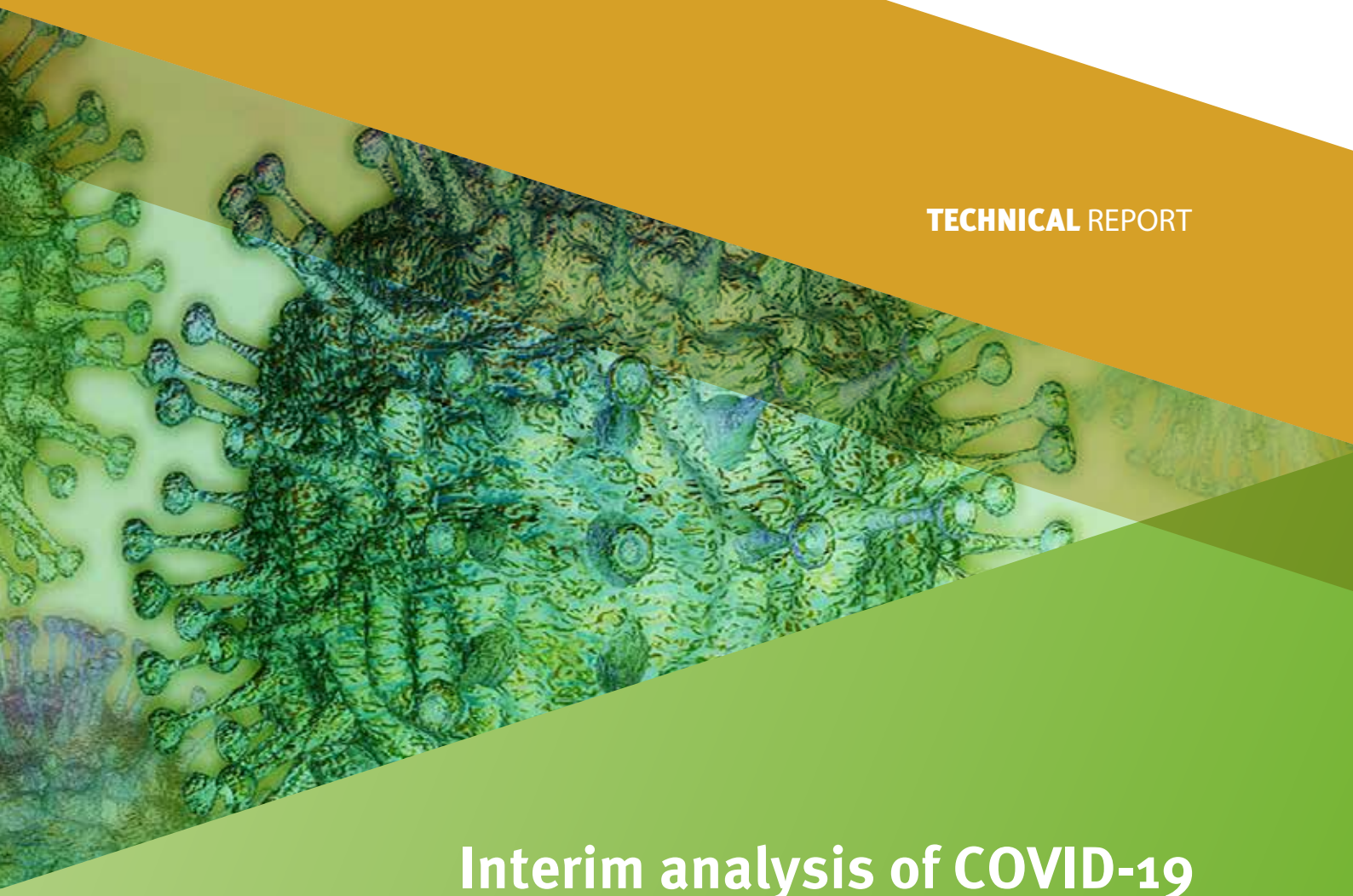

TECHNICAL REPORT

Interim analysis of COVID-19 vaccine effectiveness against hospitalisation due to COVID-19 and death using electronic health records in eight European countries: first update

April 2022 to July 2023

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This technical report was commissioned by the European Centre for Disease Prevention and Control (ECDC), as part of the activities within Framework Contract (FWC) ECDC/2021/018 'Vaccine Effectiveness, Burden and Impact Studies (VEBIS) of COVID-19 and Influenza Lot 4'. The report's production was coordinated by Nathalie Nicolay.

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Contents

Abbreviations

EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
EHR	Electronic health records
EU	European Union
SARI	Severe acute respiratory infection
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
VE	Vaccine effectiveness
VMP	Vaccine monitoring platform
rVE	Relative vaccine effectiveness
VEBIS	Vaccine Effectiveness, Burden and Impact Studies

Summary

- This report presents pooled COVID-19 vaccine effectiveness (VE) estimates for the first, second and third booster doses (compared to complete primary vaccination with no booster) against hospitalisation due to COVID-19 and COVID-19-related death in resident populations ≥50 years of age living in the community in up to eight European countries: Belgium, Denmark, Italy, Luxembourg, Spain (Navarra), Norway, Portugal, and the Netherlands.
- This study was undertaken within the Vaccine Effectiveness, Burden and Impact Studies (VEBIS) project.
- Compared to the previous report, this analysis uses the same methodology, extends the study period by four month (up to July 2023) and includes two additional countries.
- The study period covered in this report is April 2022 to July 2023. The relative VE of the first, second and third booster dose were estimated compared to the effectiveness of complete primary vaccination received at least 24 weeks ago (≥24 weeks).
- The number of countries included in the monitoring system varied throughout the observation period, with study sites/countries joining or leaving at different times. In addition, the contribution of each site/country to the different VE estimates depends on the specific roll-out of successive COVID-19 vaccine booster doses by age group and at different calendar periods.
- Compared to complete primary vaccination, the **first booster** dose rVE against hospitalisation due to COVID-19 was mostly ≤50% between April 2022 and July 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 June and July 2023, the first booster (mostly administered >24 weeks) showed little to no added protection, with rVE ranging between 6% and 27% 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 55–76% against hospitalisation due to COVID-19 and to 63–85% against COVID-19-related death. RVE also waned with time, falling to ≤50% after 24 weeks. In the most recent estimate (June and July 2023), rVE of the second booster ranged between -36 and 31% against hospitalisation and between -12 and 29% against mortality ≥24 weeks after administration.
- Compared to complete primary vaccination, rVE of the **third booster** (administrated from October 2022 onward in ≥80 years and from November 2022 onwards in ≥65 years) against hospitalisation due to COVID-19 was 72% shortly after administration (<12 weeks) in ≥80-year-olds but waned rapidly, being low or null 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). In ≥80 years, overall rVE against mortality was 64% initially (<12 weeks after administration) and waned rapidly thereafter (mostly <50% or even with negative point estimates ≥12 weeks after administration with large confidence intervals). VE was null for both outcomes in all age groups as of June–July 2023.
- The updated results presented in this report suggest that that vaccination with successive booster doses was important for restoring individual protection against COVID-19 hospitalisation in the context of waning VE. As of July 2023, most of the relative benefit (i.e. the additional protective effect of a vaccine booster) has waned, particularly in individuals ≥80 years, while some low residual relative protection was still observed in the 65–79-year-olds for those who received a first or second booster. Although there is uncertainty about the timing and the magnitude of the waning of 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 aged ≥80 years, as they have an increased risk of severe outcomes.
- 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. From the perspective of the methods to assess and monitor vaccine effectiveness, a strategy focused on the effectiveness of the last 'seasonal' dose regardless of previous boosters is probably more appropriate for future analyses.

Scope of this document

This document reports the results of long-term prospective monitoring of COVID-19 vaccine effectiveness (VE) using a multi-country approach based on established electronic health records (EHR) databases in eight participating countries.

From October 2021 to July 2023, the project began with a proof-of-concept relating to the usage of EHR in four countries, followed by pilot and prospective monitoring phases in the eventual eight participating 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 (rVE) of booster doses was estimated using as reference the individuals with complete primary vaccination ≥24 weeks ago without a booster. Since the rVE estimates presented in this report measure the additional protective effect of a vaccine booster dose, estimates are often lower than those of absolute VE reported elsewhere in the literature. RVE estimates were calculated overall and by time since the last dose. The study period runs between April 2022 and July 2023.

Table 1. Successive steps in the implementation of the study

Project stage	Study period	Study sites	Study outcome	Age groups (years)	Reference
Proof of concept	Oct 2021 to Mar 2022	Denmark, Navarra (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 2022 to Apr 2022	Denmark, Navarra (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 2022 to Jul 2022	Denmark, Navarra (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 2022 to Nov 2022	Belgium, Denmark, Luxembourg, Navarra (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 2022 to Dec 2022	Belgium, Denmark, Luxembourg, Navarra (Spain), Norway, Portugal, the Netherlands	Relative and additional VE against hospitalisation and mortality, overall and by time since the booster	≥80 65–79 50–64	Master protocol [1]
	Dec 2022 to Feb 2023	Belgium, Denmark, Luxembourg, Navarra (Spain), Norway, Portugal, the Netherlands, Italy			
	Feb 2023 to Jul 2023	Belgium, Denmark, Navarra (Spain), Norway, Portugal, the Netherlands, Italy			

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 Europe Region (WHO Euro), including 2 955 770 deaths [3].

As of July 2023, eight vaccine products were granted marketing 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); and 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 [6–8]. Some of these activities are being implemented as part of the Vaccine Monitoring Platform (VMP), 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 VMP. It encompasses various effectiveness studies implemented in different settings and populations and using different data sources: VE of COVID-19 and influenza vaccines against severe acute respiratory infections in hospital settings, VE of COVID-19 and influenza vaccines against mild diseases in primary care settings and VE of COVID-19 vaccines 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. 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, Navarra (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 [1,911], with the further addition of the Netherlands and Italy (Table 1). In this report, VE estimates under monitoring during this later monitoring period are presented. Specifically, this includes estimates of rVE of booster doses (relative VE compared to individuals with complete primary vaccination ≥24 weeks ago 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 rVE 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 rVE of first, second or third booster dose was estimated compared to individuals with COVID-19 primary vaccination administered ≥ 24 weeks ago without a subsequent booster.

Secondary objective

To measure COVID-19 rVE by time since the first, second, or third booster dose 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. Comparison of the risk of severe outcomes (hospitalisation due to COVID-19 and COVID-19-related death) was carried out between individuals with different vaccination status.

Study setting

The study was carried out in eight EU/EEA countries: Belgium, Denmark, Italy, Luxembourg, Spain (Navarra), the Netherlands, Norway, and Portugal, representing close to 51 million people aged ≥50 years. COVID-19 epidemiology and roll-out of COVID-19 vaccines have been heterogeneous across the eight countries (Table 2).

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

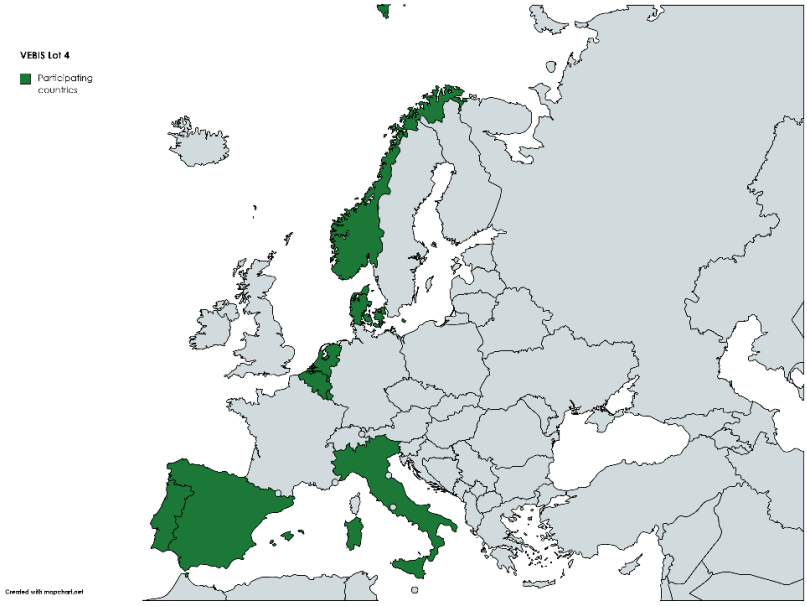


Table 2. Uptake (%) of complete vaccination with the primary series of COVID-19 vaccine*, first, second and third booster dose in participating EU/EEA countries, as of week 39, 2023**

Country	≥60 years
Belgium	98.2/92.6/71.0/14.6
Denmark	100.0/98.1/87/2.5
Italy	94/93.1/31.6/2.8
Luxembourg	91.2/85.4/49.5/0.7
The Netherlands	90.3/85.7/55.9/47
Norway	97.5/92.9/61***/12.4
Portugal	99.0/98.8/75.4/14.1
Spain	96.7/92.9/61.6/0.4
Median EU/EEA	**91.2/84.9/35.6/4**

*Source: ECDC Vaccine Tracker, age groups reflecting the ones reported in this data source [4]. *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. *** Only recommended in those ≥65 years.*

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 eight study sites for the identification of outcome variables and vaccination status. The full list of data sources used in the study is provided in Annex 1.

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

Study variable	Study site							
	Belgium	Denmark	Italy	Luxembourg	The Netherlands	Norway	Portugal	Navarra (Spain)
Hospital admission due to COVID-19	Clinical Hospital Survey database	Danish National Patient Register (DNPR)	National Integrated COVID-19 Surveillance Databases	Epidemiological national surveillance platform (MSINF) to collect daily data from hospitals	National Intensive Care Evaluation (NICE) COVID-19 database	Norwegian Intensive Care and Pandemic Registry (NIPaR)	National Hospital Discharge database (BIMH)	Enhanced COVID-19 surveillance with individual revision of events
COVID-19-related death	Not available	MiBA and Danish Civil Registration system (CPR)	National Integrated COVID-19 Surveillance Databases	MSINF + death certificate for death happened outside hospital or nursing home	Not available in near real-time	Norwegian Death Registry (DÅR)	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
Vaccination status	National vaccine registry (VACCINNET)	Danish Vaccination Registry (DVR)	National Vaccination Registry	MSVAC: National vaccination registry	COVID-vaccination Information and Monitoring System (CIMS)	The National Immunisation Register (SYSVAK)	The National Vaccination Register (VACINAS)	Vaccination register

Study period

RVE estimates were produced each month between July 2022 and September 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 rVE 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 the study period and data extraction was applied for data consolidation. The study observation period presented in this report runs from April 2022 to July 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 periods:

- Resident in any of the participating EU/EEA countries at the beginning of each study period.
- Aged between 50 and 110 years at the beginning of each study period.
- Not living in a nursing home (if available, and according to last data update).
- First vaccine dose received at a time when it was recommended for the corresponding age group (i.e. excluding individuals vaccinated before starting period of recommendation was in place for a target age group or, alternatively, for those countries with no clearly defined recommended start date by age, excluding 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.
- Did not have inconsistent or missing data on vaccination (vaccination status unknown, any vaccination date unknown, any vaccine brand unknown, number of doses unknown, interval between first and second dose shorter than 19 days, interval between complete vaccination and booster dose or between booster doses shorter than 90 days, number of doses higher than recommended, received any vaccine brand not approved by EMA, or the combination of vaccine brands not resulting in a schedule recommended by national public health authorities.

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 have been administered ≥19 days apart. Individuals became 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 rVE 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 & <24 weeks (85 to 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 rVE 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 were 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 the cause of death is not available,
  - death with laboratory-confirmed SARS-CoV-2 infection in the previous 30 days after the positive test.

For each outcome, the censoring date of 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 for age (in five-year categories) and sex and, when appropriate, some 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 variables are pre-coded in the established database, the definition for variables and categories was heterogeneous across study sites (Annex 2).

Previous SARS-CoV-2 infection

Previous infection was classified at the beginning of each study period in 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

- 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 behaviours

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 COVID-19.
- Medium risk comorbidities (for example, comorbidities that are associated with the 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 follow-up period were censored (as free of the event) from 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 the outcome as previously defined;
- Death of 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. Relative vaccine effectiveness was defined as rVE = (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 (Annex 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-effects approach using the Paule-Mantel method was used. This acknowledges the possibility that VE can differ across the 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 of events

Between April 2022 and July 2023, the number of vaccinated individuals included in the analysis across each study period varied widely: between 0.5 to 4.1 million individuals with complete primary vaccination series ≥24 weeks ago without booster, between 3.1 to 20.9 million individuals completely vaccinated with a first booster, between no individual vaccinated to 12.5 million individuals completely vaccinated with a second booster, and between no individual vaccinated and 2.7 million completely vaccinated with a third booster. Around 72 900 hospitalisations due to COVID-19 and 14 300 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 administered first in the spring of 2022 in those aged ≥80 years in Belgium, Italy, Luxembourg, and Portugal and in those aged ≥60 years in the Netherlands. This group was followed by 65–79-year-olds in the summer (Italy) or the autumn (Belgium and Portugal) of 2022, or by a recommendation for all ages (the Netherlands). The third booster dose was then deployed in October–November 2022 for ≥80-year-olds in the four countries, and in the group 65–79 years in Italy and the Netherlands. In the rest of the countries contributing to this study, the second booster was recommended initially in ≥65-year-olds from July 2022 onwards in Norway, with the roll-out starting with the oldest age groups, and in ≥80-year-olds from September (Denmark) or October (Navarra, Spain) 2022 onwards. Later, Norway recommended a third booster in ≥75-year-olds in March 2023, while Denmark and Spain have only included this recommendation for ≥80-year-olds in the autumn of 2023. Most countries have also recommended booster doses for specific groups at increased risk of severe outcomes, outside of the targeted age groups at each point in time.

