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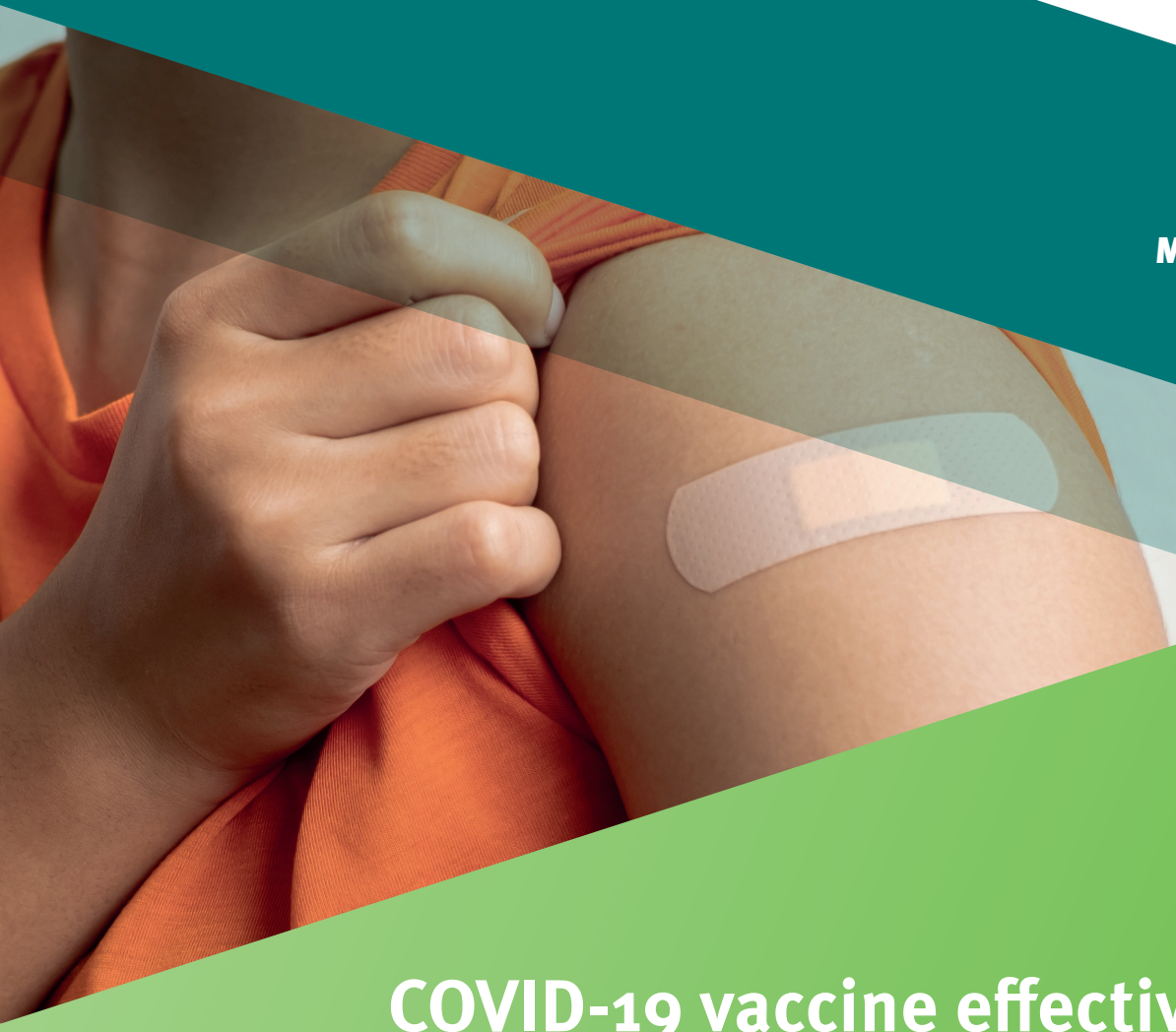

MONITORING

COVID-19 vaccine effectiveness against hospitalisation and death using electronic health records in eight European countries in the VEBIS monitoring network

October 2023 to April 2024

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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

Executive summary

This report presents pooled vaccine effectiveness (VE) estimates for the Pfizer XBB.1.5 monovalent COVID-19 vaccine dose against hospitalisation and COVID-19-related death in resident populations in eight European countries. The dose was administered during the 2023 autumn campaign against COVID-19. The study populations were those aged ≥65 years living in the community in Belgium, Denmark, Italy, the Netherlands (only until December 2023), Norway (only until February 2024), Portugal, Spain (Navarra) and Sweden (data coverage to 15 April 2024). The study was undertaken within the Vaccine Effectiveness Burden and Impact Studies (VEBIS) project.

The study period covered in this report is October 2023 to April 2024. A retrospective cohort was constructed from linked electronic health records (EHR) in each country. Country-specific (level) VE was estimated monthly, using a study period of eight weeks follow-up period. Each month, the study period was shifted forwards to the next month. Country estimates were then pooled together for each period. The VE of the 2023 autumnal dose was estimated using the not-yet-vaccinated eligible population as a reference population.

Between October 2023 and April 2024, the number of individuals aged ≥80 years included in the analysis across each study period decreased from five to four million individuals who were eligible for the 2023 autumnal dose, but who did not receive it during the study period. In the 65-79-year age group, the number of individuals eligible for the autumnal dose but who did not receive it decreased from 12.5 to 9.8 million individuals. A total of 63 876 hospitalisations due to COVID-19 and 8 212 COVID-19-related deaths were reported.

Individuals who received the 2023 autumnal dose had already received a higher number of COVID-19 vaccine doses by then compared to those who were eligible but had not received the autumnal dose by the end of the study period. There was also a higher proportion of individuals with registered co-morbidities who received the vaccination. The effectiveness of the monovalent XBB.1.5 COVID-19 vaccine dose against hospitalisation due to COVID-19 for the first eight-week observation window (from the start of the campaigns in October to 25 November 2024) was 65% (95%CI: 56 to 71) and 64% (95%CI: 55 to 72) among the population aged ≥80 and 65-79 years, respectively. Vaccine effectiveness against COVID-19-related death was 67% (95%CI: 41 to 81) and 67% (95%CI: 43 to 81) among the population aged ≥80 and 65-79 years, respectively.

Vaccine effectiveness against hospitalisation due to COVID-19 decreased steadily through the study period, down to 38% (95%CI: 31 to 45) and 48% (95%CI: 40 to 55) among the population aged ≥80 and 65-79 years, respectively, on 1 January to 25 February 2024. Most of this decrease may be attributable to new SARS-CoV-2 variants becoming dominant, increasing time since vaccination in the majority of the vaccinated population who received it in October, or even to biases, such as a depletion of susceptible individuals. Between February 2024 and April 2024, estimates had very low precision or could not be drawn in some sites.

Vaccine effectiveness estimates against COVID-19 related deaths decreased similarly to VE against hospitalisation for ≥80-year-olds, but only marginally among the 65-79 years old group. From 1 January to 25 February 2024, VE against death was 40% (95%CI: 25 to 51) for ≥80-year-olds and 54% (95%CI: 24 to 71) for 65-79-year-olds. Between February and April 2024 estimates had very low precision or could not be drawn in some sites.

Overall, the results of this study indicate that the 2023 autumnal dose was effective in restoring protection against hospitalisation and COVID-19-related death. However, VE declined over time and reached ≤55% for both outcomes and age groups after January 2024.

Scope of this document

This document reports the results of prospective monitoring of COVID-19 VE using a multi-country approach based on established EHR databases in eight participating countries since the beginning of the autumnal vaccination campaign in October 2023 up to 25 April 2024 albeit with partial contribution of data from the Netherlands (up to December 2023).

Since October 2021, the VEBIS-EHR project has gone through different phases including a proof-of-concept relating to the usage of EHR in four countries, a pilot and prospective monitoring phases. 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 [1–3]. This document reports estimates based on the Master Protocol v.2.0, published in February 2024, which focuses on the estimation of autumnal VE, rather than the estimation of VE of a specific number of booster doses.

This report contains VE estimates among individuals aged 65 years and older against hospitalisation due to COVID-19 and COVID-19-related deaths. Vaccine effectiveness of the 2023 autumnal dose is estimated using as reference, the individuals eligible for an autumnal dose but who did not receive it. Vaccine effectiveness estimates were calculated overall and by time since the autumnal dose.

Table 1. Successive steps in the implementation of the study

Project stage	Study period	Study Sites	Study outcome	Age groups	Reference
Proof of concept	Oct 21–Mar 22	Denmark, Navarra (Spain), Norway, Portugal	Absolute and relative VE against hospitalisation, overall and by time since the booster	≥80 65–79	Pilot protocol [1]
Full pilot	Mar 22–Apr 22	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 [1]
Prospective monitoring pilot	Apr 22–Jul 22	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 [2]
	Jul 22–Nov 22	Belgium, Denmark, Luxembourg, Navarra (Spain), Norway, Portugal		≥80 65–79 50–64 18–49 5–17	
Prospective monitoring	Nov 22–Dec 22	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 [2]
	Dec 22–Feb 23	Belgium, Denmark, Luxembourg, Navarra (Spain), Norway, Portugal, The Netherlands, Italy			
	Feb 23–Jul 23	Belgium, Denmark, Navarra (Spain), Norway, Portugal, The Netherlands, Italy			
	Oct 23–Dec 23	Belgium, Denmark, Navarra (Spain), Norway, Portugal, The Netherlands, Italy, Sweden	2023 Autumnal dose VE against hospitalisation and mortality, overall and by time since vaccination.	≥80 65–79	Master protocol v.2.0 [3]
	Jan 24–Apr 24	Belgium, Denmark, Navarra (Spain), Norway, Portugal, Italy, Sweden			

Background

A novel severe acute respiratory syndrome virus (SARS-CoV-2) causing COVID-19 disease emerged in late 2019. Since 31 December 2019 and up to the latest update of the COVID-19 situation in the World Health Organization (WHO) European Region on 21 November 2023 [4], 278 300 338 cases of COVID-19 (in accordance with the applied case definitions and testing strategies in the affected countries) had been reported in this region, including 2 260 650 deaths.

As of July 2024, 14 vaccine products have been granted marketing authorisation in the EU/EEA by the European Medicines Agency (EMA)[5]. Eight vaccines have been approved for primary COVID-19 vaccination, of which seven 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 BA.1 or BA.4-5 have been authorised (Comirnaty bivalent Original/Omicron BA.1, Comirnaty bivalent Original/Omicron BA.4-5, Spikevax bivalent Original/Omicron BA.1 and Spikevax bivalent Original/Omicron BA.4-5) and used from September 2022 as a second and/or third booster vaccination [6]. More recently, two monovalent vaccines targeting Omicron XBB.1.5 have been authorised (Comirnaty Omicron XBB.1.5 (adapted) and Spikevax XBB.1.5 (adapted)) and were administrated as part of the 2023 autumn vaccination campaign [7,8].

ECDC is leading activities and studies on the scope of VE as part of its now extended mandate on monitoring vaccines and vaccination programmes in the post-authorisation phase [9–11]. 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 Vaccine Effectiveness Burden and Impact Studies (VEBIS) project is funded as part of 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 diseases 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) [2,12–15].

Within VEBIS, since October 2021, a multi-country COVID-19 VE study using electronic health records (EHR) has been ongoing in EU/EEA countries. The current study monitors VE of COVID-19 vaccines using routinely collected vaccination status and outcome data from established EHR databases. Using a common protocol, 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 using a pilot protocol [1] were carried out between October 2021 and April 2022, with the participation of Denmark, Spain (Navarra), Norway and Portugal [16]. Between April and November 2022, a prospective monitoring pilot was implemented in the four study sites with the later addition of Belgium and Luxembourg (since July 2022) [17], using an updated Master Protocol [3]. Since November 2022, prospective monitoring has been ongoing in Belgium, Denmark, Luxembourg, Spain (Navarra), Norway, Portugal, and the Netherlands (up to December 2022), with the further addition of Italy (Table 1) [18]. The protocol was updated [2] to produce VE estimates of the 2023 autumnal dose [19].

In this report, VE estimates under monitoring from October 2023 up to April 2024 are presented. Specifically, this includes estimates of VE of the 2023 autumnal dose of monovalent XBB.1.5. (using individuals eligible for the autumnal dose but who did not receive it as reference group) against hospitalisation due to COVID-19 or COVID-19-related death, in the community-dwelling population aged ≥65 years or older.

Overall aim

The overall aim of the study is to monitor near real-time performance of COVID-19 vaccines administered as part of 2023 autumnal vaccination campaigns in the community-dwelling resident population aged ≥65 years in EU/EEA countries to detect any variation in VE, so that public health vaccine recommendations may be adjusted accordingly. To achieve this, the vaccine status hazard ratio (HR) of outcomes of interest will be estimated using information routinely collected in EHR, including vaccination, population and health databases, merged using deterministic data linkage.

Objectives

Principal objective

The principal objective is to estimate VE of monovalent XBB.1.5 COVID-19, given as part of 2023 autumnal vaccination campaign (hereafter referred to as autumnal dose), in community-dwelling resident populations aged ≥65 years, comparing the outcome incidence in EU/EEA countries in elderly individuals eligible for vaccination at the beginning of the campaign who received a vaccine dose, to outcome incidence in elderly individuals who were eligible but were yet to receive it at the time of vaccination status assessment, . Outcomes of interest are

- Hospital admission due to COVID-19;
- COVID-19-related death.

The reference group for the outcome incidence comparison were all the populations eligible for the 2023 autumnal vaccination campaign, and who previously completed their primary vaccination (unvaccinated are thus excluded), regardless of the number of previous COVID-19 vaccine booster doses received.

Analyses were stratified by age group (65-79 years and ≥80 years) and included eight-week study periods moving one month forward every month.

Secondary objectives

A secondary objective is to measure COVID-19 VE by time since administration, defined as the number of weeks between the time of analysis and the date of the dose administered as part of the 2023 autumnal campaign.

Methodology

Study design

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

Study setting

The study was carried out in up to eight EU/EEA countries: Belgium, Denmark, Italy, the Netherlands, Norway, Portugal, Spain (Navarra), and Sweden, representing around 37 million people ≥65 years old. The Netherlands participated until December 2023, and the remaining seven countries throughout the study period until April 2024. COVID-19 epidemiology and the rollout 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.

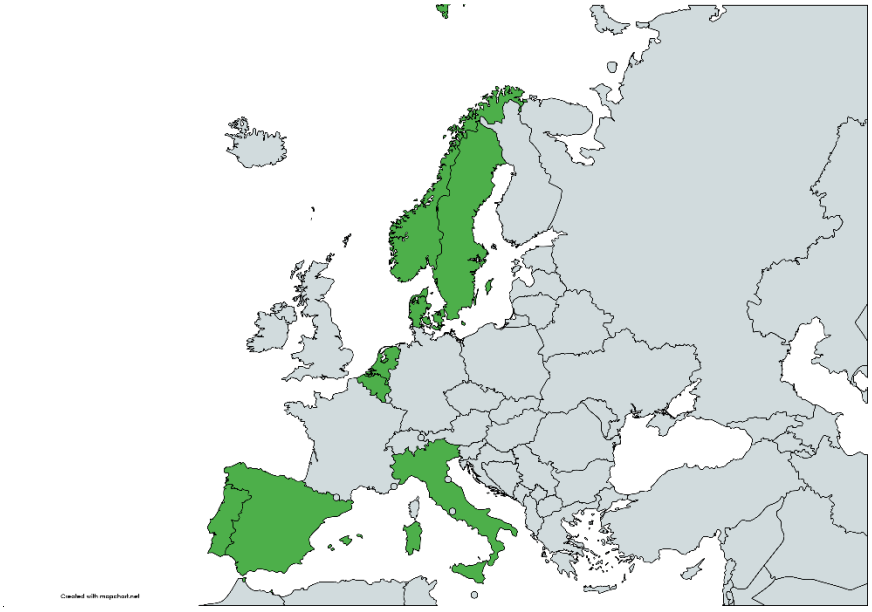


Table 2. Uptake (%) of COVID-19 2023 autumnal vaccine* in participating EU/EEA countries, as of 31 July 2024

Country	60–69 years	70–79 years	≥80 years
Belgium	35.0%	55.9%	64.6%
Denmark	43.8%	80.7%	88.6%
Italy	6%	11.7%	15.8%
The Netherlands	38.8%	63.4%	67.4%
Norway	30.3%	61.3%	61.9%
Portugal	43.5%	59.6%	63.9%
Spain	32.7%	52.4%	64.4%
Sweden	39.5%	72.7%	100%

Source: ECDC. Interim COVID-19 vaccination coverage in the EU/EEA during the 2023–24 season campaigns. Stockholm: ECDC; 2024. Age groups reflect the ones reported in this report [7,20]
** In Belgium, Denmark and Norway only recommended in those ≥65 years.*

In countries included, the XBB.1.5+F456L SARS-CoV-2 variant was predominant until weeks 45 to 50, depending on the study site (Figure 2), meaning that the vaccine component and the main SARS-CoV-2 circulating variant were the same in the first period of analysis (since the start of the campaign until 25 November 2023), one period of analysis containing the main transition between variants (from 1 November to 26 December 2023) and two periods with higher dominance of BA.2.86 and related variants and therefore a difference between the vaccine component and the circulating variants (from 1 December 2023 to 26 January 2024 and from 1 January to 25 April 2024).

Figure 2. Proportion of BA.2.86 and XBB.1.5-like among circulating SARS-Cov2 variants in countries represented in this study between October 2023 and April 2024

** Data source: https://github.com/EU-ECDC/Respiratory_viruses_weekly_data/blob/main/data/variants.csv. Variants are assigned as reported to TESSy (Denmark, Italy) or uploaded to GISAID (Belgium, the Netherlands, Norway, Portugal, Spain and Sweden).*

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 study site 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	The Netherlands	Norway	Portugal	Navarra (Spain)	Sweden
Hospital admission due to COVID-19	Clinical Hospital Survey database	Danish National Patient Register (DNPR)	National Integrated COVID-19 Surveillance Databases	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	Swedish National Patient Register
COVID-19-related death	Not available*	MiBA and Danish Civil Registration system (CPR)	National Integrated COVID-19 Surveillance Databases	Not available in near real-time*	Norwegian Death Registry (DÅR)	National Death Registry (SICO) and National Health Service User database (NHSU): cause of death is from SICO, death status and date of death from NHSU.	Administrative database of deaths and individual revision of events	Swedish Cause of Death register and Register of the Total Population Register on surveillance of notifiable communicable diseases
Vaccination status	National vaccine registry (VACCINNET)	Danish Vaccination Registry (DVR)	National Vaccination Registry	COVID-vaccination Information and Monitoring System (CIMS)	The National Immunisation Register (SYSVAK)	The National Vaccination Register (VACINAS)	Vaccination register	Swedish National Vaccination Register

**Belgium and the Netherlands did not contribute to VE against mortality*

Study period

Vaccine effectiveness estimates were produced each month from 14 days after the start of the country-specific COVID-19 vaccination autumnal campaign 2023 (Table 4), until 25 April 2024. Study periods covered an eight-week follow-up time to allow enough events for estimations, as well as to be sensitive and reactive to changes in VE over time. Each month the eight-week follow-up time is shifted forward by one month. A minimum of one month between the end of the study period and data extraction was applied for data consolidation.

Table 4. Start date of the 2023 autumnal COVID-19 vaccination campaign in each study site

Study site	First day of 2023 autumnal vaccination campaign
Belgium	11 September 2023
Denmark	1 October 2023
Italy	27 September 2023
The Netherlands	2 October 2023
Norway	1 September 2023
Portugal	29 September 2023
Spain (Navarra)	25 September 2023
Sweden	1 September 2023

Study population

The study included community-dwelling individuals aged ≥65 years in national databases, who were eligible for COVID-19 vaccination during the 2023 autumnal campaign, including those belonging to an age group for whom autumnal COVID-19 vaccination had been recommended in each site/country. Eligibility was based on the following criteria as of the first day of the vaccination campaign:

- Permanent resident in the EU/EEA territory covered in the study (for each study site, according to the most recent information).
- Aged between 65 and 110 years at the beginning of the vaccination campaign. Birth year was used instead of age in Belgium and Norway.
- Not residents of a nursing home/long-term care facility (according to the most recent information at the beginning of the autumnal vaccination campaign).
- Received their first ever COVID-19 vaccine dose as part of an age-specific vaccination campaign (i.e. excluding those vaccinated before it was generally recommended in the corresponding age group or, alternatively, excluding the first 5% of persons vaccinated within each age group – for each five-year age bracket- as these first vaccinees may not be representative of their corresponding age group).
- Completed primary vaccination at least 180 days before the start of the autumnal vaccination campaign.
- Has not received a COVID-19 vaccine dose, irrespective of the number of doses, in the last 90 days before the start of the autumnal vaccination campaign; has no documented SARS-CoV-2 infection (nor has been hospitalised due to COVID-19) in the 90 days before the start of the autumnal vaccination campaign [21].
- Does not have inconsistent or missing data on vaccination (vaccination status unknown, any vaccination date is unknown, any vaccine brand is unknown, number of doses is unknown, interval between primary course first and second dose is shorter than 19 days, interval between complete primary vaccination and booster dose or between booster doses is shorter than 90 days, number of doses higher than recommended, received any vaccine brand not approved by EMA, or the combination of vaccine brands is not a recommended schedule -may vary by age group).

Definitions

Vaccination status

Vaccination status was defined as a time-changing variable, with people changing vaccination status within the study period according to COVID-19 vaccine doses administered up to the date on which vaccination status is assessed.

For the principal objective, among those eligible for the administration of the COVID-19 vaccine as part of the 2023 autumnal campaign, they were classified into:

- Vaccinated as part of the autumn 2023 vaccination campaign: received a vaccine dose of an EMA-approved vaccine, administered on or after the date of initiation of the country-specific COVID-19 2023 autumn vaccination campaign (Table 4). The status was achieved 14 days after the date of administration.
- Reference group: any individual eligible for COVID-19 vaccination at the beginning of the country-specific autumn 2023 vaccination campaign of interest, with the primary vaccination completed, but who did not yet receive it at the time of assessment of the vaccination status

Time spent in other vaccination statuses (for example, the first 13 days after a vaccine dose administration), and events recorded during such time were dropped from the study. Any individual who received an additional COVID-19 vaccine dose that resulted in a vaccination status not defined above was censored from the study on the date of the new dose (for example, a subsequent vaccine dose in an individual already vaccinated with the autumnal vaccination).