The specific number of individuals, 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 and tables for the mortality outcome are provided in Annex 3.

Figure 2. Distribution (%) of study participants' vaccination status by number of booster doses received for each eight-week study period and by age group, April 2022 to July 2023

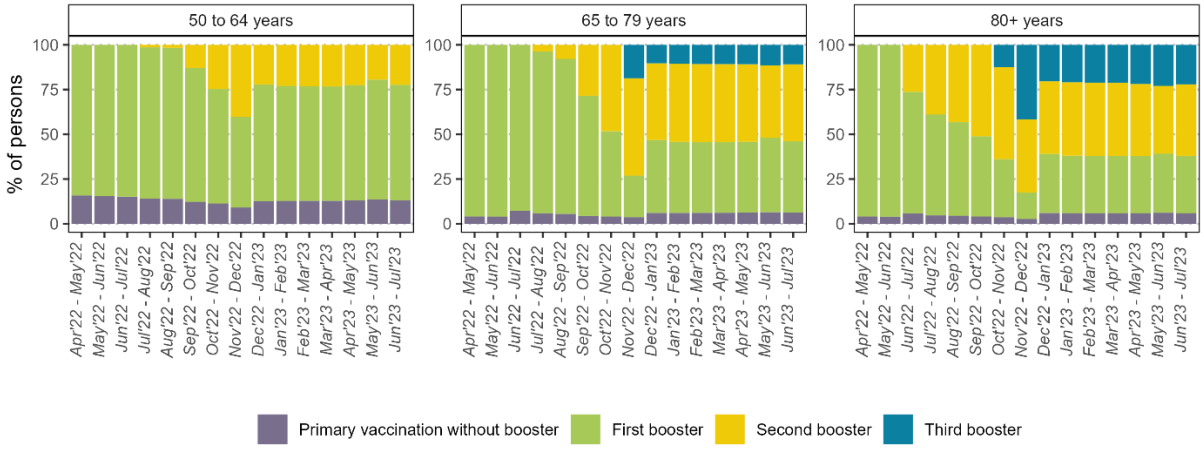


Table 4. Number of individuals, number of hospitalisations due to COVID-19, and person-months across each eight-week period in ≥80-year-olds, April 2022 to July 2023

Study period	Primary vaccination ≥24 weeks ago without a booster		Primary vaccination + fist booster dose		Primary vaccination + two booster doses		Primary vaccination + three booster doses	
	N	Events/ person-month	N	Events/ person-month	N	Events/ person-month	N	Events/ person-month
Apr to May 2022	58 016	177/ 95 455	1 016 780	1 762/ 1 843 384	0	<5/0	–	–
May to Jun 22	65 186	198/ 102 147	1 030 897	1 618/ 1 634 301	0	<5/0	–	–
Jun to Jul 2022	63 274	167/ 100 502	882 438	1 578/ 1 275 533	341 905	123/ 425 531	–	–
Jul to Aug 2022	90 479	117/ 82 641	1 173 513	2 052/ 2 018 185	866 535	584/ 1 408 781	–	–
Aug to Sep 2022	89 173	98/ 158 606	1 091 489	1 178/ 1 847 555	1 252 549	454/ 1 532 594	–	–
Sep to Oct 22	86 627	89/ 145 605	983 180	833/ 1 353 738	1 542 721	478/ 1 467 698	–	–
Oct to 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 to Dec 2022	83 704	200/ 146 444	427 355	764/ 653 291	1 026 198	1 167/ 1 697 867	927 661	648/ 1 600 878
Dec 2022 to Jan 2023	465 170	876/ 836 935	2 333 019	5 440/ 4 081 593	2 550 422	5 009/ 4 375 521	1 114 830	1 016/ 1 902 532
Jan to Feb 2023	462 487	462/ 836 927	2 256 514	2 841/ 4 029 290	2 582 067	2 761/ 4 586 400	1 173 244	1 016/ 2 078 505
Feb to Mar 2023	459 347	355/ 833 012	2 197 866	2 158/ 3 982 995	2 535 418	2 579/ 4 584 882	1 185 525	1 450/ 2 132 358
Mar to Apr 2023	458 333	383/ 832 028	2 186 666	2 212/ 3 977 836	2 517 378	2 864/ 4 584 096	1 185 721	1 305/ 2 152 304
Apr to May 2023	457 664	302/ 831 339	2 182 943	1 756/ 3 974 305	2 493 103	2 234/ 4 520 088	1 227 272	697/ 2 188 324
May to Jun 2023	454 035	137/ 825 216	2 072 663	847/ 3 769 324	1 982 081	941/ 3 559 457	984 723	322/ 1 766 726
Jun to Jul 2023	456 016	79/ 829 390	2 076 542	419/ 3 780 071	2 193 302	490/ 3 996 201	965 713	179/ 1 748 257

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–July 2023

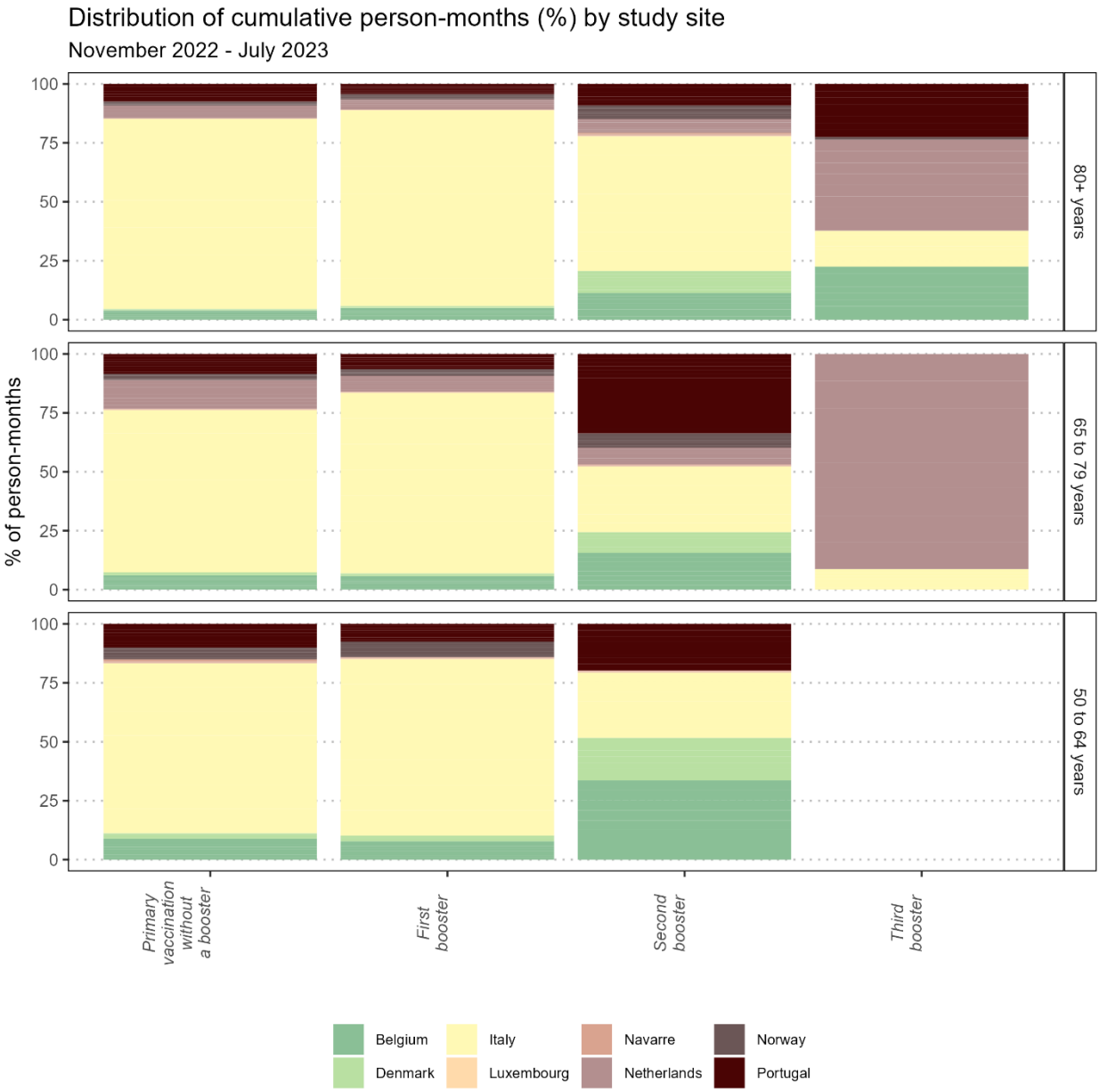
Study period	Primary vaccination ≥24 weeks ago without a booster		Primary vaccination + first booster dose		Primary vaccination + two booster doses		Primary vaccination + three booster doses	
	N	Events/ person-month	N	Events/ person-month	N	Events/ person-month	N	Events/ person-month
Apr 22 to May 22	141 891	115/ 230 175	2 723 031	920/ 4 971 604	-	-	-	-
May 22 to Jun 22	179 002	110/ 269 620	2 739 833	511/ 3 074 645	-	-	-	-
Jun 22 to Jul 22	195 234	99/ 309 256	2 698 656	1 282/ 4 935 561	-	-	-	-
Jul 22 to Aug 22	294 656	153/ 522 712	5 028 270	1 938/ 8 989 085	64 628	72/ 50 411	-	-
Aug 22 to Sep 22	295 807	102/ 538 691	4 897 957	1 153/ 8 806 671	260 009	68/ 195 897	-	-
Sep 22 to Oct 22	294 073	73/ 510 312	4 701 721	919/ 6 742 351	414 516	71/ 528 062	-	-
Oct 22 to Nov 22	281 165	75/ 460 744	3 323 770	524/ 3 752 227	3 550 638	214/ 4599274	-	-
Nov 22 to Dec 22	336 699	250/ 574 012	1 911 093	754/ 2 742 833	4 024 273	998/ 6 643 666	1 202 681	375/ 1 995 982
Dec 22 to Jan 23	1 116 297	747/ 2 015 488	6 860 521	4 213/ 1 2026 519	6 318 413	2 720/ 11 025 786	1 353 163	547/ 2 304 388
Jan 23 to Feb 23	1 117 472	476/ 2 031 916	6 587 984	2 297/ 11 801 443	6 417 000	1 687/ 11 479 756	1 408 441	534/ 2 457 090
Feb 23 to Mar 23	1 112 174	399/ 2 030 489	6 429 926	1 969/ 11 704 199	6 364 831	1 752/ 11 609 407	1 422 228	781/ 2 539 261
Mar 23 to Apr 23	1 116 291	368/ 2 039 725	6 402 563	1 889/ 11 703 573	6 348 105	1 863/ 11 641 729	1 426 943	697/ 2 567 173
Apr 23 to May 23	1 118 440	255/ 2 043 974	6 373 563	1 515/ 11 665 286	6 266 592	1 420/ 11 476 071	1 424 150	335/ 2 569 717
May 23 to Jun 23	1 107 982	128/ 2 025 876	6 283 390	799/ 11 499 953	5 461 271	602/ 9 960 057	1 423 789	152/ 2 571 486
Jun 23 to Jul 23	1 108 402	61/ 2 027 847	5 974 550	327/ 10 929 614	4 315 180	295/ 7 881 074	1 365 863	64/ 2 469 075

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–July 2023

Study period	Primary vaccination ≥24 weeks ago without a booster		Primary vaccination + first booster dose		Primary vaccination + two booster doses	
	N	Events/ person-month	N	Events/ person-month	N	Events/ person-month
Apr to May 2022	349 395	23/ 602 279	2 193 694	153/ 4 007 754	-	-
May to Jun 2022	368 291	25/ 626 713	2 201 324	96/ 4 032 618	-	-
Jun to Jul 2022	384 505	35/ 651 450	2 207 773	246/ 4 038 609	-	-
Jul to Aug 2022	974 768	74/ 1 711 719	7 072 855	480/ 11 352 815	-	-
Aug to Sep 2022	970 151	54/ 1 774 164	6 156 025	312/ 11 180 657	-	-
Sep to Oct 2022	966 106	42/ 1 753 990	6 159 876	276/ 10 516 016	-	-
Oct to Nov 2022	961 917	30/ 1 739 865	5 563 895	189/ 8 485 806	2 130 793	26/ 2 418 882
Nov to Dec 2022	689 169	65/ 1 205 770	3 293 661	207/ 5 226 832	2 463 925	137/ 3 662 514
Dec 2022 to Jan 2023	2 535 595	360/ 4 584 567	11 681 499	1575/ 20 626 765	3 608 723	387/ 6 081 053
Jan to Feb 2023	2 524 998	206/ 4 618 834	10 575 239	886/ 19 221 185	3 477 150	229/ 5 995 826
Feb to Mar 2023	2 500 939	165/ 4 584 383	11 021 285	727/ 20 174 161	3 587 431	252/ 6 578 466
Mar to Apr 2023	2 494 101	164/ 4 576 502	10 957 328	705/ 20 095 261	3 581 200	246/ 6 600 424
Apr to May 2023	2 516 701	138/ 4 619 306	10 966 215	612/ 20 126 473	3 455 344	191/ 6 383 611
May to Jun 2023	2 463 493	70/ 4 520 223	9 927 882	354/ 18 190 417	2 796 317	88/ 5 156 777
Jun to Jul 2023	2 471 549	35/ 4 536 536	9 938 765	166/ 18 214 102	1 721 060	37/ 3 152 996

Due to the timing of booster vaccination roll-out differing across participating countries, the relative contribution of each study site differed by vaccination status (Figure 3). For example, third booster rVE estimates were only based on data from the Netherlands and Italy in the group 65 to 79 years, plus Belgium and Portugal for the group ≥80 years.

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



A description of the characteristics of the study population was only available from November 2022 onwards (month where these descriptive data had to be reported by all participating countries). **As the number of vaccine doses increased so did the share of individuals with medium and high-risk comorbidities, in accordance with the preferential vaccination of these groups** (Annex 4). A series of figures in Annex 4 show the cumulative proportion of person-months throughout the study period by vaccine product according to the vaccination status at the time of the study. Pfizer vaccine products were the most administered for primary vaccination doses, followed by AstraZeneca and Moderna products. First booster doses were monovalent (Wuhan-based) Pfizer and Moderna vaccines, with a negligible 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 second booster dose including monovalent (spring 2022) and bivalent (including Wuhan and Omicron BA.1 or BA.4/5 mRNA) products (autumn 2022). Interestingly, for those contributing to the study within the third booster group, 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 later on, 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.

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

First booster

Between April 2022 and July 2023, the rVE of the first booster fluctuated, from about 50% to lower values in all age groups (Tables 7-9; Figure 4, green symbols) with rVE declining over calendar 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 dropped even more at ≥24 weeks. Between June 2022 and July 2023, a first booster showed little to no added protection at least 24 weeks after its administration compared to complete primary vaccination only, with rVE reaching down to 15% (95% CI: -38; 48) in ≥80-year-olds, 27% (95% CI: 4; 44) in 65–79-year-olds, and 6% (95% CI: -38; 36) in 50–64-year-olds at the end of the study period. Sporadic rVE estimates for a first booster <12 weeks during 2023 correspond to few people vaccinated late with a first booster and are difficult to interpret.

Second booster

The rVE of a second booster (compared to complete primary vaccination ≥24 weeks ago with no booster) was high shortly after administration, reaching 72% (95% CI: 62; 80) in ≥80-year-olds and 76% (95% CI: 68; 82) in 65–79-year-olds, in November–December 2022 and 55% (95% CI: 37; 67) 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) and then 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 (June–July 2023), the rVE of the second booster administered ≥24 weeks ago was 16% (95% CI: -26; 44) in ≥80-year-olds, 31% (95% CI: 3; 50) in 65–79-year-olds and -36% (95% CI: -133; 20) in those aged 50–64 years.