Vaccination status by time since the most recent (autumnal) COVID-19 vaccination.

For the secondary objective of estimating the VE by time since 2023 autumnal COVID-19 vaccination, using the same reference group as in the principal objective (see above), the time after the target vaccine dose (the one we want to estimate) was broken down into three periods (other vaccination statuses remained unchanged):

- Dose administered ≥14 days and <3 months (i.e. ≥14 days and ≤89 days ago);
- Dose administered ≥3 months & <6 months (i.e. 90–179 days ago);
- Dose administered ≥6 months (i.e. ≥180 days ago).

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, its censoring date was the earliest among the event dates (hospital admission or death) or the date of the positive laboratory diagnosis (i.e. the date of the first diagnosis of the infection episode that resulted in hospital admission or death, respectively). The laboratory diagnosis date was the date of the sample or, if the sample date was not available, the date of the laboratory result itself.

All study sites contributed to VE estimates against hospital admission due to COVID-19, but Belgium and the Netherlands did not have timely data on COVID-19-related deaths and could not contribute to VE estimates for this outcome.

Confounder

Models were initially adjusted by age at the beginning of the study period (in five-year categories), sex and, when appropriate, some geographical division within each country. Additionally, estimates were adjusted by the previous number of COVID-19 booster vaccine doses received before the start of the autumnal vaccination campaign (none, one, two, three, etc.), 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).

Comorbidities were included as a three-level variable across participating sites:

- No comorbidities related to increased risk of COVID-19 severe outcome;
- Medium risk comorbidities (for example, comorbidities that are associated with risk of COVID-19 severe outcome, but different from immunocompromising conditions, or other classification decided at site level), generally corresponding to comorbidities for which COVID-19 vaccination was recommended at that site;
- High-risk comorbidities (for example, immunocompromising conditions, or other classification decided at site level), for which also COVID-19 vaccination was recommended.

Data analysis

Vaccination status was a time changing variable defined at the beginning of each eight-week observation window (each study period). Eligible individuals contributed person-time to the reference group while they had not yet received the autumnal dose. In the case they received the autumnal vaccination, they were censored (as free of the event) from the non-autumnal dose group and, 14 days later, started contributing person-time to the autumnal vaccinated group (with a delayed entry into calendar time measured from the beginning of the study period).

Individuals were 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. Vaccine effectiveness was defined as VE = (1-HR) x 100. To estimate the VE of receiving the autumnal dose, we used Cox regression models adjusted by age, sex, geographical region (if applicable to the study site), previous number of booster vaccine doses, 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 on the log scale, 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 the reference category being compared was less than five and those were not included in the pooled estimates [21]. 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 (see Annex 3).

Results

Population characteristics and number of events

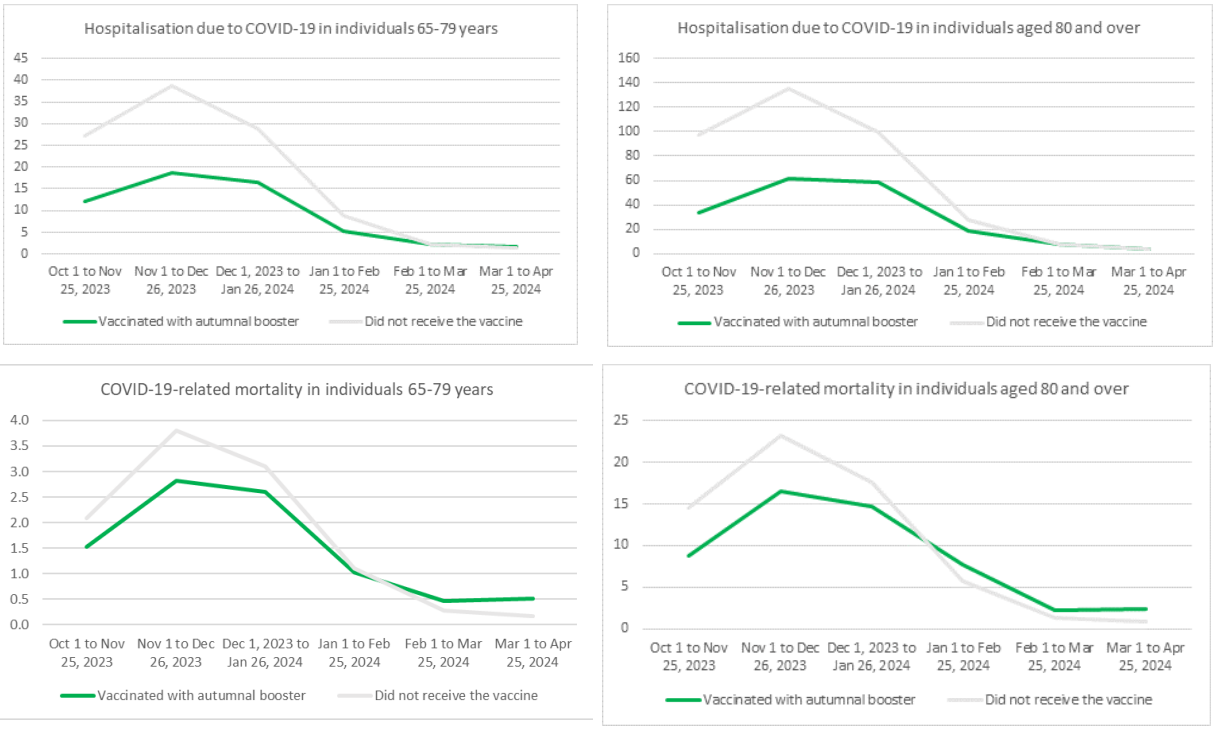
Between October 2023 and April 2024, the number of individuals aged ≥80 years included in the analysis across each study period decreased from 5.0 to 4.0 million individuals eligible for the autumnal dose but who had not received at that point. It fluctuated between 1.5 and 2.0 million individuals eligible and who had received the autumnal dose ≥14 days ago. In the 65–79 years age group, the number of individuals decreased from 12.5 to 9.8 million individuals eligible for the autumnal dose but who had not received it at that point. It increased from 3.4 to 4.5 million individuals eligible and who had received the autumnal dose ≥14 days ago. The specific number of individuals, person-months contributed to the study and number of events by study period and vaccination status are provided in Tables 5, 6, 7 and 8 for the different outcomes (hospitalisation due to COVID-19 and COVID-19-related death) and age groups (65–79 and ≥80 years). A total of 63 876 hospitalisations due to COVID-19 and 8 212 COVID-19-related deaths were analysed.

Characteristics of the person-months included were pooled across all study periods and are provided in Annex 4. Italy contributed the largest number of individuals and person-months to the study. Depending on the timing of the autumnal vaccination campaign and the coverage and speed of vaccination, the relative contribution of the study sites to the vaccinated or unvaccinated groups varied throughout the study period. More than 50% of the sample were females. Autumnal vaccination uptake during the study was higher for those with comorbidities.

The majority (98%) of vaccine types administered as the 2023 autumnal dose were Pfizer monovalent XBB.1.5. The majority of those who had been vaccinated with the autumnal dose by the end of the study (25 April 2024) had received two COVID-19 vaccine booster doses before the current campaign (52% of all vaccinated with the autumnal dose aged ≥80 years and 71% of those vaccinated aged 65–79 years). For 31% of all those vaccinated with the autumnal dose and aged ≥80 years, this autumnal dose was their fourth booster (they had received three booster doses before the current campaign). This contrasts with those who did not receive the autumnal dose, who in their majority had only one previous booster (49% of those unvaccinated with the autumnal dose ≥80 years and 60% of those 65–79 years) or two previous boosters (34% of those unvaccinated with the autumnal dose ≥80 years and 28% of those 65–79 years). These figures indicate that those taking the autumnal dose were, on average, vaccinated with more previous boosters than those not taking the autumnal dose, possibly related to comorbidities, other vulnerabilities or a general positive attitude and acceptability of COVID-19 vaccines.

The incidence rates of both hospitalisation due to COVID-19 and COVID-19-related death were several orders of magnitude higher in the group aged ≥80 years compared to the group 65-79 years (Figure 3). The overall incidence of hospitalisation due to COVID-19 was much lower in those who had received the monovalent XBB.1.5. autumnal vaccination compared to those eligible but who had not received it yet, particularly at the beginning of the vaccination campaigns. While differences in incidence rate by vaccination status were lower by the end of the study period, so was the incidence rate in both groups. Differences in COVID-19-related death by vaccination group were less evident in this crude assessment.

Figure 3. Incidence rate (per 100 000 person-months) of hospitalisation due to COVID-19 and COVID-19-related death by age group and vaccination status in overlapping eight-week study periods between October 2023 and April 2024



Effectiveness of the monovalent XBB.1.5 2023 autumnal dose

The effectiveness of the monovalent XBB.1.5 COVID-19 vaccine autumnal dose was moderate to high shortly after the start of the autumnal vaccination campaign. However, VE decreased steadily through the study period.

Vaccine effectiveness against hospitalisation due to COVID-19 among the population aged ≥80 years decreased from 65% (95%CI: 56 to 71) during the first eight-week observation window (from the start of the campaigns in October to 25 November 2024) down to 38% (95%CI: 31 to 45) on 1 January to 25 February 2024, fluctuating thereafter. Vaccine effectiveness against hospitalisation due to COVID-19 among the population aged 65–79 years decreased from 64% (95%CI: 55 to 72) to 48% (95%CI: 40 to 55) in the same two study periods, but decreased further down to 19.9% (95%CI: -48 to 57) by the end of the study (1 Mar to 25 Apr 2024).

Most of the decrease may be attributable to a calendar period effect i.e. changes along the monitoring period. These changes could be attributed to new SARS-CoV-2 variants becoming dominant or because of an increasing time since vaccination as the majority of the vaccinated population received it in October, or even to biases, such a depletion of susceptible. However, when restricting the analysis to autumnal doses administered ≤89 days, VE decreased from 65% (95%CI: 56 to 71) in the first observation period to 39% (95%CI: 32 to 46) in January–February 2024 among those aged ≥80-years, and from 64% (95%CI: 55 to 72) to 49% (95%CI: 41 to 56) in the 65–79 years age group.

This indicates that increasing time since vaccination could be playing a minor role in the decrease along calendar time, or that the category of the first three months is too broad and the waning with time since vaccination already happens within these first three months. In the most recent month (March–April) it was not possible to estimate VE for those with less than 89 days of administration. Due to the quick rollout of vaccination campaigns, there was little overlap between different categories of time since vaccination within each eight-week study period. Consequently, only the category of time since vaccination where most of the sample clustered at each study period could be accurately estimated, while other categories had low precision, not allowing the detection of VE varying by time since vaccination.

Vaccine effectiveness estimates against COVID-19 related deaths decreased similarly to VE against hospitalisation for ≥80-year-olds, but only marginally among 65–79 years age group. The latest observation period where VE against COVID-19 related deaths could be estimated with sufficient precision was January–February 2024, with wide confidence intervals thereafter. In January-February 2024, VE against COVID-19 related deaths was 40% (95%CI: 25 to 51) in ≥80-years old and 53% (95%CI: 24 to 71) in 65–79-year-olds.