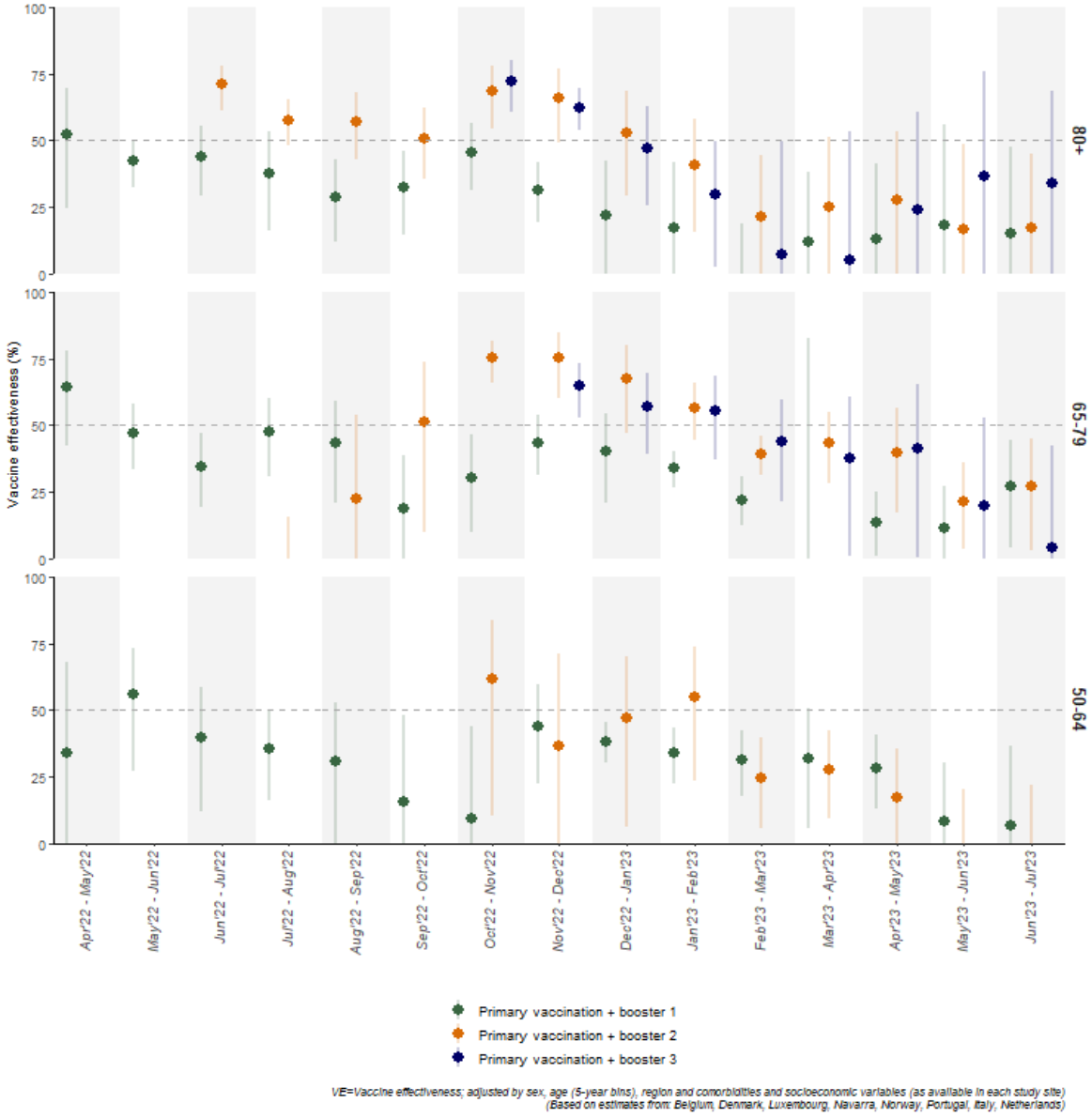
Third booster

The rVE of a third booster administered during autumn 2022 could only be estimated in those groups who received the second booster vaccination during the spring 2022 campaign in Belgium, Italy, Portugal, and the Netherlands, following the roll-out of the campaign in each country. The rVE of the third booster (compared to complete primary vaccination ≥24 weeks ago with no booster) in October–November 2022 reached 72% (95% CI: 61; 80) in ≥80-year-olds, 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 low or null beyond 12 weeks of administration (Figure 5). In the last period available (June–July 2023), the rVE of the third booster administered ≥24 weeks ago was 16% (95% CI: -42; 50) in ≥80-year-olds and 6% (95% CI: -71; 49) in 65–79-year-olds. Third booster doses were not recommended in 50–64-year-olds during the observation period for this analysis.

Sensitivity analysis

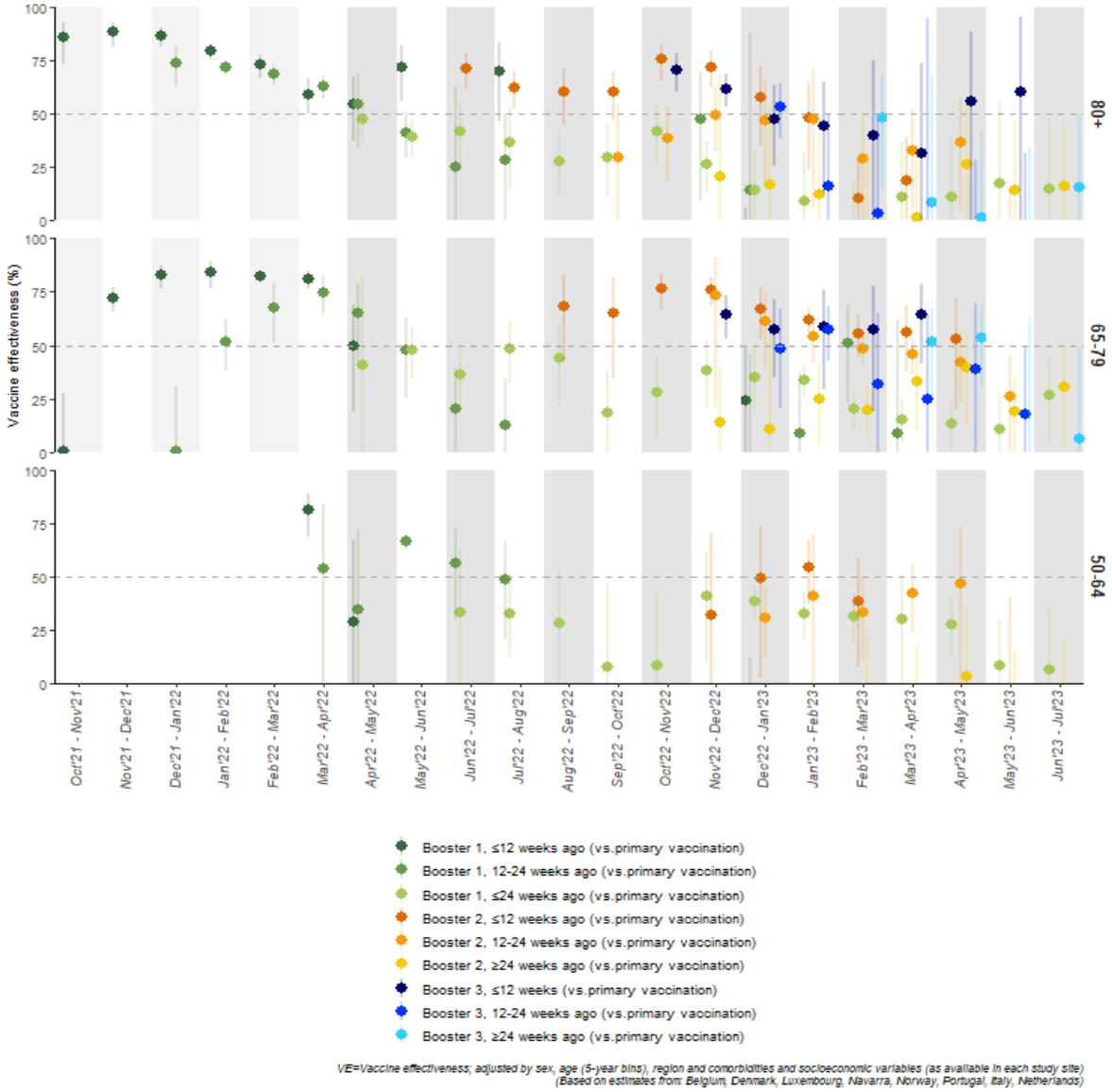
An alternative analysis was performed, restricting to the six sites that have contributed during most of the study period (Annex 5). Most of the results and conclusions remain unchanged. The most notable difference is that a moderate protection against hospitalisation was estimated for the second booster ≥24 weeks ago in the group aged ≥80 years by June–July 2023.

Figure 4. Relative* vaccine effectiveness (95% confidence intervals) against hospitalisation due to COVID-19 of first, second and third booster dose between April 2022 and July 2023



** Relative vaccine effectiveness of first, second and third booster dose compared to complete primary vaccination series without booster administered ≥24 weeks ago.*

Figure 5. Relative* vaccine effectiveness (95% confidence intervals) against hospitalisation due to COVID-19 of the first, second and third booster dose by time since the booster between April 2022 and July 2023



** Relative vaccine effectiveness of first, second and third booster dose compared to complete primary vaccination series without booster administered ≥24 weeks ago.*

Table 7. Relative* vaccine effectiveness (95% confidence intervals) in those aged ≥80 years against hospitalisation due to COVID-19 of the first, second and third booster dose between April 2022 and July 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	>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	31.6% (19.5; 41.9)	-	47.2% (8.9; 69.4)	26.4% (13.5; 37.3)	65.9% (49.1; 77.2)	72.1% (62.1; 79.5)	49.2% (31.9; 62.1)	20.9% (-100.5; 68.8)	62.4% (53.7; 69.4)	61.8% (53; 69)	-	-
December 1 2022 to January 25 2023	22.1% (-5.1; 42.4)	-38.6% (-103.7; 5.7)	14.4% (-502.1; 87.8)	14.0% (-10.2; 32.9)	52.8% (29.1; 68.6)	57.6% (35.1; 72.3)	47.0% (17.5; 66)	16.8% (-48.8; 53.4)	47.3% (25.7; 62.6)	47.7% (25.7; 63.2)	53.0% (38.4; 64.2)	-
January 1 to February 25 2023	17.4% (-17.3; 41.9)	-	-79.4% (-178.9; -15.4)	9.0% (-23.5; 32.9)	40.6% (15.6; 58.2)	48.2% (24.1; 64.6)	47.9% (5.1; 71.4)	12.2% (-29.3; 40.4)	30.0% (2.4; 49.8)	44.5% (13; 64.7)	16.2% (-39.2; 49.5)	-
February 1 to March 28 2023	-4.8% (-35.1; 18.7)	-	-	-8.0% (-42.4; 18.2)	21.6% (-11; 44.6)	10.7% (-11.7; 28.6)	28.8% (-2; 50.2)	-2.5% (-55.4; 32.4)	7.5% (-70.8; 49.9)	40.1% (-45.1; 75.3)	3.5% (-76.9; 47.4)	48.2% (14; 68.8)
March 1 to April 25 2023	11.9% (-25.1; 38)	-	-81.7% (-206.1; -7.8)	10.9% (-27; 37.5)	25.0% (-15.5; 51.3)	19.1% (-8.1; 39.4)	32.9% (4.6; 52.8)	1.2% (-52.8; 36.2)	5.0% (-93.4; 53.4)	31.4% (-80.9; 74)	-1042.7% (-Inf; 94.8)	8.8% (-153.2; 67.1)
April 1 to May 26 2023	13.1% (-28.6; 41.3)	-	-165.8% (-341.8; -59.9)	11.3% (-30.8; 39.9)	27.8% (-12.2; 53.5)	-	36.4% (4.4; 57.7)	26.3% (-16.8; 53.4)	24.2% (-45.8; 60.6)	56.2% (-64; 88.3)	-0.8% (-42.2; 28.5)	1.5% (-67.3; 42.1)

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	>24 weeks
May 1 to June 25 2023	18.3% (-52.3; 56.1)	-	-	17.6% (-53.4; 55.7)	16.6% (-34.8; 48.4)	-	-16.4% (-57.5; 14)	14.4% (-38.7; 47.2)	36.6% (-67.9; 76)	60.2% (-237.3; 95.3)	-69.3% (-319.2; 31.6)	-8.1% (-76.6; 33.9)
June 1 to July 26 2023	14.9% (-38.1; 47.6)	-	-	14.8% (-38.4; 47.6)	17.4% (-23.9; 44.9)	-	-	16.0% (-26.2; 44	33.9% (-39; 68.6)	-	-	15.8% (-41.8; 50)

[*] *Relative vaccine effectiveness of first, second and third booster dose compared to complete primary vaccination series without booster administered ≥24 weeks ago.*

Table 8. Relative* vaccine effectiveness (95% confidence intervals) in those aged 65–79 years against hospitalisation due to COVID-19 of the first, second and third booster dose between April 2022 and July 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	>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)	75.1% (65.8; 81.8)	76.6% (66.5; 83.6)	-	-	-	-	-	-
November 1 to December 26 2022	43.5% (31.1; 53.7)	-	-	38.0% (20.3; 51.8)	75.4% (60.1; 84.8)	75.7% (68.1; 81.5)	73.4% (20.8; 91.1)	14.0% (-21.7; 39.2)	64.6% (53; 73.4)	64.6% (52.9; 73.3)	-	-
December 1 2022 to January 25 2023	40.1% (21; 54.5)	24.2% (-14.7; 49.9)	-3.3% (-97.3; 45.9)	34.9% (18; 48.3)	67.4% (46.8; 80.1)	67.1% (52.6; 77.1)	61.0% (39.1; 75)	10.9% (-76; 54.9)	57.0% (39.3; 69.5)	57.2% (35.2; 71.7)	48.5% (20.4; 66.7)	-
January 1 to February 25 2023	33.7% (26.5; 40.3)	-	8.8% (-32.4; 37.2)	33.4% (26.1; 40)	56.6% (44.5; 66.1)	62.0% (55.8; 67.4)	54.0% (41.3; 63.9)	24.8% (2.2; 42.2)	55.5% (37.1; 68.5)	58.8% (29.4; 75.9)	57.3% (42.9; 68.1)	-
February 1 to March 28 2023	22.1% (12.5; 30.7)	-	51.1% (23; 68.9)	20.2% (10.3; 29)	39.1% (31.3; 46.1)	55.6% (44.8; 64.3)	48.1% (40.1; 55.1)	19.9% (7.7; 30.5)	43.7% (21.5; 59.6)	57.5% (19.1; 77.6)	31.5% (-33.7; 64.9)	-
March 1 to April 25 2023	-271.5% (-Inf; 82.8)	-	8.8% (-119.3; 62.1)	15.3% (4.4; 24.9)	43.1% (28; 55.1)	55.8% (37.5; 68.8)	45.7% (36.4; 53.7)	32.8% (10; 49.8)	37.5% (0.8; 60.7)	64.7% (41.3; 78.8)	24.8% (-59.8; 64.6)	51.3% (26.3; 67.8)
April 1 to May 26 2023	13.7% (0.7; 25)	-	-	13.4% (0.4; 24.8)	39.8% (17; 56.3)	52.6% (19.5; 72.1)	42.1% (23.1; 56.3)	39.1% (12.7; 57.6)	41.5% (0.6; 65.6)	-	39.0% (-21.8; 69.4)	53.5% (30.4; 69)

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	>24 weeks
May 1 to June 25 2023	11.3% (-7.6; 27)	-	-	10.8% (-8.2; 26.6)	21.5% (3.7; 36)	-	25.9% (0.2; 45)	19.2% (0.6; 34.4)	19.9% (-36.2; 52.8)	-	17.5% (-34.7; 49.5)	-0.4% (-167.7; 62.4)
June 1 to July 26 2023	27.1% (4.2; 44.4)	-	-	26.8% (4; 44.2)	26.9% (3; 44.9)	-	-	30.6% (3.4; 50.1)	4.1% (-58.7; 42.1)	-	-	6.3% (-71.1; 48.7)

** Relative vaccine effectiveness of first, second and third booster dose compared to complete primary vaccination series without booster administered ≥24 weeks ago.*

Table 9. Relative* vaccine effectiveness (95% confidence intervals) in those aged 50-64 years against hospitalisation due to COVID-19 of the first, second and third booster dose 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)	-	-	-	-

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
October 1 to November 25 2022	9.4% (-46.9; 44.1)	-	-	8.1% (-47.3; 42.6)	61.6% (10.2; 83.6)	-	-	-
November 1 to December 26 2022	44.0% (22.1; 59.7)	-	-	40.8% (9.8; 61.2)	36.3% (-40.8; 71.2)	32.2% (-54.7; 70.3)	-	-
December 1 2022 to January 25 2023	38.2% (30.4; 45.2)	-	-39.9% (-122.4; 12.1)	38.1% (30.2; 45.1)	47.2% (6.2; 70.2)	49.0% (2.4; 73.4)	30.9% (12.1; 45.7)	-89.0% (-146.4; -45)
January 1 to February 25 2023	33.9% (22.6; 43.6)	-	-	32.8% (21.3; 42.6)	54.9% (23.2; 73.5)	54.6% (36.9; 67.4)	41.0% (-16; 70)	-38.4% (-88.3; -1.8)
February 1 to March 28 2023	31.1% (17.8; 42.3)	-	-	31.1% (17.7; 42.2)	24.5% (5.6; 39.6)	38.4% (7.7; 58.9)	33.2% (11.1; 49.9)	-4.7% (-44.2; 24)
March 1 to April 25 2023	31.8% (5.8; 50.7)	-	-	30.1% (0; 51.1)	27.7% (9.4; 42.2)	-	42.2% (23.6; 56.3)	-10.9% (-48.6; 17.2)
April 1 to May 26 2023	28.2% (13; 40.7)	-	-	27.7% (12.2; 40.5)	16.9% (-6.5; 35.2)	-	46.9% (-4.3; 73)	3.2% (-44; 35)
May 1 to June 25 2023	8.4% (-20.1; 30.2)	-	-	8.2% (-20.4; 30)	-13.0% (-59.7; 20.1)	-	-2.2% (-75.2; 40.3)	-24.7% (-83.2; 15.1)
June 1 to July 26 2023	6.7% (-36.9; 36.4)	-	-	6.1% (-37.7; 36)	-31.6% (-122; 21.9)	-	-	-36.1% (-132.5; 20.4)

[*] *Relative vaccine effectiveness of first, second and third booster dose compared to complete primary vaccination series without booster administered ≥24 weeks ago.*

Relative vaccine effectiveness of first, second and third booster against COVID-19-related death

First booster

Between April 2022 and July 2023, the overall rVE of the first booster against COVID-19 related death showed a similar range and trend to that of rVE against hospitalisation due to COVID-19, although estimates had high uncertainty, particularly in the 50–64-year-olds group (Tables 10, 11, 12, Figures 6, 7).

Second booster

The second booster dose substantially restored the protection against COVID-19-related death (Figure 7). The overall rVE (compared to complete primary vaccination ≥24 weeks ago with no booster) reached 73% (95% CI: 38; 88) in ≥80-year-olds in October–November 2022, 83% (95% CI: 68; 91) in 65–79-year-olds November–December 2022, and 63% (95% CI: 25; 82) in 50–64-year-olds in December 2022–January 2023. rVE was higher when restricting to those within the first 12 weeks of second booster administration.