The sites contributing to VE estimates varied throughout the study, since the number of events was insufficient at some moments, particularly at the beginning and the end of the study, to support VE estimates. In the first period (beginning of autumnal vaccination up to 25 November 2023), VE estimates against hospitalisation excluded Navarra for both the 65–79 and 80 years and above age groups and Portugal for the 65-79 age group, while VE against COVID-19-related deaths only included Portugal, Norway and Denmark. Towards the end of the study, for hospitalisation due to COVID-19 in the group 65-79 years, the number of events was insufficient in February onwards in Belgium and Portugal, and from March onwards also in Navarre. For hospitalisation due to COVID-19 in the group 80 plus, the number of events was insufficient in Belgium from February onwards and also in Navarre from March onwards.

For VE against COVID-19-related deaths in the 65–79 years age group, there were also insufficient events in Navarra from January onwards, and from all sites except Portugal and Denmark from February onwards. For VE against COVID-19-related deaths in the 80 years and above group, the events were insufficient in Navarre from February onwards, and from all sites except Portugal and Denmark from March onwards. The low number of events among the sites still contributing to the study in the last study period (March–April 2024) explain the very wide confidence intervals for these estimates, and the high level of uncertainty of the last period estimates.

Table 5. Autumnal vaccine effectiveness against COVID-19 hospitalisation in individuals 80 years or older, for all reporting periods between 1 October to 25 November 2023 and 1 March to 25 April 2024, EU/EEA: random effects meta-analysis

Study period	Status (days since)	VE (95%CI)	N*	Events/ Person-months	I^2 (min-max VE study estimate)**
1 Oct to 25 Nov 2023	Not yet vaccinated	ref	6 606 874	9 913/ 10 142 962	ref
	Overall vaccinated (>=14)	64.6% (56.4; 71.4)	1 516 579	352/ 1 058 956	56.7% (41%, BE to 78%, NL)
	Vaccinated 14–89)	64.6% (56.4; 71.4)	1 516 579	352/ 1 058 956	56.7% (41%, BE to 78%, NL)
	Vaccinated (90–179)	-	0	0/0	-
	Vaccinated (>=180)	-	0	0/0	-
1 Nov to 26 Dec 2023	Not yet vaccinated	ref	5 522 233	11 959/ 8 730 627	ref
	Overall vaccinated (>=14)	58.7% (52.2; 64.4)	2 159 327	1 758/ 2 845 117	75.1% (23%, BE to 69%, NL)
	Vaccinated 14–89)	58.8% (52.4; 64.4)	2 159 327	1 753/ 2 836 772	74% (24%, BE to 69%, NL)
	Vaccinated (90–179)	-	0	0/0	-
	Vaccinated (>=180)	-	0	0/0	-
1 Dec 2023 to 26 Jan2024	Not yet vaccinated	ref	4 368 944	7 619/ 7 547 281	ref
	Overall vaccinated (>=14)	48.3% (44.6; 51.8)	1 895 697	1 819/ 3 108 690	0% (17%, BE to 55%, SE)
	Vaccinated 14–89)	48.9% (43.7; 53.6)	1 895 630	1 777/ 2 785 388	30.2% (12%, BE to 59.1%, NV)
	Vaccinated (90–179)	41.7% (11.1; 61.7)	517 801	29/ 273 583	0% (36%, BE to 45%, NO)
	Vaccinated (>=180)	-	0	0/0	-
1 Jan to 25 Feb 2024	Not yet vaccinated	ref	4 095 253	2 043/ 7 339 201	ref
	Overall vaccinated (>=14)	38.3% (30.7; 45)	1 979 251	675/ 3 522 728	0% (33%, IT to 51%, PT)
	Vaccinated 14–89)	39.4% (31.7; 46.3)	1 635 534	539/ 1 924 370	0% (35%, IT to 52.5%, NV)
	Vaccinated (90–179)	38.9% (15.8; 55.6)	1 513 053	134/ 1 486 381	40.2% (-5%, IT to 68.5%, DK)
	Vaccinated (>=180)	-	0	0/0	-
1 Feb to 25 Mar 2024	Not yet vaccinated	ref	3 984 882	548/ 7 239 787	ref
	Overall vaccinated (>=14)	35.3% (20.8; 47.1)	1 660 149	228/ 3 008 418	0% (-15.8%, NV to 64.1%, DK)
	Vaccinated 14–89)	42.9% (22.6; 57.8)	919 699	68/ 718 520	0% (23%, SE to 61.1%, DK)
	Vaccinated (90–179)	35.0% (6.2; 54.9)	1 555 359	159/ 2 197 430	47.1% (-15.6%, NV to 64.7%, DK)

Study period	Status (days since)	VE (95%CI)	N*	Events/ Person-months	I^2 (min-max VE study estimate)**
	Vaccinated (>=180)	-	0	0/0	-
1 Mar to 25 Apr 2024	Not yet vaccinated	ref	3 947 571	293/ 7 178 251	ref
	Overall vaccinated (>=14)	45.4% (11.2; 66.4)	1 648 134	124/ 2 886 345	57.8% (-322.8%, NV to 76.1%, DK)
	Vaccinated 14–89)	-	0	0/0	-
	Vaccinated (90–179)	37.7% (-22.5; 68.3)	1 501 121	84/ 2 245 522	61.5% (-340.8%, NV to 74.3%, DK)
	Vaccinated (>=180)	-	0	0/0	-

** N = total number of individuals classified according to their vaccination status at the end of follow-up of each eight-week observation period; ** Country abbreviations: BE = Belgium, DK = Denmark, IT = Italy, NL = the Netherlands, NO = Norway, PT = Portugal, NV = Spain (Navarra), SE = Sweden. - = no VE estimate as number of events in reference group <15, VE = Vaccine effectiveness; adjusted by sex, age (five-year bins), region and comorbidities and socioeconomic variables (as available in each study site).*

Table 6. Autumnal vaccine effectiveness against COVID-19 hospitalisation in individuals 65–79 years old, for all reporting periods between 1 October 25 November 2023 and 1 March to 25 April 2024, EU/EEA: random effects meta-analysis

Study period	Status (days since)	VE (95%CI)	N*	Events/ Person-months	I^2 (min-max VE study estimate)**
1 Oct to 25 Nov 2023	Not yet vaccinated	ref	16 294 260	6 926/ 25 350 388	ref
	Overall vaccinated (>=14)	64.4% (55.3; 71.7)	2 761 926	237/ 1 944 012	46.3% (44%, BE to 75%, NL)
	Vaccinated 14–89)	64.4% (55.3; 71.7)	2 761 926	237/ 1 944 012	46.3% (44%, BE to 75%, NL)
	Vaccinated (90v179)	-	0	0/0	
	Vaccinated (>=180)	-	0	0/0	
1 Nov to 26 Dec 2023	Not yet vaccinated	ref	14 096 197	8 630/ 22 113 043	ref
	Overall vaccinated (>=14)	61.1% (51.5; 68.9)	5 334 318	1 239/ 6 602 781	83.6% (7%, PT to 72%, NL)
	Vaccinated 14–89)	61.1% (51.5; 68.9)	5 334 318	1 237/ 6 588 722	83.6% (7%, PT to 72%, NL)
	Vaccinated (90–179)	-	0	0/0	-
	Vaccinated (>=180)	-	0	0/0	-
1 Dec 2023 to 26 Jan 2024	Not yet vaccinated	ref	10 444 529	5 334/ 18 280 397	ref
	Overall vaccinated (>=14)	54.3% (49.9; 58.3)	4 406 290	1 215/ 7 346 408	11.7% (46%, PT to 63%, BE)
	Vaccinated 14–89)	55.2% (50.4; 59.6)	4 405 858	1 182/ 6 566 741	18.9% (46%, PT to 67%, BE)
	Vaccinated (90v179)	57.0% (26; 75)	162 547	15/ 55 923	0% (57%, NO to 57%, NO)
	Vaccinated (>=180)	-	0	0/0	-
1 Jan to 25 Feb 2024	Not yet vaccinated	ref	9 944 086	1 604/ 17 976 335	ref
	Overall vaccinated (>=14)	48.2% (40.4; 55)	4 503 529	426/ 8 088 270	0% (12%, DK to 55%, BE)
	Vaccinated 14–89)	48.8% (40.5; 56)	3 641 514	333/ 4 319 874	0% (8.8%, DK to 54%, SE)
	Vaccinated (90–179)	41.3% (20; 56.9)	2 079 354	82/ 2 308 352	7.1% (-38.7%, NV to 59%, BE)
	Vaccinated (>=180)	-	0	0/0	-
1 Feb to 25 Mar 2024	Not yet vaccinated	ref	9 773 413	411/ 17 858 242	ref
	Overall vaccinated (>=14)	31.9% (3; 52.2)	3 716 972	153/ 6 797 494	28.5% (-130%, PT to 58%, IT)
	Vaccinated 14–89)	25.6% (-48.8; 62.8)	1 765 953	40/ 1 359 357	66.7% (-34%, SE to 60%, IT)
	Vaccinated (90–179)	32.3% (3.2; 52.6)	3 464 077	103/ 4 954 556	12.4% (-175%, PT to 55%, IT)
	Vaccinated (>=180)	-	0	0/0	-
1 Mar to 25 Apr 2024	Not yet vaccinated	ref	9 739 215	241/ 17 820 193	ref

Study period	Status (days since)	VE (95%CI)	N*	Events/ Person-months	I^2 (min-max VE study estimate)**
	Overall vaccinated (>=14)	19.9% (-47.7; 56.5)	3 660 240	107/ 6 693 033	68.3% (-156%, PT to 74.9%, DK)
	Vaccinated 14–89)	-	0	0/0	-
	Vaccinated (90–179)	25.8% (-43.6; 61.6)	3 622 914	89/ 5 764 249	70.3% (-114%, PT to 79.2% DK)
	Vaccinated (>=180)	-	0	0/0	-

** N = total number of individuals classified according to their vaccination status at the end of follow-up of each 8-week observation period; ** Country abbreviations: BE = Belgium, DK = Denmark, IT = Italy, NL = the Netherlands, NO = Norway, PT = Portugal, NV = Spain (Navarra), SE = Sweden. - = no VE estimate as number of events in reference group <15, VE = Vaccine effectiveness; adjusted by sex, age (five-year bins), region and comorbidities and socioeconomic variables (as available in each study site)*

Table 7. Autumnal vaccine effectiveness against COVID-19 mortality in individuals 80 years or older, for all reporting periods between 1 October to 25 November 2023 and 1 March to 25 April 2024, EU/EEA: random effects meta-analysis