In the last available period, June–July 2023, the rVE of the second booster administered ≥24 weeks ago (compared to complete primary vaccination ≥24 weeks ago with no booster), was -12% (95% CI: -579; 82) in ≥80-year-olds and 29% (95% CI: -34; 63) in 65–79-year-olds. The observed trend was similar to the one shown against hospitalisation.

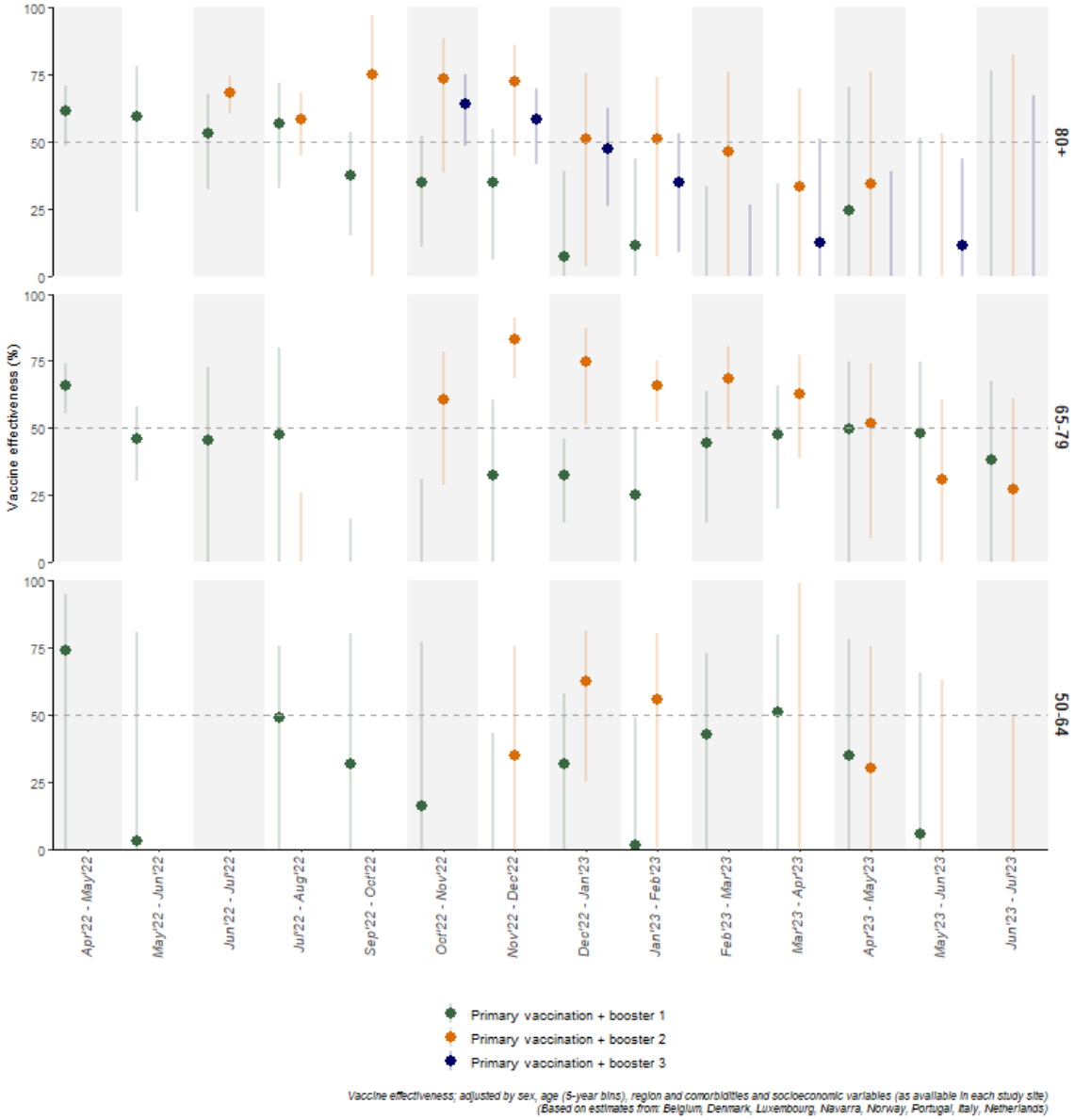
Third booster

The rVE of the third booster dose administered in the autumn 2022 in the population who had received the second booster vaccination during spring 2022, could only be consistently estimated against death in ≥80-year-olds based on data provided by Portugal (even though a third booster was recommended for population 65–79 years, there were not sufficient events to allow estimation in this group). The rVE of the third booster (compared to complete primary vaccination ≥24 weeks ago with no booster) in October–November 2022, administered less than <12 weeks after administration, was 62% (95% CI: 45; 74), similar to rVE estimates for the second booster administered simultaneously in other study sites (Figure a). The rVE of third boosters waned rapidly thereafter. In June–July 2023, the rVE of a third booster administered ≥24 weeks ago (compared to complete primary vaccination ≥24 weeks ago with no booster) was -213% (95% CI: -3242; 71), the wide confidence interval showing that it was based on a very small number of events, particularly in the reference group of people with complete primary vaccination without boosters (≥24 weeks ago).

Sensitivity analysis

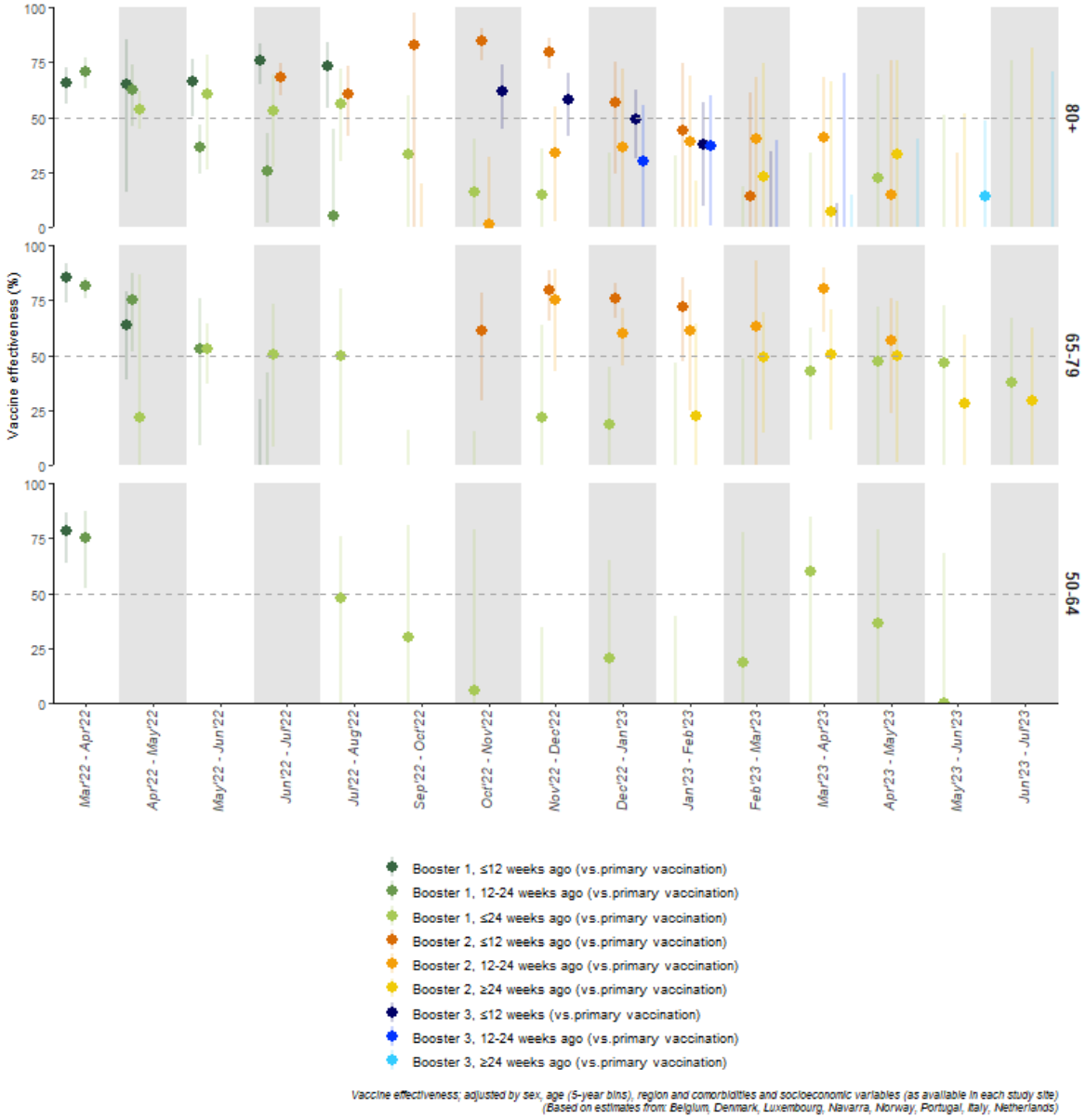
An alternative analysis was performed, restricting to the six sites that have contributed during most of the study period, with no changes in the conclusion (Annex 5).

Figure 6. Relative* vaccine effectiveness (95% confidence intervals) against COVID-19-related death of the first, second and third booster dose between April 2022 and July 2023



** Relative vaccine effectiveness of first, second and third booster dose compared to complete primary vaccination series without booster administered ≥24 weeks ago.*

Figure 7. Relative* vaccine effectiveness (95% confidence intervals) against COVID-19-related death of the first, second and third booster dose by time since the booster between April 2022 and July 2023



** Relative vaccine effectiveness of first, second and third booster dose compared to complete primary vaccination series without booster administered ≥24 weeks ago.*

Table 10. Relative* vaccine effectiveness (95% confidence intervals) in ≥80 years against COVID-19-related death of the first, second and third booster dose between April 2022 and July 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	>24 weeks
April 1 to May 26 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 June 25 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 July 26 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 August 25 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 September 25 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 October 26 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 November 25 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 December 26 2022	34.6% (5.8; 54.5)	-	-	15.0% (-12.8; 35.9)	72.1% (44.5; 86)	79.9% (71.7; 85.7)	33.5% (2.8; 54.6)	-	58.0% (41.6; 69.8)	58.0% (41.1; 70.1)	-	-
December 1 2022 to January 25 2023	7.0% (-41; 38 .7)	-	-90.3% (-219.1; -13.5)	-3.3% (-61.5; 33.9)	51.2% (3.3; 75.4)	56.7% (24.1; 75.3)	36.0% (-44.9; 71.8)	-26.8% (-52; -5.7)	47.4% (26; 62.6)	49.1% (31.4; 62.3)	30.0% (-10.7; 55.7)	-
January 1 to February 25 2023	11.0% (-39.8; 43.4)	-	-	-2.6% (-55.3; 32.2)	51.0% (7.1; 74.1)	43.7% (-23.1; 74.2)	39.0% (-19.7; 69)	-11.8% (-57.9; 20.9)	34.6% (8.9; 53)	37.4% (9.3; 56.8)	37.0% (0.4; 60.2)	-
February 1 to March 28 2023	-5.7% (-67.8; 33.4)	-	-	-16.2% (-65.1; 18.2)	46.3% (-19.5; 75.9)	14.0% (-88.6; 60.8)	40.1% (-13.5; 68.4)	23.1% (-131.1; 74.4)	-5.5% (-51.5; 26.5)	-20.4% (-120.8; 34.4)	-25.2% (-160.5; 39.8)	-
March 1 to April 25 2023	-3.3% (-62.2; 34.2)	-	-	-7.4% (-74.4; 33.9)	33.1% (-47; 69.5)	-	41.0% (-9.2; 68.1)	7.0% (-154; 66)	12.1% (-56.6; 50.7)	-100.4% (-350.2; 10.8)	-14.4% (-338.3; 70.2)	-99.0% (-364.9; 14.8)

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	>24 weeks
April 1 to May 26 2023	24.3% (-93.4; 70.4)	-	-	22.6% (-95.6; 69.4)	34.1% (-82; 76.2)	-	14.7% (-204; 76.1)	33.3% (-81.9; 75.5)	-4.2% (-77.9; 39)	-	-	-61.3% (-333.5; 40
May 1 to June 25 2023	-11.9% (-158.5; 51.6)	-	-	-12.5% (-159.5; 51.2)	-10.6% (-159.5; 52.8)	-	-42.1% (-205.3; 33.9)	-13.7% (-167.5; 51.7)	11.1% (-39.7; 43.4)	-	-	14.0% (-42.6; 48.1)
June 1 to July 26 2023	-30.8% (-625.6; 76.4)	-	-	-32.2% (-622.7; 75.8)	-8.8% (-574.2; 82.4)	-	-	-11.8% (-579.1; 81.6)	-172.8% (-2170.8; 67.2)	-	-	-213.4% (-3242.4; 70.6)

[*] *Relative vaccine effectiveness of first, second and third booster dose compared to complete primary vaccination series without booster administered ≥24 weeks ago.*

Table 11. Relative[*] vaccine effectiveness (95% confidence intervals) in those aged 65–79 years against COVID-19-related death of the first, second and third booster dose, April 2022 and July 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	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 June 25 2022	45.8% (30.3; 57.9)	-	52.9% (9; 75.6)	52.7% (36.7; 64.6)	-	-	-	-
June 1 to July 26 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 August 25 2022	47.5% (-37.9; 80)	-	-110.0% (-282.7; -15.2)	49.8% (-26.6; 80.1)	-	-	-	-
August 1 to September 25 2022	27.2% (-215.3; 83.2)	-	-	27.3% (-206.3; 82.8)	-	-	-	-
September 1 to October 26 2022	-33.0% (-111.8; 16.5)	-	-	-34.0% (-114; 16.1)	-	-	-	-

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
October 1 to November 25 2022	-8.5% (-69.6; 30.6)	-	-	-34.2% (-112.6; 15.3)	60.6% (28.8; 78.2)	61.0% (29.3; 78.5)	-	-
November 1 to December 26 2022	32.2% (-16.3; 60.5)	-	-	21.9% (-68.5; 63.8)	82.9% (68.3; 90.8)	79.9% (65.6; 88.3)	75.2% (42.5; 89.3)	-
December 1 2022 to January 25 2023	32.3% (14.9; 46.1)	-	-	18.3% (-20.6; 44.6)	74.9% (51.1; 87.1)	76.0% (66.9; 82.6)	60.2% (45.2; 71)	-49.2% (-121.1; -0.6)
January 1 to February 25 2023	25.2% (-13.8; 50.8)	-	-	-11.3% (-130.3; 46.2)	65.6% (52.5; 75.1)	72.0% (47.2; 85.2)	61.0% (25.1; 79.7)	22.1% (-69.9; 64.3)
February 1 to March 28 2023	44.4% (14.6; 63.8)	-	-	-26.7% (-209.9; 48.2)	68.7% (49.8; 80.4)	-	62.9% (-89; 92.7)	49.0% (14.6; 69.5)
March 1 to April 25 2023	47.7% (19.8; 65.9)	-	-	42.5% (11.4; 62.7)	62.9% (38.7; 77.6)	-	80.2% (60.4; 90.1)	50.2% (16.1; 70.5)
April 1 to May 26 2023	49.7% (0.2; 74.7)	-	-	47.1% (-0.9; 72.3)	51.5% (9; 74.2)	-	57.0% (23.3; 75.9)	49.9% (1.1; 74.7)
May 1 to June 25 2023	48.0% (-6; 74.5)	-	-	46.8% (-3; 72.5)	30.6% (-22.2; 60.6)	-	-	28.0% (-27.1; 59.2)
June 1 to July 26 2023	38.1% (-16.7; 67.1)	-	-	37.4% (-18.5; 66.9)	27.3% (-36.9; 61.4)	-	-	29.1% (-34.1; 62.5)

** Relative vaccine effectiveness of first, second and third booster dose compared to complete primary vaccination series without booster administered ≥24 weeks ago.*

Table 12. Relative* vaccine effectiveness (95% confidence intervals) in those aged 50–64 years against COVID-19-related death of the first, second and third booster dose, April 2022 and July 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	73.8% (-31.6; 94.8)	-	-	-	-	-	-	-
May 1 to June 25 2022	3.2% (-387.9; 80.8)	-	-	-	-	-	-	-
June 1 to July 26 2022	-	-	-	-	-	-	-	-
July 1 to August 25 2022	48.8% (-7.9; 75.7)	-	-	48.0% (-11.2; 75.7)	-	-	-	-
August 1 to September 25 2022	-14.8% (-588.8; 80.9)	-	-	-17.6% (-637.1; 81.2)	-	-	-	-
September 1 to October 26 2022	31.8% (-137.1; 80.4)	-	-	30.0% (-153.4; 80.7)	-	-	-	-
October 1 to November 25 2022	16.0% (-206; 76.9)	-	-	5.6% (-324.4; 79)	-	-	-	-
November 1 to December 26 2022	-17.2% (-141.3; 43.1)	-	-	-36.4% (-183.3; 34.3)	34.6% (-74; 75.5)	-	-	-
December 1 2022 to January 25 2023	31.5% (-10.8; 57.7)	-	-	20.4% (-80.8; 64.9)	62.7% (24.7; 81.5)	-	-	-
January 1 to February 25 2023	1.2% (-90; 48.7)	-	-	-20.1% (-137.4; 39.2)	55.6% (0.2; 80.3)	-	-	-
February 1 to March 28 2023	42.9% (-19.8; 72.8)	-	-	18.6% (-195.9; 77.6)	-	-	-	-

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
March 1 to April 25 2023	51.2% (-18.8; 80)	-	-	59.8% (-6.7; 84.9)	-1898.6% (-Inf; 98.9)	-	-	-
April 1 to May 26 2023	34.8% (-96.7; 78.4)	-	-	36.1% (-96.4; 79.2)	30.2% (-98.8; 75.5)	-	-	-
May 1 to June 25 2023	5.6% (-157.8; 65.4)	-	-	0.0% (-215.4; 68.3)	-7.4% (-210.1; 62.8)	-	-	-
June 1 to July 26 2023	-	-	-	-	-86.0% (-587.9; 49.7)	-	-	-

** Relative vaccine effectiveness of first, second and third booster dose compared to complete primary vaccination series without booster administered ≥24 weeks ago.*

Main findings

In this study, after April 2022, which was about six months after the first booster vaccination campaign that took place in most countries in the autumn of 2021, the additional protection conferred by this 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 less than 50% and showed little or no additional protection as of July 2023.