Study period	Status (days since)	VE (95%CI)	N*	Events/ Person-months	I^2 (min-max VE study estimate)**
1 Oct to 25 Nov 2023	Not yet vaccinated	ref	5 557 633	1 321/ 9 076 323	ref
	Overall vaccinated (>=14)	66.7% (40.6; 81.4)	732 343	41/ 466 626	62.2% (36%, SE to 84%, NO)
	Vaccinated 14–89)	66.7% (40.6; 81.4)	732 343	41/ 466 626	62.2% (36%, SE to 84%, NO)
	Vaccinated (90–179)	-	0	0/0	-
	Vaccinated (>=180)	-	0	0/0	-
1 Nov to 26 Dec 2023	Not yet vaccinated	ref	4 969 210	1 846/ 7 930 660	ref
	Overall vaccinated (>=14)	65.0% (59; 70.1)	1 432 061	282/ 1 702 417	0% (58.1%, DK to 74%, SE)
	Vaccinated 14–89)	64.7% (58.6; 70)	1 432 061	281/ 1 701 419	0% (58.1%, DK to 73%, SE)
	Vaccinated (90–179)	-	0	0/0	-
	Vaccinated (>=180)	-	0	0/0	-
1 Dec 2023 to 26 Jan 2024	Not yet vaccinated	ref	4 087 096	1 231/ 7 061 303	ref
	Overall vaccinated (>=14)	59.0% (47; 68.3)	1 493 164	353/ 2 394 155	54.8% (47.8%, NV to 75%, SE)
	Vaccinated 14–89)	58.8% (46.5; 68.3)	1 493 120	343/ 2 251 164	56.2% (45.6%, NV to 75%, SE)
	Vaccinated (90–179)	62.0% (15.5; 82.9)	231 063	7/ 93 242	0% (62%, PT***)
	Vaccinated (>=180)	-	0	0/0	-
1 Jan to 25 Feb 2024	Not yet vaccinated	ref	3 898 429	400/ 6 984 183	ref
	Overall vaccinated (>=14)	39.7% (25.2; 51.3)	1 666 042	226/ 2 954 498	0% (16.3%, DK to 62%, SE)
	Vaccinated (14–89)	44.0% (29.1; 55.7)	1 637 981	167/ 1 927 838	0% (12.1%, DK to 63%, SE)
	Vaccinated (90–179)	-	890 389	54/ 854 181	66.5% (-163%, IT to 45%, PT)
	Vaccinated (>=180)	-	0	0/0	-
1 Feb to 25 Mar 2024	Not yet vaccinated	ref	3 791 792	96/ 6 888 887	ref
	Overall vaccinated (>=14)	38.1% (-6; 63.9)	1 636 114	60/ 2 963 462	43.5% (-3%, IT to 79%, SE)
	Vaccinated (14–89)	-	0	0/0	-
	Vaccinated (90–179)	23.8% (-76; 67)	1 398 706	40/ 1 944 680	62.9% (-105%, IT to 69%, SE)
	Vaccinated (>=180)	-	0	0/0	-

1 Mar to 25 Apr 2024	Not yet vaccinated	ref	3 756 213	54/ 6 829 880	ref
	Overall vaccinated (>=14)	56.9% (-44.3; 87.1)	984 682	33/ 1 672 912	71.5% (-29%, PT to 81%, SE)
	Vaccinated (14–89)	-	0	0/0	-
	Vaccinated (90–179)	54.5% (-63.5; 87.3)	977 585	31/ 1 453 822	73.6% (-46%, PT to 81%, SE)
	Vaccinated (>=180)	-	0	0/0	-

** N = total number of individuals classified according to their vaccination status at the end of follow-up of each 8-week observation period; ** Country abbreviations: BE = Belgium, DK = Denmark, IT = Italy, NL = the Netherlands, NO = Norway, PT = Portugal, NV = Spain (Navarra), SE = Sweden. - = no VE estimate as number of events in reference group <15, VE = Vaccine effectiveness; adjusted by sex, age (5-year bins), region and comorbidities and socioeconomic variables (as available in each study site). *** Estimate based on just one study site.*

Table 8. Autumnal vaccine effectiveness against COVID-19 mortality in individuals 65–79 years old, for all reporting periods between 1 October to 25 November 2023 and 1 March to 25 April 2024, EU/EEA. Random effects meta-analysis.

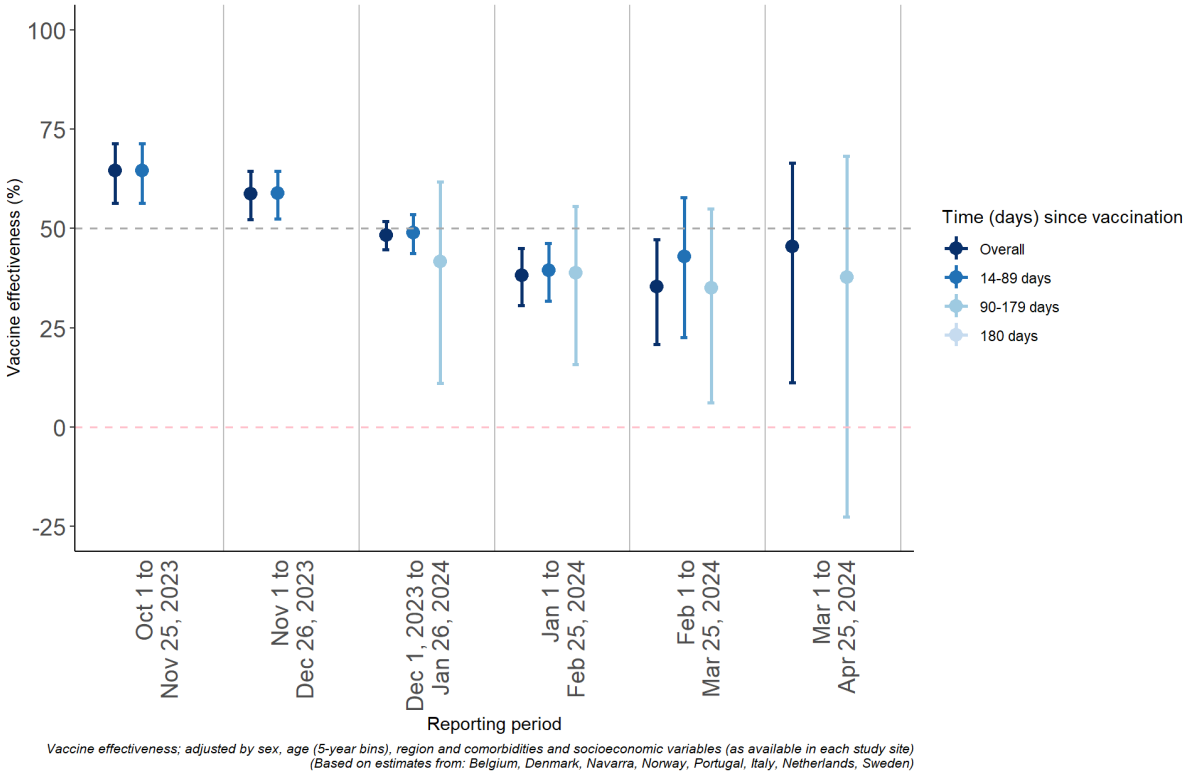
Study period	Status (days since)	VE (95%CI)	N*	Events/ Person-months	I^2 (min-max VE study estimate)**
1 Oct to 25 Nov 2023	Not yet vaccinated	ref	12 684 571	434/ 20 766 132	ref
	Overall vaccinated (>=14)	67.0% (42.5; 81)	1 422 008	16/ 1 049 202	0% (46%, PT to 74%, NO)
	Vaccinated 14–89)	67.0% (42.5; 81)	1 422 008	16/ 1 049 202	0% (46%, PT to 74%, NO)
	Vaccinated (90–179)	-	0	0/0	-
	Vaccinated (>=180)	-	0	0/0	-
1 Nov to 26 Dec 2023	Not yet vaccinated	ref	11 394 619	696/ 18 339 493	ref
	Overall vaccinated (>=14)	73.4% (65.7; 79.4)	3 191 865	107/ 3 782 124	0% (64%, IT to 85%, SE)
	Vaccinated 14–89)	73.4% (65.6; 79.5)	3 191 865	107/ 3 777 912	0% (64%, IT to 85%, SE)
	Vaccinated (90–179)	-	0	0/0	-
	Vaccinated (>=180)	-	0	0/0	-
1 Dec 2023 to 26 Jan 2024	Not yet vaccinated	ref	9 343 622	495/ 16 335 545	ref
	Overall vaccinated (>=14)	66.0% (56.1; 73.6)	3 171 560	134/ 5 147 693	0% (49%, IT to 71.2%, DK)
	Vaccinated 14–89)	65.2% (54.9; 73.1)	3 171 237	131/ 4 839 882	0% (48%, IT to 71%, DK)
	Vaccinated (90–179)	-	0	0/0	-
	Vaccinated (>=180)	-	0	0/0	-
1 Jan to 25 Feb 2024	Not yet vaccinated	ref	9 138 659	181/ 16 508 254	ref
	Overall vaccinated (>=14)	53.2% (24; 71.2)	3 658 852	67/ 6 545 607	37.5% (21%, SE to 81.7%, DK)
	Vaccinated 14–89)	54.8% (27.6; 71.7)	3 589 786	50/ 4 266 176	25.1% (32%, SE to 81.7%, DK)
	Vaccinated (90–179)	51.0% (-25.7; 80.9)	714 421	7/ 775 825	0% (51% PT***)
	Vaccinated (>=180)	-	0	0/0	-
1 Feb to 25 Mar 2024	Not yet vaccinated	ref	8 973 067	42/ 16 394 848	ref
	Overall vaccinated (>=14)	15.6% (-190.4; 75.5)	1 499 052	13/ 2 755 500	0% (-28%, PT to 43.5%, DK)
	Vaccinated 14–89)	-	0	0/0	-
	Vaccinated (90–179)	27.6% (-158.4; 79.7)	1 445 684	10/ 2 376 375	0% (-16%, PT to 54.1%, DK)
	Vaccinated (>=180)	-	0	0/0	-