The second and third boosters each increased rVE to >70% compared to only primary vaccination in the groups ≥65 years (55% in the group 50–64 years), shortly after the booster administration. 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 Belgium, Italy, Portugal, and the Netherlands, 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. However, their effect also waned rapidly to low or null. The only groups where protection was still significant as of July 2023 (only against hospitalisation) are among individuals 65–79 years with a first or a second booster dose (compared to complete primary vaccination without boosters) and, in a sensitivity analysis restricted to the six sites that contributed throughout the whole study period, among individuals ≥80 years with a second booster dose.

These differences (with residual protection estimated first or second booster but not for third booster) probably reflect the uncontrolled selection of different populations accepting the successive booster doses, rather than true differences in the effectiveness of different boosters or in different age groups. The higher proportion of individuals with comorbidities among those with a third booster, the lower uptake in people with past infection, particularly if recent, and vaccination of individuals in the comparison group during the vaccination campaigns may explain the more rapid decrease and lower magnitude of rVE for the third boosters. Further analyses focusing on the additional VE regardless of number of doses have been planned for the upcoming season.

Challenges, limitations

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 to monitor less frequent events by pooling results from several countries, also achieving good comparability across participating sites. Nonetheless, the number of events was sometimes too low to provide estimates with good precision. This occurred for rVE against COVID-19-related death in younger age groups or when using as reference group individuals with complete primary vaccination only, particularly among those aged ≥80 years, due to the high uptake of boosters in this age group in the participating countries.

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 to analyse an observation period covering the time from three days up to one month before the time of data analysis. In the current epidemiological context, with a reduced number of events captured during the pre-defined eight-week observation periods, longer observation times may be needed to be able to reach precise estimates of rVE. Moreover, less frequent estimates (i.e. less than monthly) may be acceptable and timely enough to guide decision-making, suggesting the need to re-evaluate the monitoring strategy.

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 used to target vulnerable groups for vaccination, allowing them to 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 over time, which can make interpretation complex, but is also an opportunity to compare the effectiveness of vaccine doses across countries with different vaccine roll-out calendars (i.e. second and third booster campaigns deployed simultaneously in different countries). Finally, the heterogeneity between sites may be related to factors not captured in this study such as different local SARS-CoV-2 epidemiology and/or different control measures in place.

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

The different roll-outs of COVID-19 vaccine boosters in the different participating countries needs to be taken into account 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 dose was only administered to people with a second booster during the previous spring vaccination campaign in the countries that implemented it, thus representing different populations, with higher probability to accept repeated boosters. These results suggest 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 probably that the time since vaccination is more relevant to protection against COVID-19 than the number of doses.

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, having less benefit from hybrid immunity [12]. On the other hand, the reference group for the rVE estimations are those with a previous vaccination ≥24 weeks ago with no boosters, who may correspond more likely to individuals with no comorbidities and low self-perceived risk, or who have had SARS-CoV-2 infections post-vaccination and decided (or were recommended by national vaccination policies) to postpone booster vaccination. Changing in SARS-CoV-2 local testing recommendations and the increase in the use of self-tests that are not captured in EHR is likely to have resulted in previous infection probably being highly misclassified, and adjustment for this variable probably incomplete. In addition, adjustment by post-vaccination infection may bring additional methodological challenges [13,14].

All the above limitations could result in the underestimation of rVE and partially explain the low residual benefit from previous booster doses as well as the lower and more rapid waning of effectiveness of the third booster dose, which was only administered to population who opted for a second booster in the spring and a third dose later in the autumn in Belgium, Italy, the Netherlands, and Portugal. Nevertheless, it is also plausible that a lower rVE 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 [15].

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 death [15,16]. However, rVE point estimates declined over time, particularly for the third booster dose, which was only administered to the population ≥65 years in Italy and the Netherlands and to population ≥80 years in Belgium and Portugal. Although there is uncertainty about the timing and the magnitude of the waning of 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, as they have an increased risk of severe outcomes.

References

1. European Centre for Disease Prevention and Control (ECDC). Protocol for a COVID-19 vaccine effectiveness study using health data registries: version 1.0. Stockholm: ECDC; 2023. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-vacine-effectivenessvebis-study-health-registries-data.pdf
2. European Centre for Disease Prevention and Control (ECDC). Pilot protocol for a COVID-19 vaccine effectiveness study using health data registries: version 1.0. Stockholm: ECDC; 2022. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/Pilot%20protocol%20for%20a%20COVID-19%20vaccine%20effectiveness%20study%20using%20routinely%20collected%20vaccination%20status.pdf
3. World Health Organization European Region (WHO Euro). COVID-19 situation in the WHO European Region [cited 2023 Jun 19]. Available at: https://www.arcgis.com/apps/dashboards/ead3c6475654481ca51c248d52ab9c61
4. European Centre for Disease Prevention and Control (ECDC). COVID-19 Vaccine Tracker [cited 19 Jun 2023]. Available at: https://vaccinetracker.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#uptake-tab
5. European Medicines Agency. COVID-19 Vaccines [cited 2023 Jun 19]. Available at: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-authorised#authorised-covid-19-vaccines-section%0Ahttps://www.ema.europa.eu/en/human-regulato
6. EMA and ECDC join forces for enhanced post-marketing monitoring of COVID-19 vaccines in Europe. Press release 2022. Available at: https://www.ecdc.europa.eu/en/news-events/ema-and-ecdc-join-forces-enhanced-post-marketing-monitoring-covid-19-vaccines-europe
7. COUNCIL RECOMMENDATION of 7 December 2018 on strengthened cooperation against vaccine-preventable diseases (2018/C466/01) Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018H1228(01)
8. REGULATION (EU) 2022/2370 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 23 November 2022 amending Regulation (EC) No 851/2004 establishing a European centre for disease prevention and control Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32022R2370&qid=1670582843806&from=EN
9. Kislaya I, Sentís A, Starrfelt J, Nunes B, Martínez-Baz I, Nielsen KF, AlKerwi A, Braeye T, Fontán-Vela M, Bacci S, Meijerink H, Castilla J, Emborg HD, Hansen CH, Schmitz S, Van Evercooren I, Valenciano M, Nardone A, Nicolay N, Monge S; VEBIS-Lot4 working group. Monitoring COVID-19 vaccine effectiveness against COVID-19 hospitalisation and death using electronic health registries in ≥65 years old population in six European countries, October 2021 to November 2022. Influenza Other Respir Viruses. 2023 Nov;17(11):e13195.
10. Sentís A, Kislaya I, Nicolay N, Meijerink H, Starrfelt J, Martínez-Baz I, Castilla J, Nielsen KF, Hansen CH, Emborg HD, Nardone A, Derrough T, Valenciano M, Nunes B, Monge S; VEBIS-Lot4 working group. Estimation of COVID-19 vaccine effectiveness against hospitalisation in individuals aged ≥ 65 years using electronic health registries; a pilot study in four EU/EEA countries, October 2021 to March 2022. Euro Surveill. 2022 Jul;27(30):2200551.
11. European Centre for Disease Prevention and Control (ECDC). Interim analysis of COVID-19 vaccine effectiveness against hospitalisation and death using electronic health records in six European countries. Stockholm: ECDC; 2023. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/COVID-19-vaccine-effectiveness-hospitalisation.pdf
12. Bobrovitz N, Ware H, Ma X, et al. Protective effectiveness of previous SARS-CoV-2 infection and hybrid immunity against the omicron variant and severe disease: a systematic review and meta-regression. Lancet Infect Dis. 2023;23(5):556-567.
13. Monge S, Pastor-Barriuso R, Hernán MA. The imprinting effect of covid-19 vaccines: an expected selection bias in observational studies. BMJ. 2023 Jun 7;e074404.
14. Hernán MA, Monge S. Selection bias due to conditioning on a collider. BMJ. 2023 Jun 7;p1135.
15. Uraki R, Ito M, Furusawa Y, Yamayoshi S, Iwatsuki-Horimoto K, Adachi E, et al. Humoral immune evasion of the omicron subvariants BQ.1.1 and XBB. The Lancet Infectious Diseases. 2023 Jan;23(1):30–2.
16. De Gier B, van Asten L, Boere TM, et al. Effect of COVID-19 vaccination on mortality by COVID-19 and on mortality by other causes, the Netherlands, January 2021-January 2022. Vaccine. 2023;41(31):4488-4496.

Annex 1. Data sources used in the eight study sites to extract the study variables

Type of variables	Study variable	Study site							
		Belgium	Denmark	Italy	Luxembourg	Navarra (Spain)	The Netherlands	Norway*	Portugal
Outcomes	Hospital admission due to COVID-19	Clinical Hospital Survey database	Danish National Patient Register (DNPR)	National Integrated COVID-19 Surveillance Databases	Epidemiological national surveillance platform (MSINF) to collect daily data from hospitals	Enhanced COVID surveillance with individual revision of events	NICE COVID-19 registration	Norwegian Intensive Care and Pandemic Registry (NIPaR)	National Hospital Discharge database (BIMH)
	Death due to COVID-19	NA	MiBA and Danish Civil Registration System (CPR)	National Integrated COVID-19 Surveillance Databases	Idem + death certificate for death happened outside hospital or nursing home	Administrative database of deaths and individual revision of events	NA	Norwegian Death Registry (DÅR)	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.
Exposures	Vaccination status	National vaccine registry (VACCINNET)	Danish Vaccination Registry (DVR)	National Vaccination Registry	MSVAC: National vaccination registry	Vaccination register	COVID-19 vaccination registry (CIMS)	The National Immunisation Register (SYSVAK)	The National Vaccination Register (VACINAS)
Variables for adjustment or stratification	Age	The national population register	CPR	National Vaccination Registry	Statutory health insurance database	Administrative database	The national population register	The National Population Register (Folkeregisteret)	National Health Service User databaset (NHSU)
	Sex	national population register	CPR	National Vaccination Registry	Statutory health insurance database	Administrative database	The national population register	The National Population Register (Folkeregisteret)	National Health Service User databaset (NHSU)
	Health Region	Province of residence: national population register	CPR	Region where vaccination took place	Statutory health insurance database	Not applicable	NA	County of residence at end of study period: The National Population Register (Folkeregisteret)	Region of residence: National Health Service User databaset (NHSU)

Type of variables	Study variable	Study site							
		Belgium	Denmark	Italy	Luxembourg	Navarra (Spain)	The Netherlands	Norway*	Portugal
				National Vaccination Registry					
	Comorbidities	Intermutualistic Agency database	DNPR	National Vaccination Registry	Not applicable	Primary Care Information System	Specialised health care utilisation combined with prescribed medication register, both from 2020	Risk groups / Comorbidities: Based on Norwegian Patient Registry (NPR)	Primary Care Information System (SIM@SNS).
	Previous infection	COVID-19 Laboratory test results database from Healthdata.be register	MiBA	National Integrated COVID-19 Surveillance Databases	MSINF (see above)	Previous infections are excluded, pendent of a separate analysis	NA	The Surveillance System for Infectious Diseases (MSIS)	National Information System for Epidemiologic Surveillance (BI-SINAVE)
	Others specific to the study site	Household income (according to tax records) categorised as low (lowest 40%), mid (middle 30%), and high (highest 30%): STATBEL database	NA	Country of birth National Vaccination Registry	Statutory health insurance database	Country of birth and high functional dependence: Administrative database	Months of death and emigration from population registry, LTCF residency from Central Administration Office	1. Conditions of living – Crowding: Statistics Norway (SSB). Most recent data from 2019 – separate level for missing data 2. *County of birth:* Folkeregisteret	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

NA: not applicable.
***All data in Norway were 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*

Annex 2. Methodological details in the different study sites

Variable	Definition, categorisation, use in the model							
	Belgium	Denmark	Italy	Luxembourg	The Netherlands	Navarra (Spain)	Norway	Portugal
Age	Age in years at the end of the year in which the study period begins. For adjustment: five-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 five-year categories until the final category, 90+ years	Age at the start of study period (for adjustment: five-year age groups up to 90–94 years and then grouping ≥95 years))	Age at the start of follow up, five-year categories	Age at the start of study period (five-year categories)	Age at the start of study period (five-year categories)	Age at end of 2022 (birth cohorts) (For adjustment: five-year age groups)	Age at the start of study period (five-year categories)
Comorbidities	No comorbidities associated with an increased risk for severe COVID-19 infection. At least one comorbidity which increases the risk for severe COVID-19 infection and not being immunocompromised (medium risk): - 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	Immunocompromised, including: - HIV - Immunological disease - Radiation therapy - Organ-transplanted 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	Immunocompromised, including: - Immunocompromised defects of the complement system - Other specified disorders involving the immune mechanism - Deficiency or dysfunction of a single component (C1-C9) - Deficiency of cell-mediated immunity - Deficiency of humoral immunity - Human immunodeficiency virus [HIV] disease, Human immunodeficiency virus, type 2 [HIV-2], Asymptomatic human immunodeficiency virus [HIV] infection status - Disorders involving the immune mechanism - Congenital and acquired disorders with poor antibody production - Drug-induced immunosuppression	Not included	Three-level variable (no risk, medium risk, high risk) Medium risk is defined as eligibility for influenza vaccination based on comorbid conditions. High risk is defined as comorbid conditions based on increased risk of severe covid. Methods, data and codes used are extensively described in the article by de Gier et al [16].	Immuno-compromised 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	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

Variable	Definition, categorisation, use in the model							
	Belgium	Denmark	Italy	Luxembourg	The Netherlands	Navarra (Spain)	Norway	Portugal
	- 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 years or younger - Multiple sclerosis - Thrombosis while treated with antithrombotic medicines - Thyroid disorder - HIV - 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.		Other comorbidities, including: - Respiratory diseases requiring oxygen therapy, idiopathic pulmonary fibrosis - Advanced heart failure (Classes III-IV NYHA) and post cardiogenic shock patients - Amyotrophic lateral sclerosis and other motor neuron disorders, multiple sclerosis, muscular dystrophy, infantile cerebral palsy, myasthenia gravis, dysimmune neuropathies - Type 1 diabetes, Type 2 diabetes with complications or requiring combination therapy (with at least two anti-diabetes drugs) - Addison's disease - Panhypopituitarism - Cystic fibrosis - -Cirrhosis of the liver - Intracerebral ischemic or hemorrhagic event that has led to impaired neurological and cognitive autonomy - Individuals who have had a stroke on 2020 or later ranked as level 3 or higher - Thalassemia major - Sickle cell anemia - Other severe anemias - Down syndrome - Body Mass Index >35 - Severely disabled persons pursuant to law				- Obesity with a body mass index (BMI) of ≥35 kg/m2 - Dementia - Chronic heart and vascular disease (with the exception of high blood pressure) and stroke	

Variable	Definition, categorisation, use in the model							
	Belgium	Denmark	Italy	Luxembourg	The Netherlands	Navarra (Spain)	Norway	Portugal
			104/1992 art. 3 paragraph 3 - Chronic Alcohol Misuse - Functional or anatomic asplenia - COPD - Chemotherapy or Radiotherapy - Coagulopathies - Diabetes Mellitus and other endocrinopathies - Patients in hemodialysis or with chronic kidney diseases expected to start dialysis - Hemoglobinopathy such as sickle cell anemia or thalassemia - Chronic Liver Disease - Cochlear implant - Chronic Kidney Disease - Chronic eczema or psoriasis - Diseases associated with a high risk of aspiration pneumonia - Chronic Cardiovascular Disease - Chronic Respiratory Disease - Motor neuron diseases - Chronic inflammatory diseases and malabsorption syndromes - Blood cancers (leukemia, lymphoma and myeloma) - Solid tumors - Obesity (Body Mass Index 30-35) - Bone marrow transplant - Drug Misuse - Solid organ transplant					

Variable	Definition, categorisation, use in the model							
	Belgium	Denmark	Italy	Luxembourg	The Netherlands	Navarra (Spain)	Norway	Portugal
			- Patients with CSF leak from trauma or intervention - Patients going to start immunosuppressive treatment - Metabolic diseases - Hematopoietic diseases - Pathologies that require important surgical interventions - Neurological diseases - Cerebrovascular diseases - Down Syndrome - Disabilities (physical, sensorial, learning or psychic)					
Country of residence / country of birth / nationality	Not included	Not included	Country of birth: born in Italy; born in other countries	Country of residence = administrative address in Luxembourg (as of September 2021) Country of birth = Luxembourg / Other Nationality = Citizenship Luxembourg / Other	Not included	Country of birth	As registered at time of analysis (June 2022)	Not included
Deprivation index or similar	Household income: low (lowest 40%)-medium (middle 30%)-high (highest 30%)	Not included	Not included	Not included	Not included	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	European deprivation index quintile Q1 (least deprived) to Q5 (most deprived)

Variable	Definition, categorisation, use in the model							
	Belgium	Denmark	Italy	Luxembourg	The Netherlands	Navarra (Spain)	Norway	Portugal
							met (incomplete and slightly outdated data)	
Geographic level	Province of residence	Adjustment for residency in the 5 geographical regions of Denmark (EU NUTS-2 regions)	19 regions and two autonomous provinces of Italy where vaccination took place	Canton	Not included	Not included	County of residence	Region of residence (North, Centre, Lisbon and Tagus Valley, Alentejo, Algarve)
Other vaccines uptake	Not included	Not included	Not included	Not included	Not included	Not included	Not included	Vaccination against influenza, PCV7, PCV10, PCV13 or PPV23 in the last three years
Number of COVID-19 tests in 2020-2022	Not included	Positive RT-PCR test for SARS-CoV-2	Not included	Not included	Not included	Not included	Not included	0, 1, 2, 3, 4-9, 10+

Annex 3. Numbers of individuals, COVID-19 related deaths and person-months by eight-week period, between April 2022 to July 2023, by age group

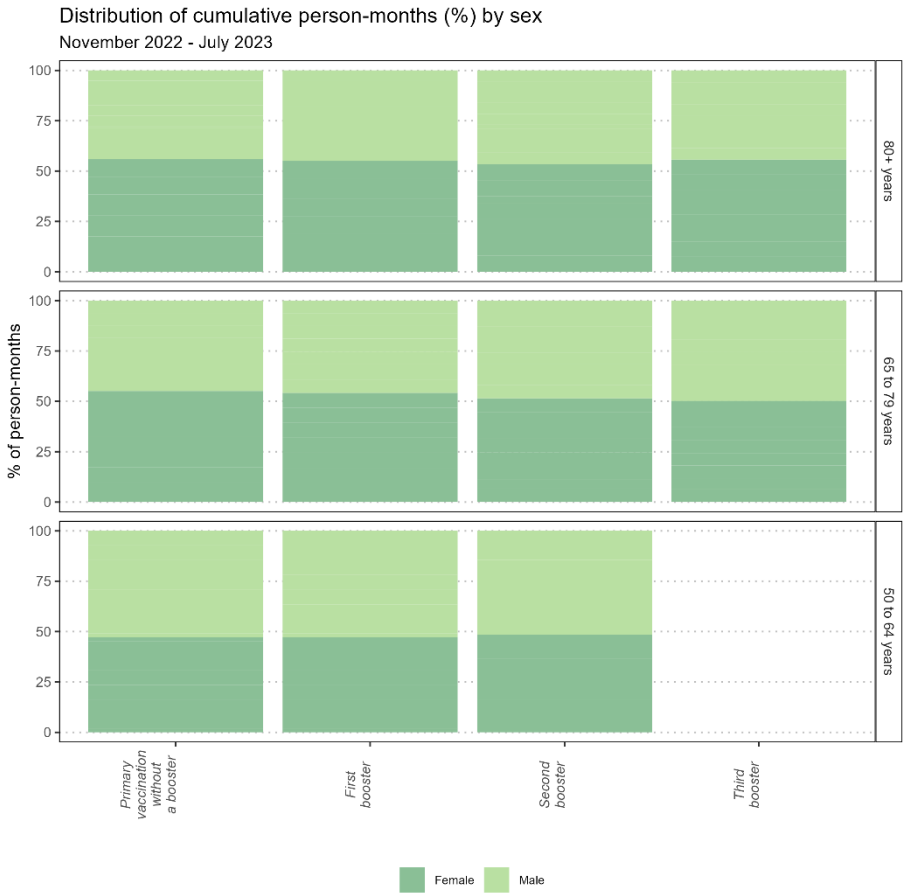
Age group	Study period	Primary vaccination without booster ≥24 weeks		Complete vaccination + first booster		Complete vaccination + two booster doses		Complete vaccination + three booster doses	
		N	Events/ person-month	N	Events/ person-month	N	Events/ person-month	N	Events/ person-month
≥ 80	Apr to May 2022	58 361	175/ 96 037	1 017 584	1 397/ 1 848 699	-	-	-	-
	May to Jun 2022	65 577	222/ 102 836	1 031 854	1 480/ 1 636 612	-	-	-	-
	Jun to Jul 2022	63 671	177/ 101 232	883 489	923/ 1 277 984	341 905	247/ 425 607	-	-
	Jul to Aug 2022	63 625	96/ 109 291	740 744	600/ 1 276 266	408 209	227/ 658 215	-	-
	Aug to Sep 22	62 265	59/ 108 984	696 778	320/ 1 153 938	488 519	190/ 729 420	-	-
	Sep to Oct 22	60 265	55/ 98 519	607 410	268/ 785 472	579 689	174/ 660 644	-	-
	Oct to Nov 22	52 839	51/ 90 233	452 513	228/ 464 819	501 043	179/ 610 239	259 940	121/ 391 152
	Nov to Dec 22	60 673	71/ 106 489	214 422	234/ 311 223	609 353	361/ 1 024 948	271 444	189/ 466 658
	Dec 22 to Jan 23	429 927	204/ 774 124	2 158 678	1 140/ 3 776 125	2 188 895	1 063/ 3 740 739	450 091	218/ 709 232
	Jan to Feb 23	424 704	109/ 768 764	2 064 013	528/ 3 682 615	2 168 881	560/ 3 839 081	481 156	180/ 823 152

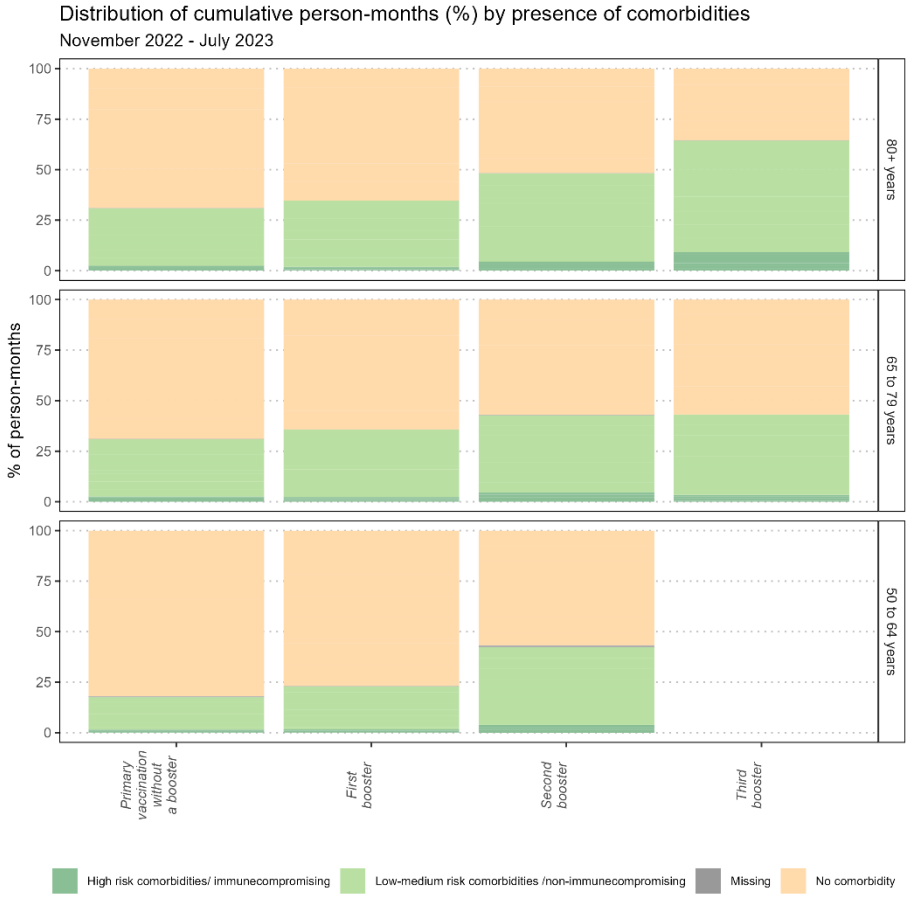
Age group	Study period	Primary vaccination without booster ≥24 weeks		Complete vaccination + first booster		Complete vaccination + two booster doses		Complete vaccination + three booster doses	
		N	Events/ person-month	N	Events/ person-month	N	Events/ person-month	N	Events/ person-month
	Feb to Mar 23	421 752	64/ 764 927	2 018 434	330/ 3 657 445	2 113 944	416/ 3 815 297	491 382	210/ 871 606
	Mar to Apr 23	420 965	52/ 764 364	2 008 943	276/ 3 654 651	2 100 556	413/ 3 816 488	493 848	188/ 890 191
	Apr to May 23	419 649	32/ 762 591	2 008 651	165/ 3 657 053	2 077 413	301/ 3 755 342	495 165	141/ 899 543
	May to Jun 23	416 699	32/ 757 364	1 989 387	155/ 3 620 456	1 827 436	217/ 3 279 901	493 433	136/ 896 559
	Jun to Jul 23	415 804	23/ 756 047	1 990 890	91/ 3 626 217	1 799 882	130/ 3 272 266	490 679	127/ 893 761
65-79	Apr to May 22	138 587	70/ 224 508	1 841 200	377/ 3 357 694	-	-	-	-
	May to Jun 22	175 656	76/ 263 982	2 660 119	499/ 4 913 682	-	-	-	-
	Jun to Jul 22	191 889	59/ 303 450	2 619 538	173/ 2 910 279	-	-	-	-
	Jul to Aug 22	204 930	41/ 356 594	2 773 095	323/ 5 091 730	-	-	-	-
	Aug to Sep 22	205 096	25/ 370 298	2 765 211	244/ 4 941 744	260 763	12/ 196 709	-	-
	Sep to Oct 22	202 968	23/ 345 006	2 699 610	243/ 3 968 103	0	<5/0	-	-
	Oct to Nov 22	191 550	25/ 298 826	2 035 729	169/ 1 922 702	1 541 106	60/ 1 443 320	-	-
	Nov to Dec 22	204 585	45/ 344 948	1 069 168	166/ 1 344 492	2 180 996	132/ 3 563 394	-	-

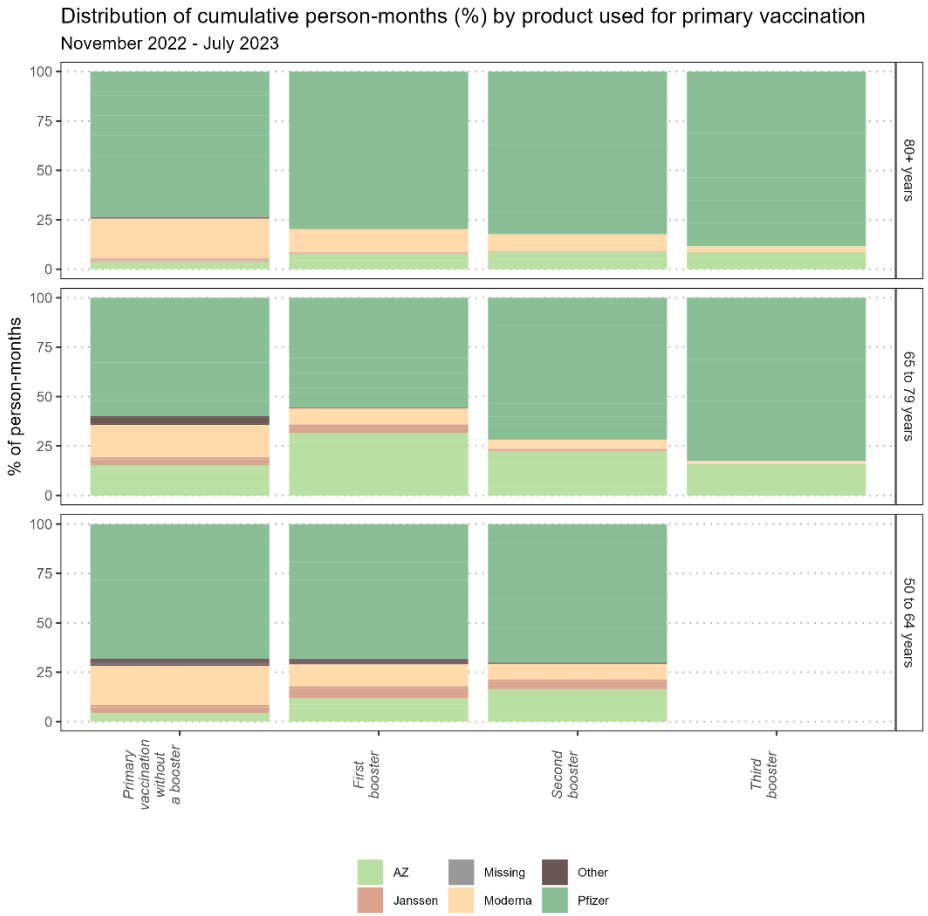
Age group	Study period	Primary vaccination without booster ≥24 weeks		Complete vaccination + first booster		Complete vaccination + two booster doses		Complete vaccination + three booster doses	
		N	Events/ person-month	N	Events/ person-month	N	Events/ person-month	N	Events/ person-month
	Dec 22 to Jan 23	938 113	90/ 1 694 435	6 115 214	503/ 10 702 984	4 587 699	310/ 7 942 353	111 014	5/ 135 118
	Jan to Feb 23	934 452	56/ 1 699 564	5 840 533	289/ 10 453 115	4 663 817	195/ 8 317 321	0	<5/0
	Feb to Mar 23	928 449	42/ 1 696 136	5 694 754	201/ 10 366 555	4 647 111	171/ 8 456 564	0	<5/0
	Mar to Apr 23	931 653	27/ 1 703 449	5 501 784	121/ 10 057 298	4 150 732	161/ 7 597 085	0	<5/0
	Apr to May 23	935 429	24/ 1 710 882	5 647 928	77/ 10 339 556	4 552 049	162/ 8 312 664	0	<5/0
	May to Jun 23	921 517	16/ 1 686 000	5 430 605	60/ 9 941 579	3 413 552	98/ 6 246 009	0	<5/0
	Jun to Jul 23	924 488	13/ 1 692 300	5 439 476	42/ 9 959 824	3 404 875	78/ 6 233 768	0	<5/0
50-64	Apr to May 22	327 750	8/ 565 383	2 098 543	19/ 3 838 848	-	-	-	-
	May to Jun 22	344 451	8/ 584 101	2 104 957	15/ 3 864 131	-	-	-	-
	Jun to Jul 22	358 093	4/ 610 379	906 491	13/ 1 672 935	-	-	-	-
	Jul to Aug 22	669 900	12/ 1 151 030	2 247 438	34/ 4 157 885	-	-	-	-
	Aug to Sep 22	664 092	12/ 1 206 551	2 251 885	30/ 4 171 008	-	-	-	-
	Sep to Oct 22	659 605	15/ 1 187 926	2 251 285	34/ 3 847 105	-	-	-	-

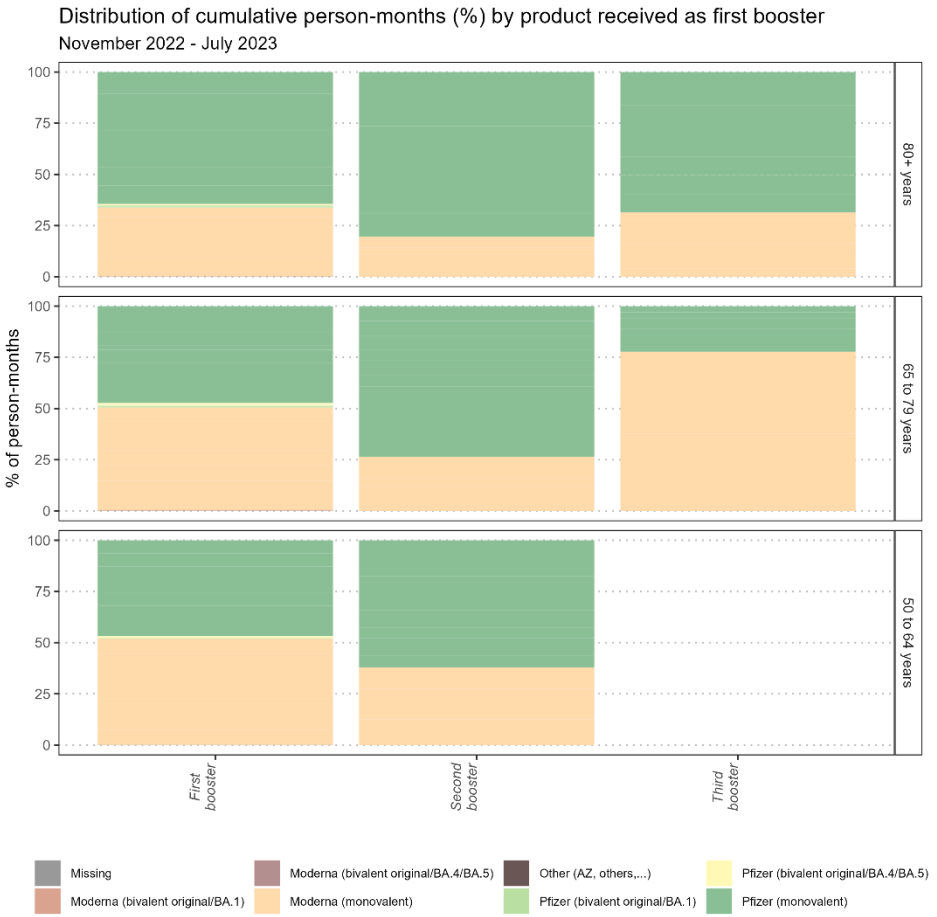
Age group	Study period	Primary vaccination without booster ≥24 weeks		Complete vaccination + first booster		Complete vaccination + two booster doses		Complete vaccination + three booster doses	
		N	Events/ person-month	N	Events/ person-month	N	Events/ person-month	N	Events/ person-month
	Oct to Nov 22	652 814	8/ 1 172 401	2 223 597	26/ 3 194 991	588 203	7/ 492 583	-	-
	Nov to Dec 22	653 950	14/ 1 144 119	2 422 428	40/ 3 658 08	1 230 727	16/ 1 514 380	-	-
	Dec 22 to Jan 23	2 320 101	22/ 4 185 536	10 127 026	112/ 17 827 142	1 664 929	23/ 2 808 957	-	-
	Jan to Feb 23	2 287 477	14/ 4 177 978	9 709 827	68/ 17 613 547	2 415 107	17/ 4 288 779	-	-
	Feb to Mar 23	2 262 496	13/ 4 141 950	9 296 680	39/ 16 988 111	711 253	8/ 1 288 753	-	-
	Mar to Apr 23	2 256 159	14/ 4 133 048	9 237 724	29/ 16 912 086	2 405 075	17/ 4 411 359	-	-
	Apr to May 23	2 284 065	12/ 4 185 708	9 345 725	18/ 17 124 701	2 385 575	19/ 4 389 030	-	-
	May to Jun 23	2 224 708	5/ 4 074 734	9 348 466	24/ 17 130 208	1 735 159	17/ 3 176 602	-	-
	Jun to Jul 23	2 232 487	3/ 4 090 485	723 048	12/ 1 324 775	704 038	15/ 1 290 080	-	-