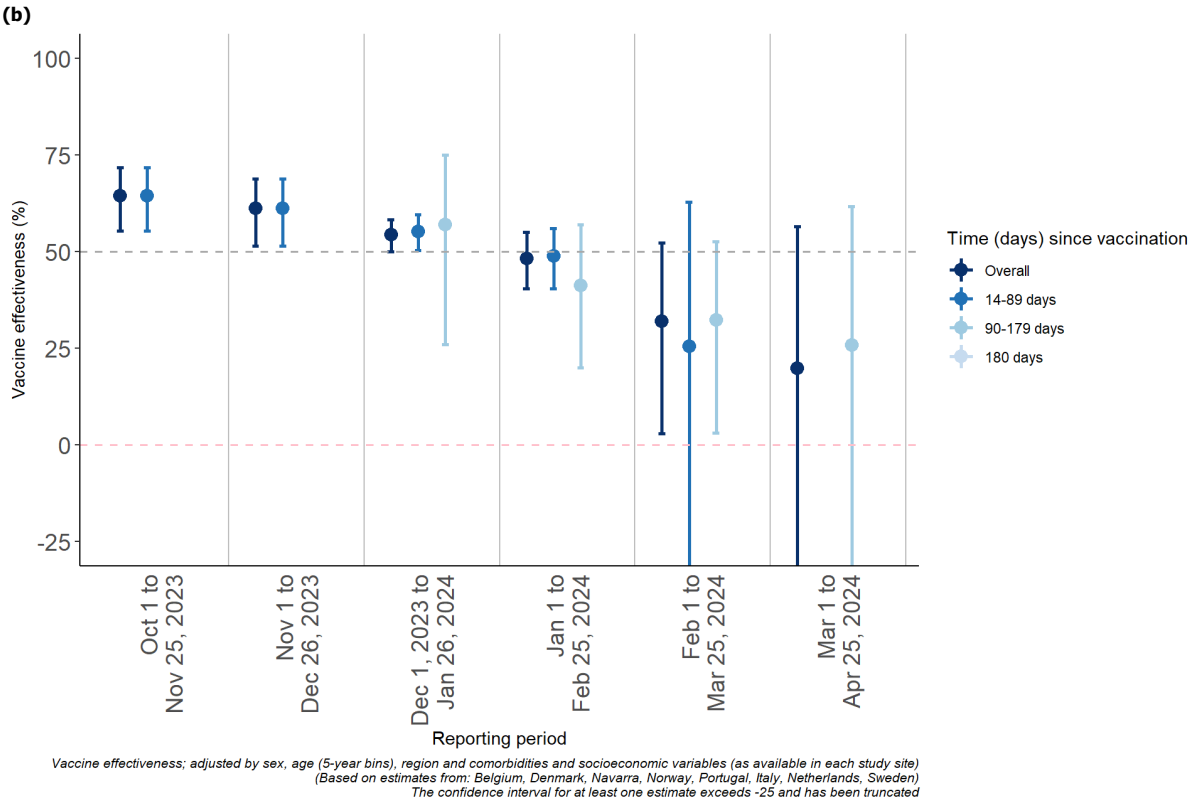
Study period	Status (days since)	VE (95%CI)	N*	Events/ Person-months	I^2 (min-max VE study estimate)**
1 Mar to 25 Apr 2024	Not yet vaccinated	ref	8 940 706	26/ 16 359 208	ref
	Overall vaccinated (>=14)	36.0% (-66.8; 75.4)	1 498 374	14/ 2 763 192	0% (27%, PT to 55.7%, DK)
	Vaccinated 14–89)	-	0	0/0	-
	Vaccinated (90–179)	28.0% (-126.2; 77.1)	822 670	8/ 1 256 877	0% (28%, PT***)
	Vaccinated (>=180)	-	0	0/0	-

** N = total number of individuals classified according to their vaccination status at the end of follow-up of each 8-week observation period; ** Country abbreviations: BE = Belgium, DK = Denmark, IT = Italy, NL = the Netherlands, NO = Norway, PT = Portugal, NV = Spain (Navarra), SE = Sweden. - = no VE estimate as number of events in reference group <15, VE = Vaccine effectiveness; adjusted by sex, age (5-year bins), region and comorbidities and socioeconomic variables (as available in each study site). *** Estimate based on just one study site.*

Figure 4. Autumnal vaccine effectiveness against COVID-19 hospitalisation, for all reporting periods between 1 October to 25 November 2023 and 1 March to 25 April 2024, EU/EEA: random effects meta-analysis, in individuals aged ≥80 years (a) or 65–79 years (b)

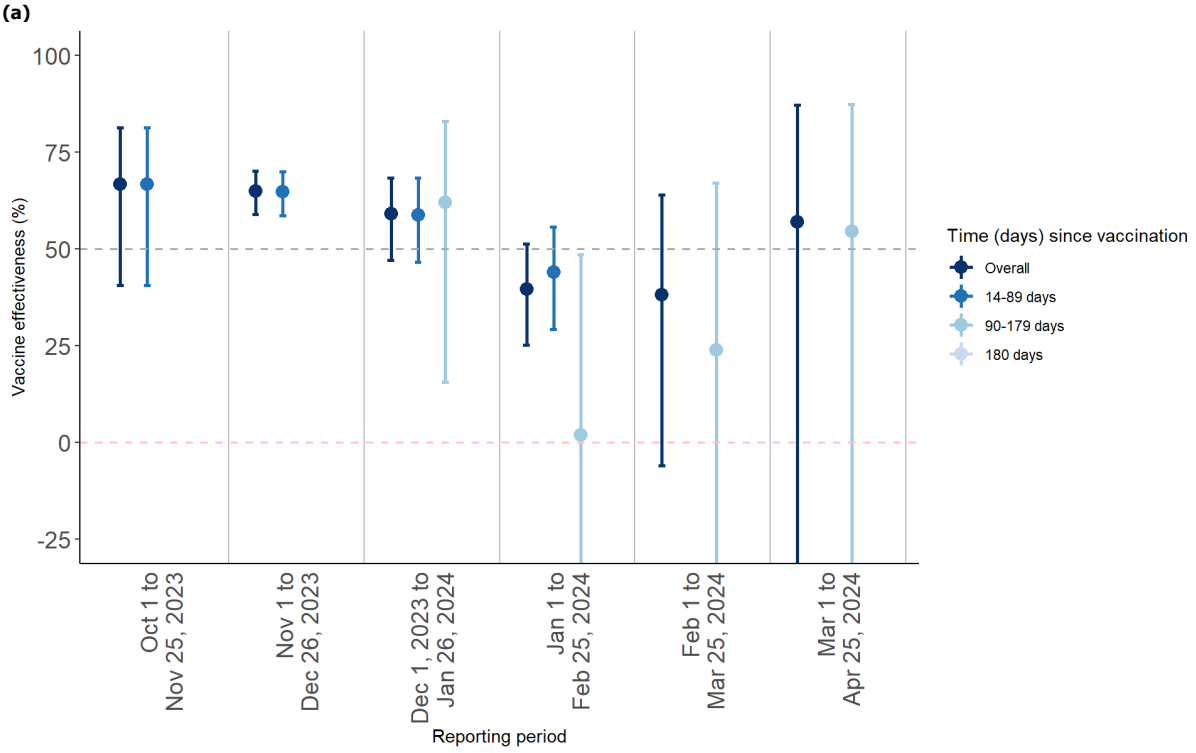
(a)





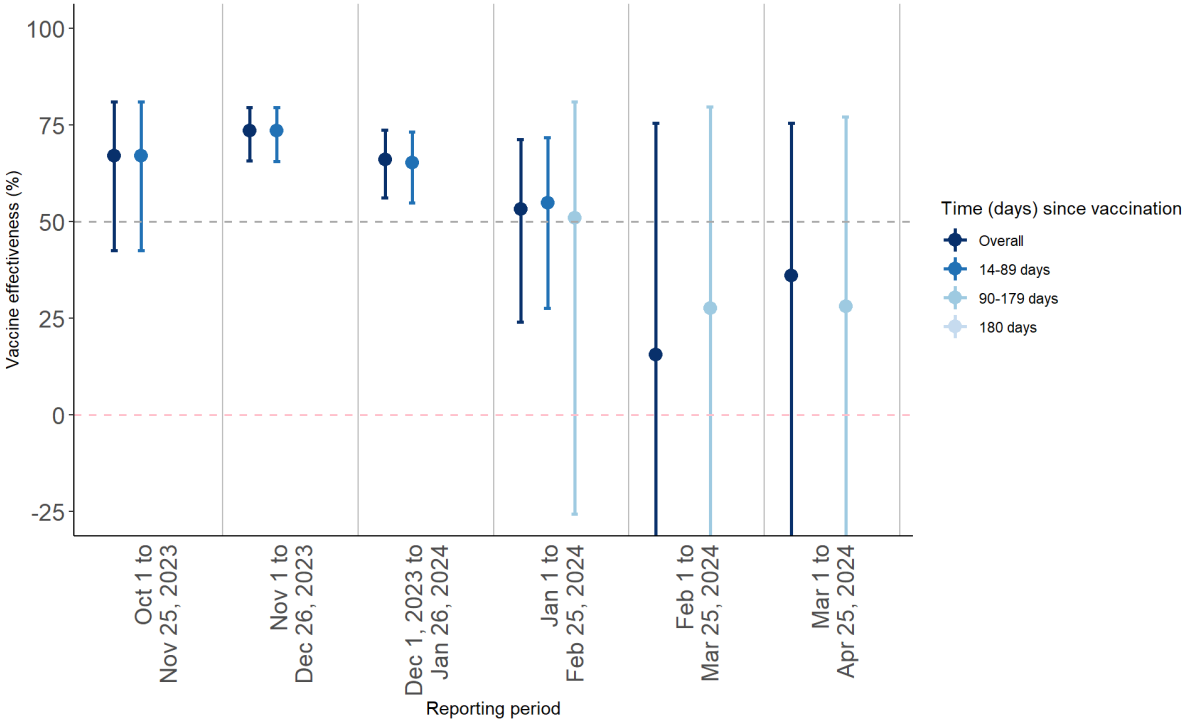
Vaccine effectiveness; adjusted by sex, age (5-year bins), region and comorbidities and socioeconomic variables (as available in each study site)
(Based on estimates from: Belgium, Denmark, Navarra, Norway, Portugal, Italy, Netherlands, Sweden)
The confidence interval for at least one estimate exceeds -25 and has been truncated

Figure 5. Autumnal vaccine effectiveness against COVID-19 mortality, for all reporting periods between 1 October to 25 November 2023 and 1 March to 25 April 2024, EU/EEA: random effects meta-analysis, in individuals aged ≥80+ years (a) or 65–79 years (b)



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, Navarra, Norway, Portugal, Italy, Netherlands, Sweden)
The confidence interval for at least one estimate exceeds -25 and has been truncated

(b)



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, Navarra, Norway, Portugal, Italy, Netherlands, Sweden)
The confidence interval for at least one estimate exceeds -25 and has been truncated

Challenges, limitations and interpretations

The 2023 autumnal dose with monovalent XBB.1.5 vaccines has shown moderate to high VE against hospitalisation due to COVID-19 and COVID-19-related mortality and for groups aged 65-79 years or ≥80 years old. However, waning effectiveness has been rapid, particularly for the group aged ≥80 years and there was also a higher probability of being hospitalised for this age group. The decrease in VE seems to be driven by a decrease across calendar times, however, we could not demonstrate waning protection with time since vaccination due to there being too few overlaps in time since vaccination thresholds and wide confidence intervals. This is evident because the decrease in VE is more pronounced when comparing different time periods of the study than when comparing individuals within the same time period who were vaccinated at different times. The changes in virus circulation with Omicron subvariant XBB.1.5 initially dominating, with the emergence of BA.2.86 and sub-lineages along the study period, probably explains most of the decrease in protection due to changes in the genetic composition of the spike protein [22–24]. Other factors such as the depletion of those susceptible from the unvaccinated group [25] may have also influenced the decrease in protection with time.

The multi-country approach for VE monitoring using data routinely collected in EHR and according to a common protocol, offers multiple advantages. The relatively rapid availability of data in EHR allows 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 us to analyse an observation period covering the time from three up to one month before the time of data analysis. The increased sample size allows for monitoring less frequent events by pooling results from several countries, while also achieving wider representativity and good comparability across participating sites.

Nonetheless, despite the increase in sample size in this multi-country network, during the monitoring of the vaccine campaigns in 2022 and its follow-up during the first half of 2023, the number of events was sometimes too low to provide precise estimates. This occurred particularly for VE against COVID-19-related death, in younger age groups and/or in moments of lower COVID-19 incidence. Previous monitoring was focused on the estimation of the VE of first, second or third boosters compared to primary vaccination only [26,27].