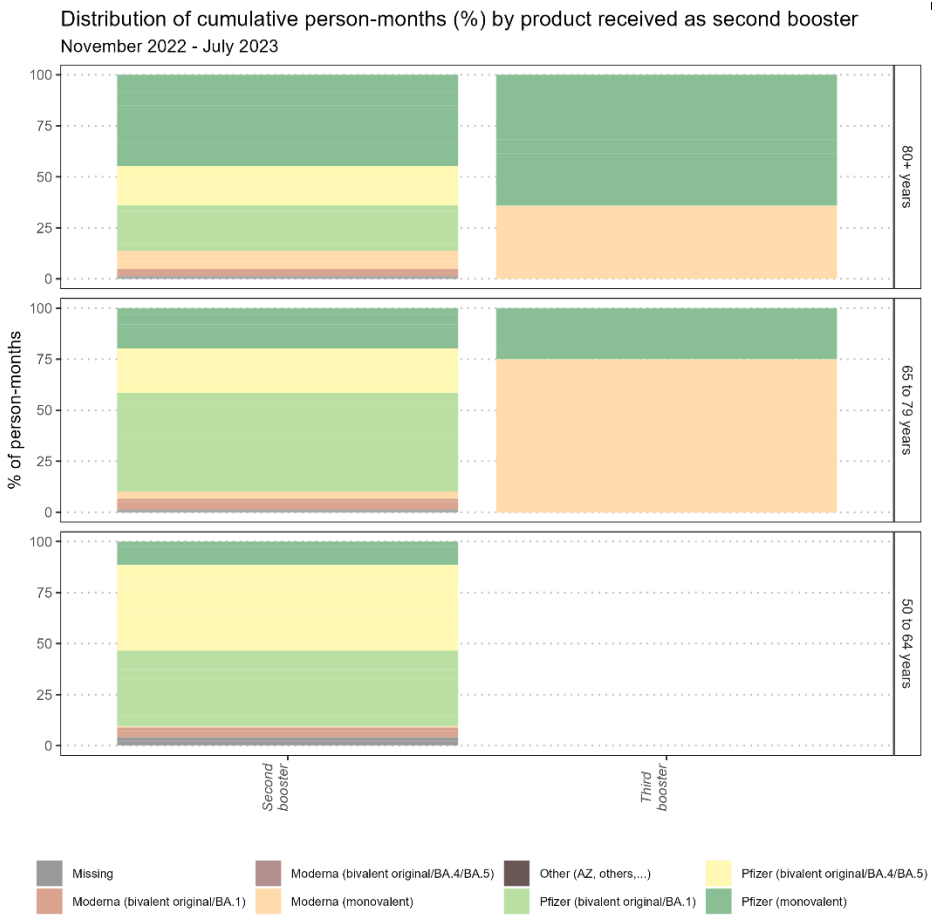
Annex 4. Distribution of person-months in the study by covariates, from November 2022* to July 2023

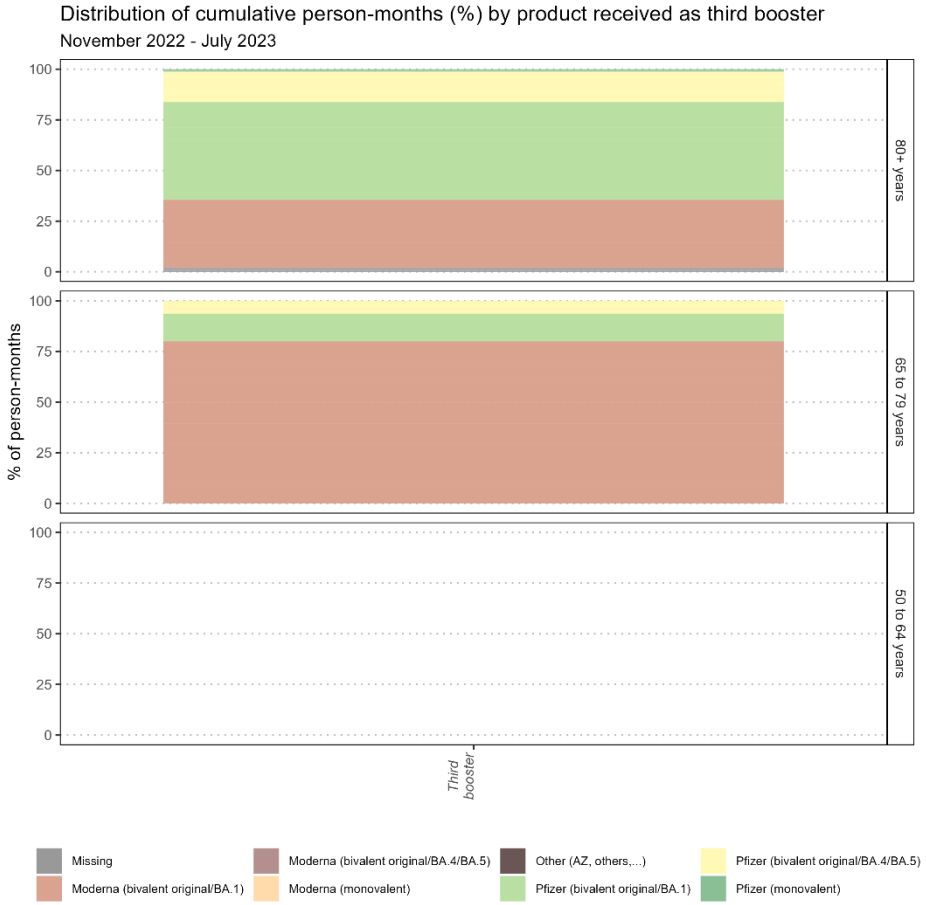





Distribution of cumulative person-months (%) by product used for primary vaccination
November 2022 - July 2023
% of person-months
80+ years
65 to 79 years
50 to 64 years
Primary vaccination without a booster
First booster
Second booster
Third booster
AZ
Janssen
Missing
Moderna
Other
Pfizer


Distribution of cumulative person-months (%) by product received as first booster
November 2022 - July 2023
% of person-months
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)

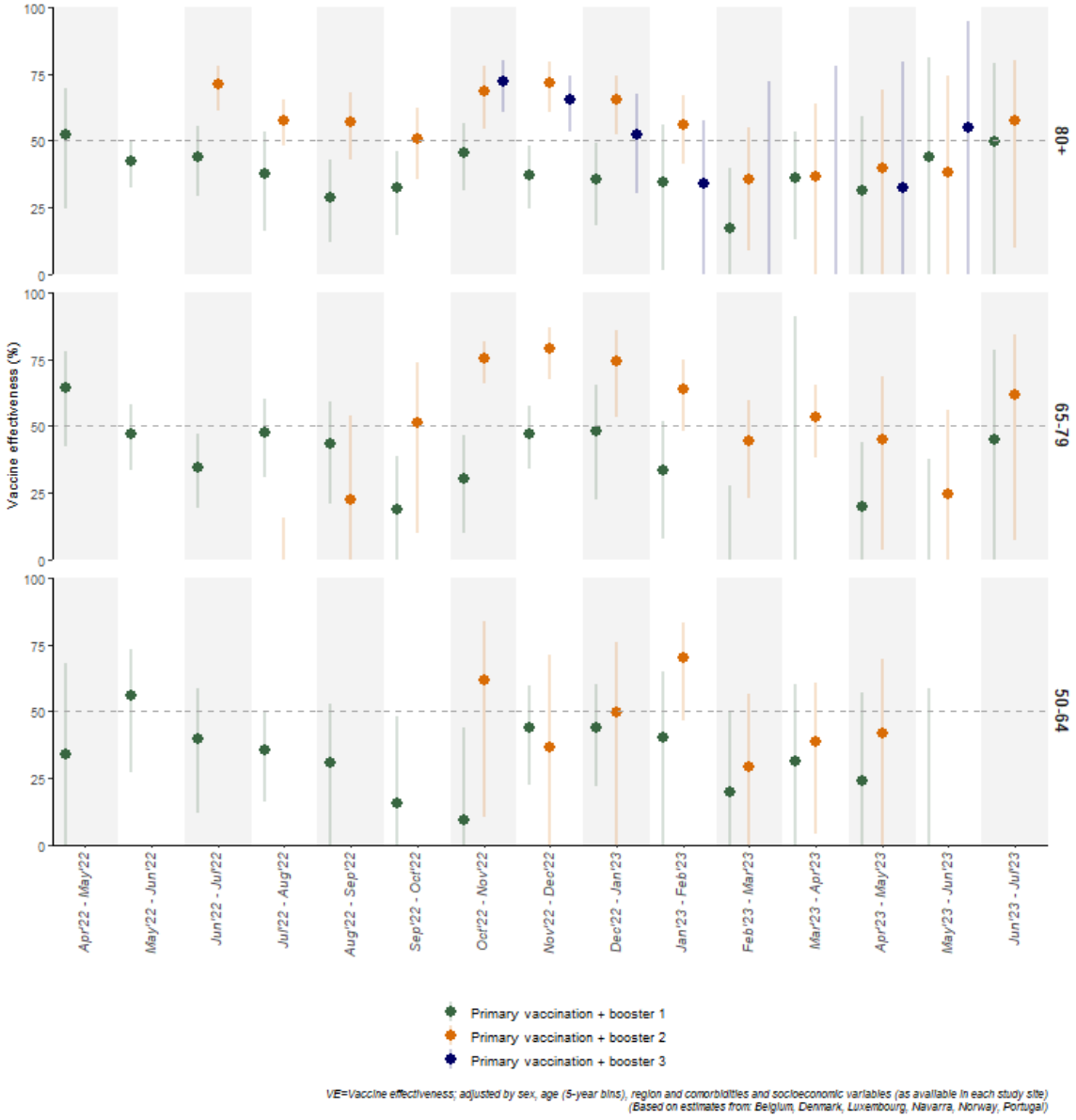




**Information collected for all participating study sites from November 2022 onward.*

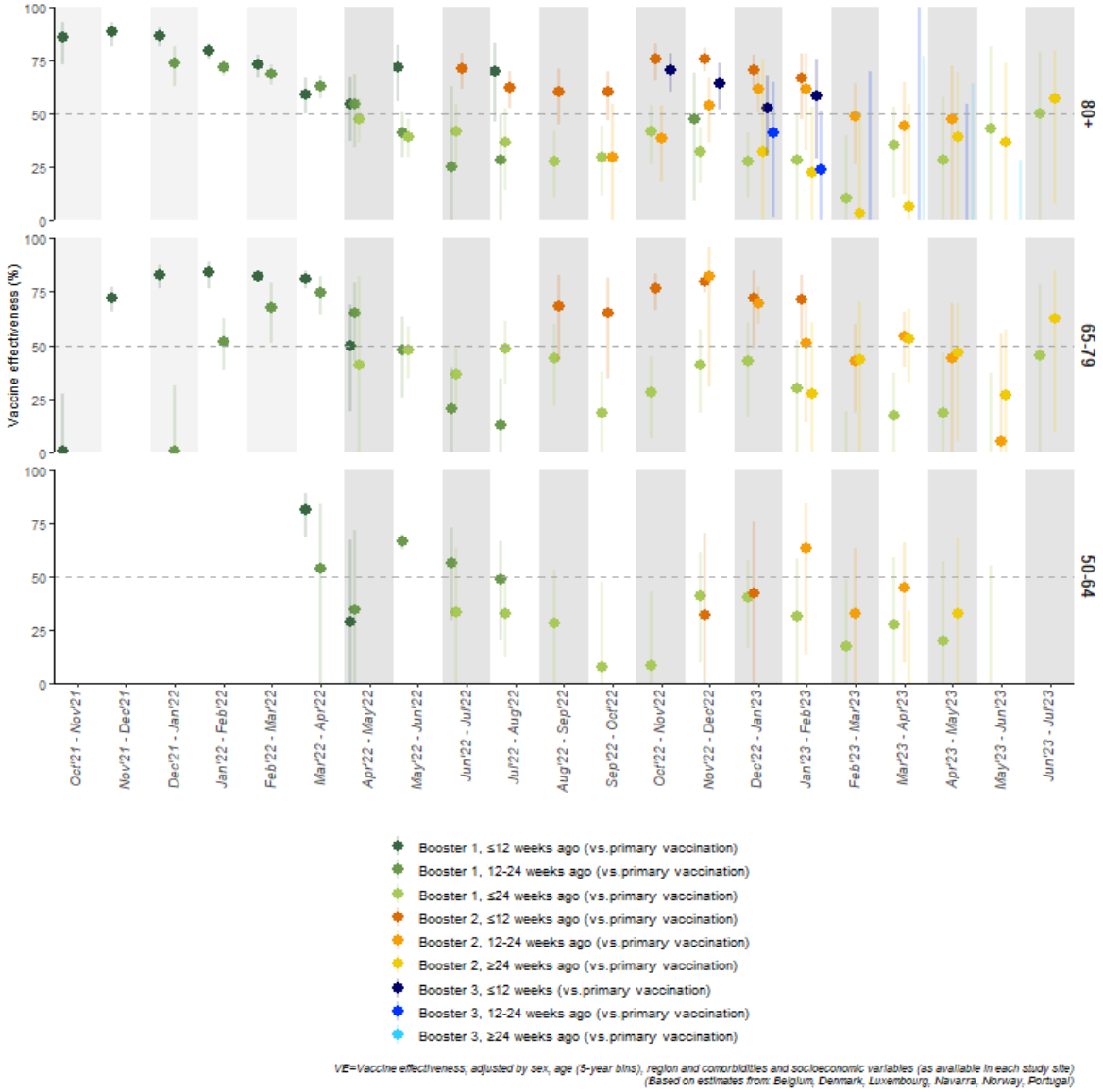
Annex 5. Results restricted to the six study sites that contributed since the start of the study period

Figure 1A. Relative vaccine effectiveness (95% confidence intervals) 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 July 2023, restricting to the six study sites that contributed since the start of the study period (Belgium, Denmark, Luxembourg, Navarra (Spain), Norway, and Portugal)



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 2A. Relative vaccine effectiveness (95% confidence intervals) 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 July 2023, restricting to the six study sites that contributed since the start of the study period (Belgium, Denmark, Luxembourg, Navarra (Spain), Norway, and Portugal)



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 3A. Relative vaccine effectiveness (95% confidence intervals) 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 July 2023, restricting to the six study sites that contributed since the start of the study period (Belgium, Denmark, Luxembourg, Navarra (Spain), Norway, and Portugal)

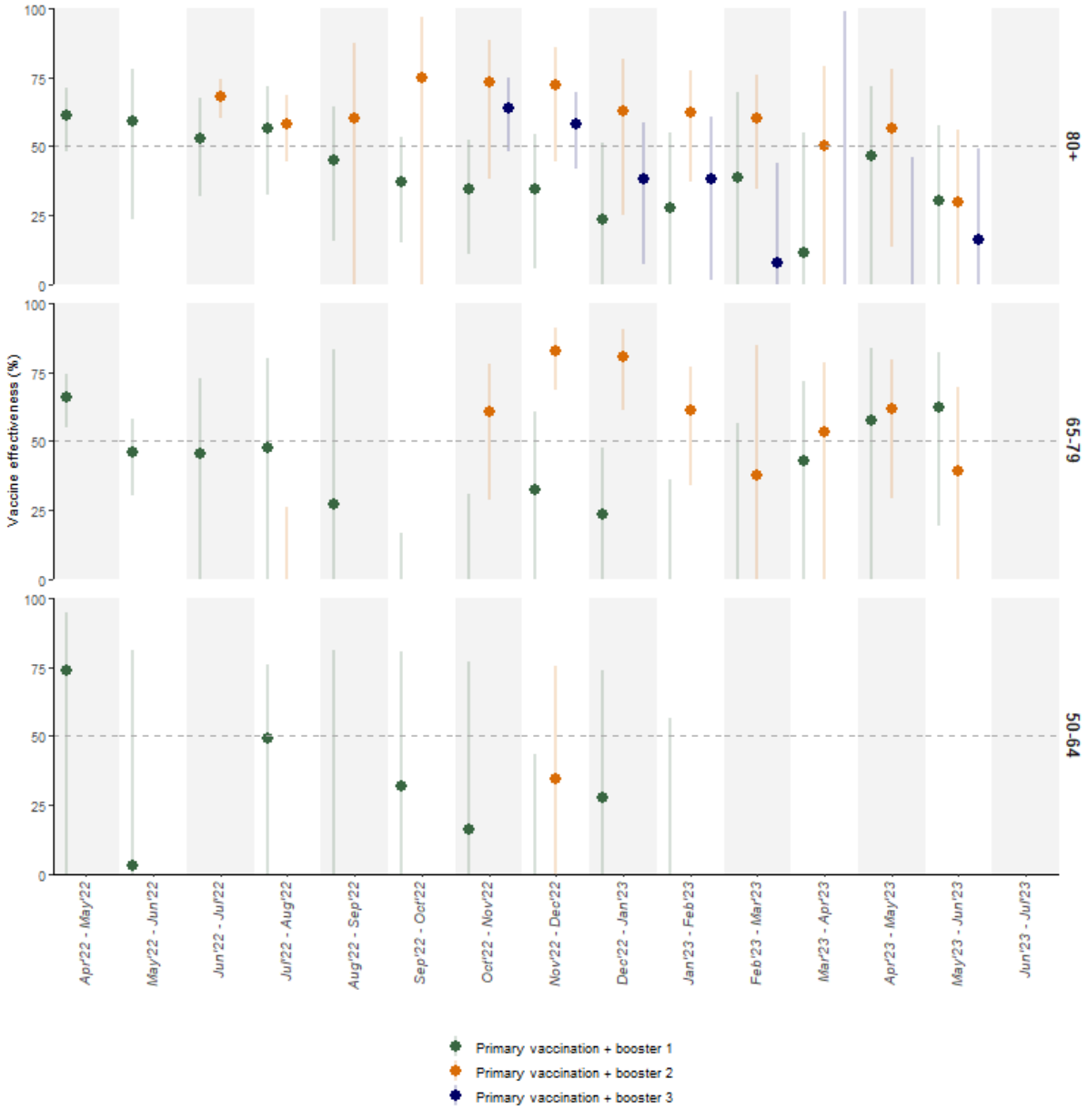


Figure 4A. Relative vaccine effectiveness (95% confidence intervals) against COVID-19 related mortality of the first, second and third booster dose, compared to complete primary vaccination administered ≥24 weeks ago without booster, by time since the booster, for each eight-week overlapping study period, April 2022 and July 2023, restricting to the six study sites that contributed since the start of the study period (Belgium, Denmark, Luxembourg, Navarra (Spain), Norway, and Portugal)