In the current monitoring protocol [2], a single exposed category has been considered for those who received the autumnal dose, and only one reference group is used for all those eligible for that dose but who had not received it at that point, regardless of the number of vaccines doses received before the start of the autumnal campaign. This change has negated the limitation previously observed [28], while also increasing the precision and usefulness of the VE estimates for the current 2023 autumnal dose monitoring, at least until February 2024.

This update of the study protocol for the 2023 autumnal dose monitoring was also supported by previous results from the VEBIS EHR network that suggested that the vaccine dose in the autumn of 2022 was equally effective, regardless of the number of previous booster doses, and that the time since last vaccination was probably more relevant to protection against COVID-19 than number of previous doses [18]. Further, the effectiveness of the third booster dose was probably greatly underestimated in the 2022 autumnal VE estimates, as that cohort likely comprised a high proportion of individuals with high-risk/immunocompromising comorbidities and vulnerabilities compared with proportions in the present study or, alternately, such estimates could be due to lower levels of previous infections among the most frequently vaccinated [18,26]. The current protocol for 2023 autumnal vaccination provides more stable estimates, with less likely residual confounding [28].

A limitation of the results are that there was low to moderate variability across study sites. This heterogeneity in the estimates may come from different sources. To start with, 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 how variables are defined across sites (e.g. comorbidity variables were usually pre-coded at the 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 and observation periods over time, which can make interpretation complex, but is also an opportunity to compare the effectiveness of vaccine doses across countries with different vaccine rollout 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. In the context of this heterogeneity, the different participation of countries at different points in time within the study may influence the pooled result.

Additionally, EHRs are less flexible than primary data collection in including 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. Also, as outcome identification is based on previously collected data, there is a risk of 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 a positive SARS-CoV-2 test. Because the cause of death is not generally available promptly in most countries, it is likely that deaths in which SARS-CoV-2 was detected but were 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 the systematic use of SARS-CoV-2 tests in the hospital setting, the probability of underdiagnosis and/or misclassification of events may increase. A reduction in the scale and/or focus in the systematic approach to testing and COVID-19 case notification could impact the accuracy of VE estimates in several ways. One proposed phenomenon is misclassification due to increased delays in reporting complex COVID-19 cases. Where previously such cases would be recorded in EHRs as a priority, a reduced focus on the timeliness of reporting COVID cases could result in some COVID records being updated later than in the pandemic period, and possibly after the point of data extraction from source EHRs by VEBIS EHR study sites. Should complex cases take longer to resolve due to their requiring more information than straightforward COVID cases and, simultaneously, should vaccinated cases be less likely to progress to severe illness, there could be some degree of misclassification causing a lower number of events in the unvaccinated than the true total and, in turn, leading to an overestimation of VE.

Conclusions

Overall, results of this study indicate that the 2023 autumnal dose with monovalent XBB.1.5 vaccines was effective in restoring protection against both hospitalisation due to COVID-19 and COVID-19-related death. However, VE declined over time and reached ≤55% for both outcomes by January to February 2024. This needs to be interpreted in the context of the genetic evolution of circulating SARS-CoV-2 variants after December 2023, to increasing time since vaccination in the majority of the vaccinated population who received it in October, or even to biases, such as a depletion of susceptible individuals. The difference between study periods was much higher than between time since vaccination cohorts in the same period, indicating that any waning of protection may have had little relevance in the decrease of protection so far. After February and March 2024, the incidence of both hospitalisation due to COVID-19 and COVID-19 related death was too low and the number of events was insufficient to support reliable vaccine effectiveness estimates.

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

Type of variables	Study variable	Study site							
		Belgium	Denmark	Italy	Spain (Navarra)	The Netherlands	Norway*	Portugal	Sweden
Outcomes	Hospital admission due to COVID-19	Clinical Hospital Survey database	Danish National Patient Register (DNPR)	National Integrated COVID-19 Surveillance Databases	Enhanced COVID surveillance with individual revision of events	NICE COVID-19 registration	Norwegian Intensive Care and Pandemic Registry (NIPaR)	National Hospital Discharge database (BIMH)	Swedish National Patient Register
	Death due to COVID-19	Not applicable	MiBA and Danish Civil Registration system (CPR)	National Integrated COVID-19 Surveillance Databases	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): cause of death is from SICO, death status and date of death from NHSU.	Swedish Cause of Death register and Register of the Total Population Register on surveillance of notifiable communicable diseases
Exposures	Vaccination status	National vaccine registry (VACCINNET)	Danish Vaccination Registry (DVR)	National Vaccination Registry	Vaccination register	COVID-19 vaccination registry (CIMS)	The National Immunisation Register (SYSVAK)	The National Vaccination Register (VACINAS)	Swedish National Vaccination Register
Variables for adjustment or stratification	Age	The national population register	CPR	National Vaccination Registry	Administrative database	The national population register	The National Population Register (Folkeregisteret)	National Health Service User database (NHSU)	Register of the Total Population
	Sex	national population register	CPR	National Vaccination Registry	Administrative database	The national population register	The National Population Register (Folkeregisteret)	National Health Service User database (NHSU)	Register of the Total Population
	Health Region	Province of residence: national population register	CPR	Region where vaccination took place National Vaccination Registry	Not applicable	NA	County of residence at end of study period: The National Population Register (Folkeregisteret)	Region of residence: National Health Service User database (NHSU)	Register of the Total Population
	Comorbidities	Intermutualistic Agency database	DNPR	National Vaccination Registry	Primary Care Information System	Specialized health care utilization combined with prescribed medication register, both from year 2020	Risk groups / Comorbidities: Based on Norwegian Patient Registry (NPR)	Primary Care Information System (SIM@SNS).	Swedish National Patient Register
	Previous infection	COVID-19 Laboratory test results database from Healthdata.be register	MiBA	National Integrated COVID-19 Surveillance Databases	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)	Swedish National Vaccination Register
	Others specific to the study site	Household income (according to tax records) categorized as low (lowest 40%), mid (middle 30%), and high (highest 30%): STATBEL database	Not applicable	Country of birth National Vaccination Registry	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	Conditions of living – Deprivation at municipality level: Most recent data from 2011.	Marital status, educational level, country of birth The Longitudinal integrated database for health insurance and labour market studies

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

Annex 2. Methodological details in the participating study sites

Variable	Definition, categorisation, use in the model							
	Belgium	Denmark	Italy	The Netherlands	Spain (Navarra)	Norway	Portugal	Sweden
Age	Age in years at the end of the year in which the study period begins. For adjustment: 5-year age groups.	5–17, 18–49, 50–64, 65–79, ≥80, adjusted in categories: 5-9, 10–14, 15–17, 18–24 and then 5-year categories until the final category, 90+ years	Age at the start of study period (for adjustment: 5-year age groups up to 90-94 years and then grouping ≥95 years))	Age at the start of study period (5-year categories)	Age at the start of study period (5-year categories)	Age at end of 2022 (birth cohorts) (For adjustment: 5-year age groups)	Age at the start of study period (5-year categories)	Age in years at the end of the year in which the study period begins.
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): - *Cardiovascular illness – general* - *Cardiovascular illness-specifically a heart disease* - *Alzheimer* - *Asthma* - *Haemophilia* - *Chronic obstructive pulmonary disease* - *Diabetes with cardiovascular compilations* - *Diabetes Mellitus with insulin treatment* - *Epilepsy and neuropathic pain* - *Chronic hepatitis type B or C* - *Exocrine pancreatic disease* - *Disease of Parkinson* - *Psychosis occurring with people older than 70 years* - *Psychosis occurring with people of 70 years or younger.* - *Thrombosis while treated with antithrombotic medicines* - *Thyroid disorder* - *HIV* Immunocompromised (high risk): if a person has one of the following comorbidities	Immunocompromised, including: - *HIV* - *Immunological disease* - *Radiation therapy* - *Organtransplanted* Other, including: - *Diabetes* - *Obesity* - *Cancer* - *Neurological Disease* - *Kidney disease* - *Haematological cancers* - *Heart disease* - *Chronic respiratory disease* - *Liver disease (incl. alcohol lever)* - *Endocrine Disease* - *Hematological Disease* - *Coagulation Disease* - *Innate Diseases* - *TB* - *Missing a lung* - *Missing a kidney*	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* Other comorbidities, including: - *Respiratory diseases requiring oxygen*	3-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].	Immunocompromised Other major chronic conditions - *Diabetes* - *Severe Obesity* - *Cancer* - *Ictus* - *Dementia* - *Kidney disease* - *Haematological cancers* - *Heart disease* - *Chronic respiratory disease* - *Liver disease* - *Rheumatic arthritis*	High risk: - *Organ transplant* - *Immunodeficiency* - *Haematological cancer in the last five years* - *Other active cancers* - *Neurological or neuromuscular diseases that cause impaired cough or lung function (e.g., ALS and cerebral palsy)* - *Chronic kidney disease, or significant renal impairment.* Medium risk: - *Chronic liver disease or significant hepatic impairment* - *Immunosuppressive therapy* - *Diabetes* - *Chronic lung disease including cystic fibrosis and severe asthma which have required the use of high dose inhaled or oral steroids within the past year*	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*	Vaccine priority groups: *LISA Healthcare worker (status per October 2018)* *SOL Nursing home resident (status per December 31, 2020).* Comorbidity groups: *(binary)* *Any records with ICD-10 codes as primary/secondary diagnosis from inpatient stay or outpatient contact in hospital or from privatepracticing specialists, January 1, 2017 – December 27, 2020)* *Chronic pulmonary disease NPR J41 J42 J43 J44 J45 J46 J47 J84 J98 E84* *Cardiovascular conditions and diabetes* *NPR, SPDR I05 I06 I07 I08 I09 I110 I2 I34 I35 I36 I37 I39 I42 I43 I46 I48 I49 I50 E10-E14* ATC: *A10 (at least two filled prescriptions during 2020, before December 27, 2020)*

Variable	Definition, categorisation, use in the model							
	Belgium	Denmark	Italy	The Netherlands	Spain (Navarra)	Norway	Portugal	Sweden
	associated with immunodeficiency: - *Disease of Crohn, Colitis Ulcerosa, Psoriatrische arthritis, Reumatoid arthritis* - *Kidney failure* - *Cystic fibrosis* - *Psoriasis* - *Multiple sclerosis* - *Organ transplantation* - *Received chemotherapy/radiotherapy against cancer* - *Received multidisciplinary oncologic consult*		*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 104/1992 art. 3 paragraph 3* - *Chronic Alcohol Misuse* - *Functional or anatomic asplenia*			- *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*		*Autoimmunity-related conditions* *NPR D86 G35 K50 K51 L40 M05 M06 M07 M08 M09 M13 M14 M45* *Malignancy NPR, CAN C0 C1 C2 C3 C4 C5 C6 C7 C8 C9 D45 D46 D47* *(CAN from 2017-2019, NPR for 2020)* *Moderate to severe renal disease* *NPR I12 I13 N00 N01 N02 N03 N04 N05 N07 N11 N14 N17* *N18 N19 Q61*

Variable	Definition, categorisation, use in the model							
	Belgium	Denmark	Italy	The Netherlands	Spain (Navarra)	Norway	Portugal	Sweden
			- *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* - *Patients with CSF leak from trauma or intervention* - *Patients going to start immunosuppressive treatment* - *Metabolic diseases*				