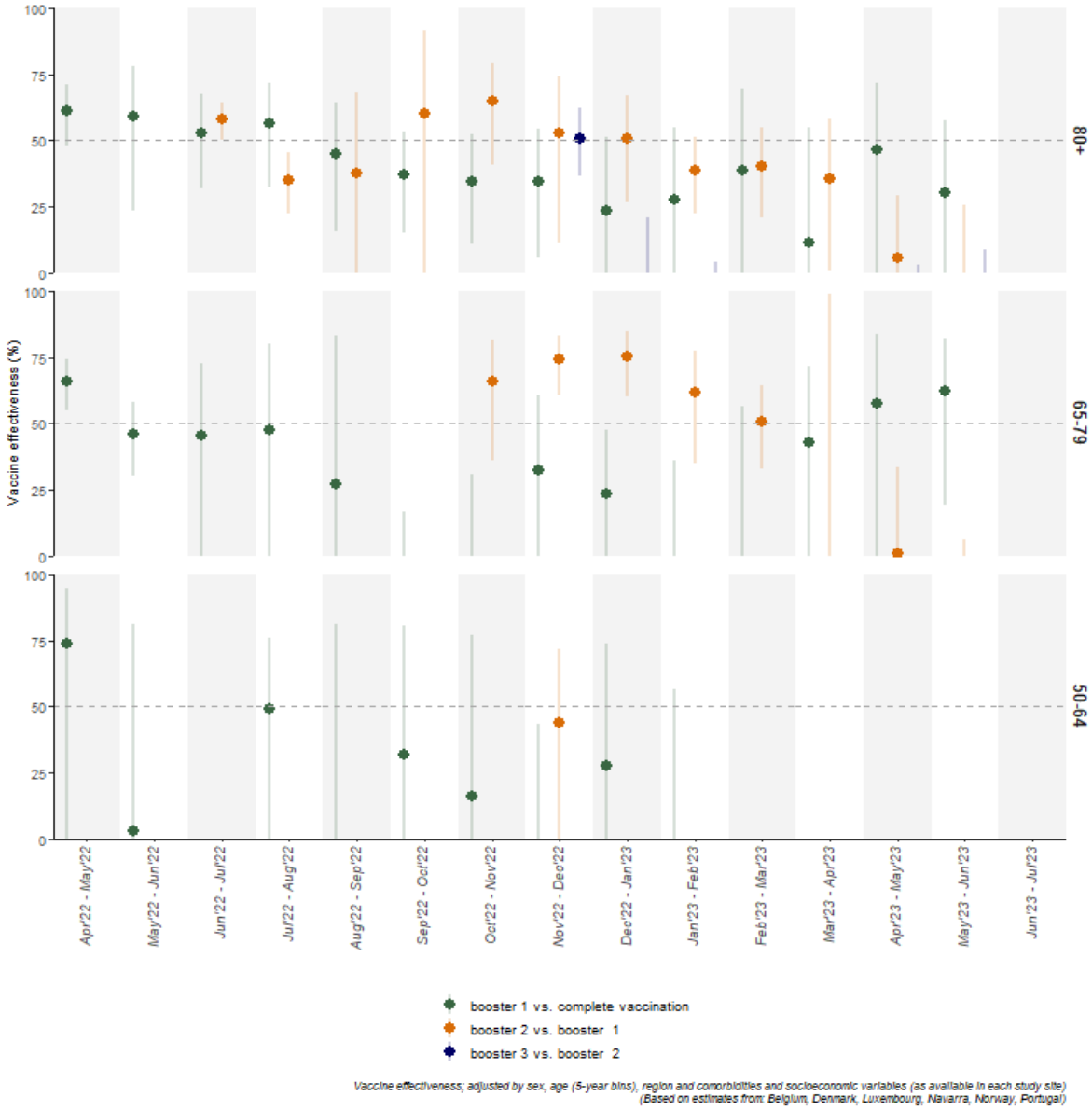


Table 1A. Relative vaccine effectiveness (95% Confidence Intervals) in ≥80 years against hospitalisation due to COVID-19 of the first, second and third booster dose, compared to complete primary vaccination without booster administered ≥24 weeks ago, for each eight-week overlapping study period between April 2022 and July 2023, restricting to the six study sites that contributed since the start of the study period (Belgium, Denmark, Luxembourg, Navarra (Spain), Norway, and Portugal)

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	>24 weeks
1 April to 26 May 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)	-	-	-	-	-	-	-	-
1 May to 25 June 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)	-	-	-	-	-	-	-	-
1 June to 26 July 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)	-	-	-	-	-	-
1 July to 25 August 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)	-	-	-	-	-	-
1 August to 25 September 2022	28.9% (11.8; 42.7)	-	-	27.8% (10.4; 41.9)	57.2% (43.1; 67.9)	60.2% (45; 71.3)	-	-	-	-	-	-
1 September to 26 October 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)	-	-	-	-	-
1 October to 25 November 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)	-	-
1 November to 26 December 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)	-	-
1 December 2022 to 25 January 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)	-
1 January to 25 February 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)	-
1 February to 28 March 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)	-
1 March to 25 April 2023	6.2% (13.2; 53.2)	-	-	35.3% (10.3; 53.4)	36.5% (-11.4; 63.8)	-	44.6% (12.5; 65)	6.4% (-92.6; 54.5)	-19.8% (-550; 77.9)	-	-15530.0% (-Inf; 99.8)	-20.0% (-518; 76.7)

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	>24 weeks
1 April to 26 May 2023	31.2% (-15.5; 59)	-	-	28.7% (-21.4; 58.1)	39.6% (-17.4; 68.9)	-	47.6% (-0.5; 72.7)	39.1% (-19.6; 69)	32.6% (-123.5; 79.7)	-	-14.9% (-189.6; 54.4)	-14.7% (-270.2; 64.4)
1 May to 25 June 2023	43.9% (-68.6; 81.3)	-	-	42.8% (-76; 81.4)	38.4% (-48.6; 74.5)	-	-	36.7% (-53.6; 73.9)	55.0% (-275.9; 94.6)	-	-	-37.0% (-163.2; 28.7
1 June to 26 July 2023	49.9% (-19.6; 79)	-	-	49.9% (-19.4; 79)	57.8% (9.8; 80.2)	-	-	56.9% (7.8; 79.8)	-	-	-	-

Table 2A. 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 July 2023, restricting to the six study sites that contributed since the start of the study period (Belgium, Denmark, Luxembourg, Navarra (Spain), Norway, and Portugal)

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
1 April to 26 May 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)	-	-	-	-
1 May to 25 June 2022	47.1% (33.6; 57.8)	-	47.7% (25.5; 63.3)	47.6% (34.1; 58.4)	-	-	-	-
1 June to 26 July 2022	34.6% (19.2; 47)	-	20.5% (-4.5; 39.6)	36.0% (20.9; 48.3)	-	-	-	-
1 July to 25 August 2022	47.5% (30.6; 60.3)	-	12.9% -16.1; 34.6)	48.5% (31.6; 61.3)	-	-	-	-
1 August to 25 September 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)	-	-
1 September to 26 October 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)	-	-
1 October to 25 November 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)	-	-
1 November to 26 December 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)	-
1 December 2022 to 25 January 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)	-
1 January to 25 February 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)
1 February to 28 March 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)

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
1 March to 25 April 2023	-582.5% (-Inf; 90.9)	-	-	16.8% (-10; 37.1)	53.5% (38; 65.1)	-	54.3% (39.4; 65.5)	52.8% (32.7; 66.9)
1 April to 26 May 2023	19.9% (-14.3; 43.9)	-	-	18.2% (-25.1; 46.5)	45.0% (3.7; 68.5)	-	43.6% (-4.5; 69.6)	46.5% (5.2; 69.7)
1 May to 25 June 2023	-8.8% (-89.4; 37.5	-	-	-10.1% (-91.4; 36.7)	24.8% (-29.2; 56.2)	-	4.7% (-102.6; 55.2)	26.5% (-26.5; 57.3)
1 June to 26 July 2023	45.2% (-39.2; 78.4)	-	-	45.1% (-39.1; 78.4)	61.6% (7.2; 84.1)	-	-	62.6% (9.6; 84.6)

Table 3A. 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 July 2023, restricting to the six study sites that contributed since the start of the study period (Belgium, Denmark, Luxembourg, Navarra (Spain), Norway, and Portugal)

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
1 April to 26 May 2022	33.8% (-36.6; 67.9)	28.6% (-55.9; 67.3)	34.2% (-54.1; 71.9)	-	-	-	-	-
1 May to 25 June 2022	55.6% (27; 73)	-	66.6% (62.9; 69.9)	-	-	-	-	-
1 June to 26 July 2022	39.5% (11.8; 58.5)	-	56.0% (29.2; 72.7)	33.3% (-21.3; 63.4)	-	-	-	-
1 July to 25 August 2022	35.4% (16.2; 50.2)	-	48.6% (20.6; 66.7)	32.8% (12.5; 48.4)	-	-	-	-
1 August to 25 September 2022	31.0% (-0.8; 52.7)	-	-	28.1% (-10.1; 53)	-	-	-	-
1 September to 26 October 2022	15.6% (-37.5; 48.2)	-	-	7.4% (-62.7; 47.3)	-	-	-	-
1 October to 25 November 2022	9.4% (-46.9; 44.1)	-	-	8.1% (-47.3; 42.6)	-	-	-	-
1 November to 26 December 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)	-	-
1 December 2022 to 25 January 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)	-	-
1 January to 25 February 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)	-
1 February to 28 March 2023	19.6% (-28.7; 49.8)	-	-	17.5% (-32.4; 48.6)	29.3% (-15; 56.5)	-	32.5% (-25.2; 63.6)	-

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
1 March to 25 April 2023	31.5% (-17.3; 60)	-	-	27.5% (-28.2; 59)	38.6% (3.9; 60.7)	-	44.5% (9.6; 65.9)	-66.0% (-315.4; 33.7)
1 April to 26 May 2023	23.8% (-35.4; 57.1)	-	-	20.1% (-47.7; 56.8)	41.9% (-9.9; 69.3)	-	-	32.4% (-41.7; 67.8)
1 May to 25 June 2023	-12.4% (-202.9; 58.3)	-	-	-21.1% (-226.8; 55.1)	-	-	-	-
1 June to 26 July 2023	-	-	-	-	-	-	-	-

Table 4A. 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 July 2023, restricting to the six study sites that contributed since the start of the study period (Belgium, Denmark, Luxembourg, Navarra (Spain), Norway, and Portugal)

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	>24 weeks
1 April 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)	-	-	-	-	-	-	-	-
1 May 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)	-	-	-	-	-	-	-	-
1 June 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)	-	-	-	-	-	-
1 July 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)	-	-	-	-	-	-
1 August 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)	-	-	-	-	-	-
1 September 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)	-	-	-	-	-
1 October 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)	-	-
1 November 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)	-	-
1 December 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)	-
1 January to 25 February 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)	-
1 February 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)	-
1 March to 25 April 2023	11.7% (-72.8; 54.9)	-	-	4.3% (-100.8; 54.4)	50.4% (-17.9; 79.2)	-	54.4% (6.6; 77.7	30.9% (-213.3; 84.8)	-116.0% (-Inf; 99)	-	-129.0% (-427.8; 0.7)	-99.0% (-364.9; 14.8)
1 April to 26 May 2023	46.5% (-1; 71.7)	-	-	45.1% (-3.4; 70.9)	56.7% (13.7; 78.2)	-	46.3% (-152.5; 88.6)	30.9% (-213.3; 84.8)	1.0% (-88.5; 45.9)	-	-	-7.0% (-100.4; 42.9)
1 May to 25 June 2023	30.3% (-15; 57.8)	-	-	30.1% (-15.8; 57.8)	30.0% (-11.8; 56.2)	-	-	29.9% (-12.3; 56.2)	16.0% (-38.7; 49.1)	-	-	14.0% (-42.6; 48.1)
1 June to 26 July 2023*	-	-	-	-	-	-	-	-	-	-	-	-

** Only Norway contributed valid estimates of VE against COVID-19-related death in this period and age group and did not reach the 15 events of threshold for pooled results to be reported.*

Table 5A. 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 July 2023, restricting to the six study sites that contributed since the start of the study period (Belgium, Denmark, Luxembourg, Navarra (Spain), Norway, and Portugal)

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
1 April 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)	-	-	-	-
1 May to 25 June 2022	45.8% (30.3; 57.9)	-	52.9% (9; 75.6)	52.7% (36.7; 64.6)	-	-	-	-
1 June 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)	-	-	-	-
1 July to 25 August 2022	47.5% (-37.9; 80)	-	-110.0% (-282.7; -15.2)	49.8% (-26.6; 80.1)	-	-	-	-
1 August to 25 September 2022	27.2% (-215.3; 83.2)	-	-	27.3% (-206.3; 82.8)	-	-	-	-
1 September to 26 October 2022	-33.0% (-111.8; 16.5)	-	-	-34.0% (-114; 16.1)	-	-	-	-
1 October 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)	-	-
1 November 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)	-	-
1 December 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)	-	-
1 January to 25 February 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)	-
1 February 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)	-
1 March to 25 April 2023	42.7% (-16.2; 71.7)	-	-	23.0% (-60.5; 63.1)	53.1% (-1.3; 78.3)	-	68.7% (-0.9; 90.3)	30.0% (-82.7; 73.2)
1 April to 26 May 2023	57.7% (-7.8; 83.4)	-	-	54.7% (-13.4; 81.9)	61.8% (29.3; 79.4)	-	62.4% (27.9; 80.4)	60.9% (19.6; 81)
1 May to 25 June 2023	62.0% (19.4; 82.1)	-	-	60.0% (14.9; 81.2)	39.0% (-23; 69.8)	-	-	37.0% (-27; 68.8)
1 June to 26 July 2023*	-	-	-	-	-	-	-	-

** No study site contributed valid estimates of VE against COVID-19-related death in this period and age group.*

Table 6A. 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 July 2023, restricting to the six study sites that contributed since the start of the study period (Belgium, Denmark, Luxembourg, Navarra (Spain), Norway, and Portugal)

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
1 April to 26 May 2022	73.8% (-31.6; 94.8)	-	-	-	-	-	-	-
1 May to 25 June 2022	3.2% (-387.9; 80.8)	-	-	-	-	-	-	-
1 June to 26 July 2022	-	-	-	-	-	-	-	-
1 July to 25 August 2022	48.8% (-7.9; 75.7)	-	-	48.0% (-11.2; 75.7)	-	-	-	-
1 August to 25 September 2022	-14.8% (-588.8; 80.9)	-	-	-17.6% (-637.1; 81.2)	-	-	-	-
1 September to 26 October 2022	31.8% (-137.1; 80.4)	-	-	30.0% (-153.4; 80.7)	-	-	-	-
1 October to 25 November 2022	16.0% (-206; 76.9)	-	-	5.6% (-324.4; 79)	-	-	-	-
1 November to 26 December 2022	-12.0% (-148.9; 49.6)	-	-	-32.9% (-245.3; 48.8)	34.6% (-74; 75.5)	-	-	-
1 December 2022 to 25 January 2023	27.5% (-100.7; 73.8)	-	-	7.4% (-325.7; 79.9)	-	-	-	-
1 January to 25 February 2023	-9.2% (-173.6; 56.4)	-	-	-73.1% (-368.8; 36.1)	-	-	-	-
1 February to 28 March 2023*	-	-	-	-	-	-	-	-
1 March to 25 April 2023*	-	-	-	-	-	-	-	-
1 April to 26 May 2023*	-	-	-	-	-	-	-	-
1 May to 25 June 2023*	-	-	-	-	-	-	-	-
1 June to 26 July 2023*	-	-	-	-	-	-	-	-

** No study site contributed valid estimates of VE against COVID-19-related death in this period and age group.*

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