Variable	Definition, categorisation, use in the model							
	Belgium	Denmark	Italy	The Netherlands	Spain (Navarra)	Norway	Portugal	Sweden
			- *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	Not included	Country of birth	As registered at time of analysis (June 2022)	Not included	Country of birth. Sweden, Nordic, Eu, Other
Deprivation index or similar	Household income: low (lowest 40%)-medium (middle 30%)-high (highest 30%)	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 met (incomplete and slightly outdated data)	European deprivation index quintile Q1 (least deprived) to Q5 (most deprived)	Individual education, marital status
Geographic level	Province of residence	Adjustment for residency in the 5 geographical regions of Denmark (EU NUTS-2 regions)	19 regions and 2 autonomous provinces of Italy where vaccination took place	Not included	Not included	County of residence	Region of residence (North, Center, Lisbon and Tagus Valey, Alentejo, Algarve)	Categories of rural/urban/metropolitan areas
Other vaccines uptake	Not included	Not included	Not included	Not included	Not included	Not included	Vaccination against influenza, PCV7, PCV10, PCV13 or PPV23 in the last 3 years	Not included
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	Positive RT-PCR test for SARS-CoV-2

Annex 3. Ethical statements from participating sites

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

Belgium: Data linkage and collection within the data-warehouse have been approved by the information security committee. The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was granted for the gathering of data from hospitalised patients by the Committee for Medical Ethics from the Ghent University Hospital (reference number BC-07507) and authorization for possible individual data linkage using the national register number from the Information Security Committee (ISC) Social Security and Health (reference number IVC/KSZG/20/384). Linkage of hospitalized patient data to vaccination and testing within the LINK-VACC project was approved by the Medical Ethics Committee UZ Brussels–VUB on 3 February 2021 (reference number 2020/523), and authorization from the ISC Social Security and Health (reference number IVC/KSZG/21/034).

Denmark: We used only administrative register data for the study. According to Danish law, ethics approval is exempt for such research, and the Danish Data Protection Agency, which is a dedicated ethics and legal oversight body, thus waives ethical approval for our study of administrative register data when no individual contact of participants is necessary, and only aggregate results are included as findings. The study is, therefore, fully compliant with all legal and ethical requirements, and there are no further processes available regarding such studies.

Navarre (Spain): The study was approved by Navarre's Ethical Committee for Clinical Research, which waived the requirement of obtaining informed consent.

Norway: Ethical approval was granted by Regional Committees for Medical and Health Research Ethics (REC) Southeast (reference number 122745). The Norwegian Institute of Public Health has performed a Data Protection Impact Assessment (DPIA) for Beredt C19.

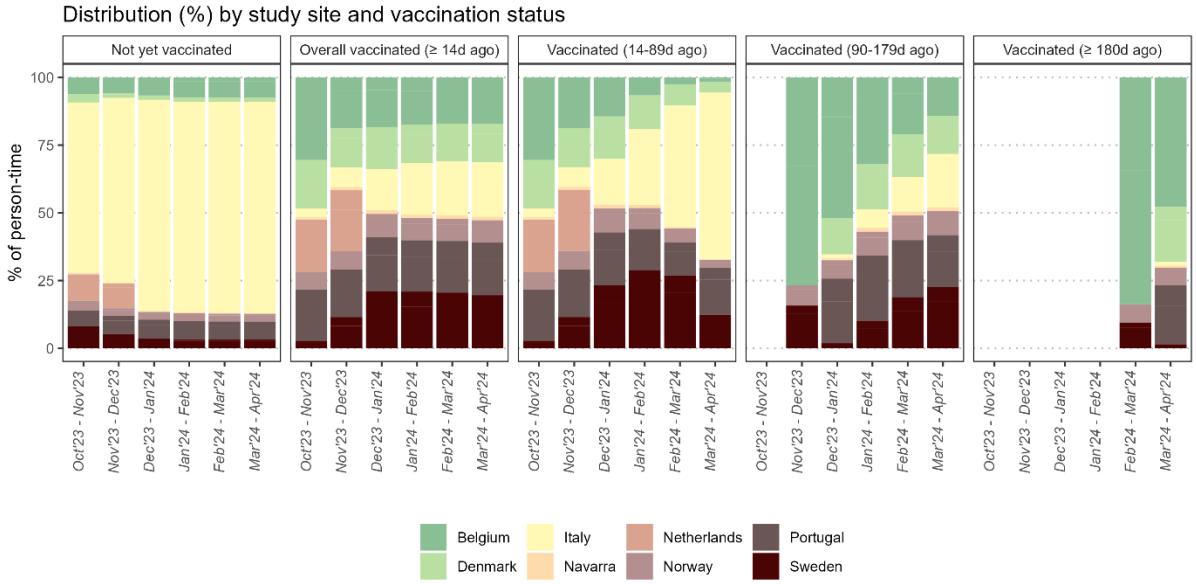
Portugal: The study received approval from the Ethical Committee and the Data Protection Officer of the Instituto Nacional de Saúde Doutor Ricardo Jorge. Given that data was irreversibly anonymised, the need for the participants' informed consent was waived by the Ethical Committee.

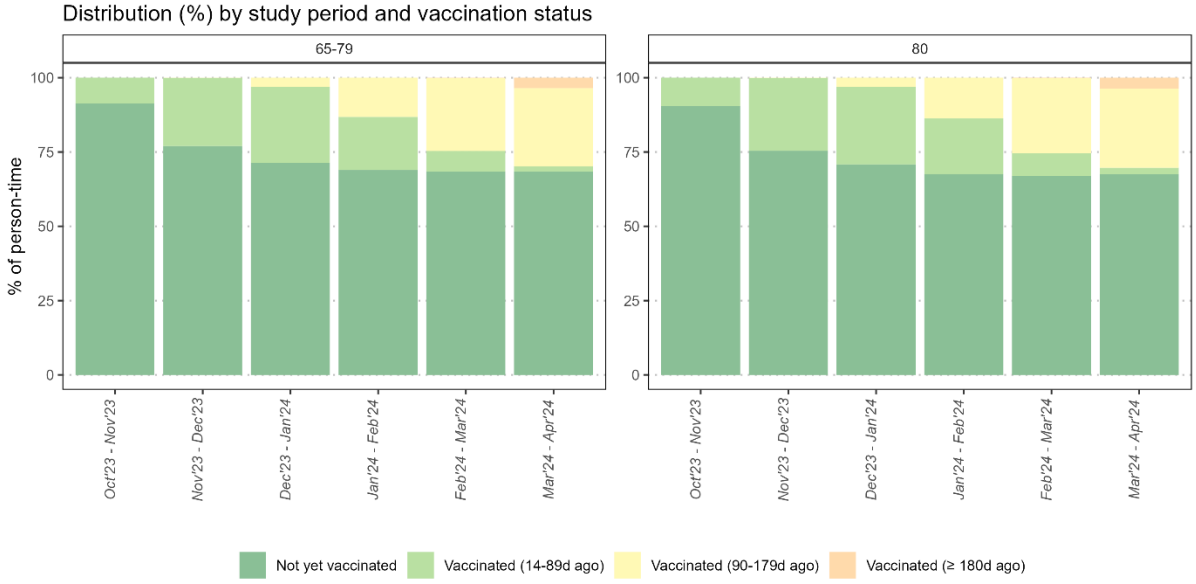
The Netherlands: We performed a Data Protection Impact Assessment to identify potential protection and privacy risks and measures to mitigate or manage these risks. Based on this document the study has been assessed by the Central Privacy Team of the National Institute of Public Health after consultation with the Data Protection Officer from the Ministry of Health. Final approval was achieved from the Head of the Centre for Infectious Disease Epidemiology and Surveillance. Ethical approval and patient consent were not required although necessary measures have been taken to ensure patients' privacy.

Italy: This study, based on routinely collected data, was not submitted for approval to an ethical committee because the dissemination of COVID-19 surveillance data was authorised by the Italian law N. 52 of 19 May 2022, following the law decree N. 24 of 24 March 2022 (Article n. 13). Based on the same acts, the information on COVID-19 vaccination was retrieved by the Italian National Institute of Health using data from the National Immunisation Information System of the Italian Ministry of Health. Because of the retrospective design and the large size of the population under study, in accordance with the Authorization n. 9 released by the Italian data protection authority on 15 December 2016, the individual informed consent was not requested for the conduction of this study.

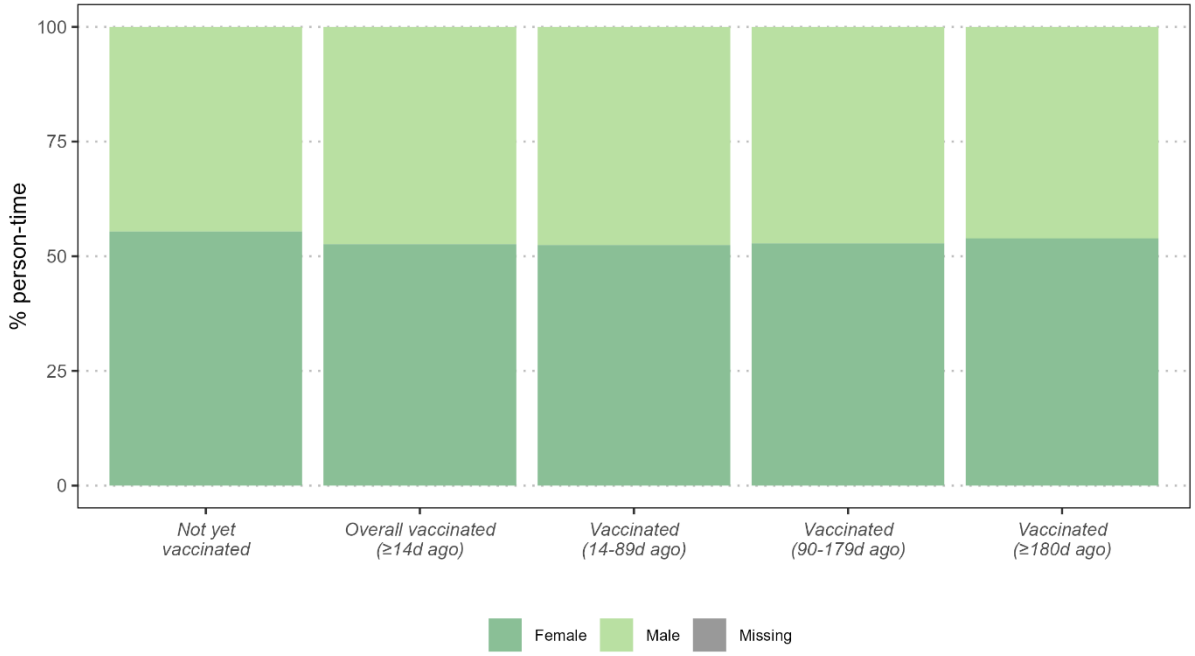
Sweden: The Swedish study is approved by the Swedish Ethical Review Authority (2020-06859, 2021-02186) and has conformed to the principles embodied in the Declaration of Helsinki. Consent to participate is not applicable as this is a register-based study.

Annex 4. Characteristics of the study sample

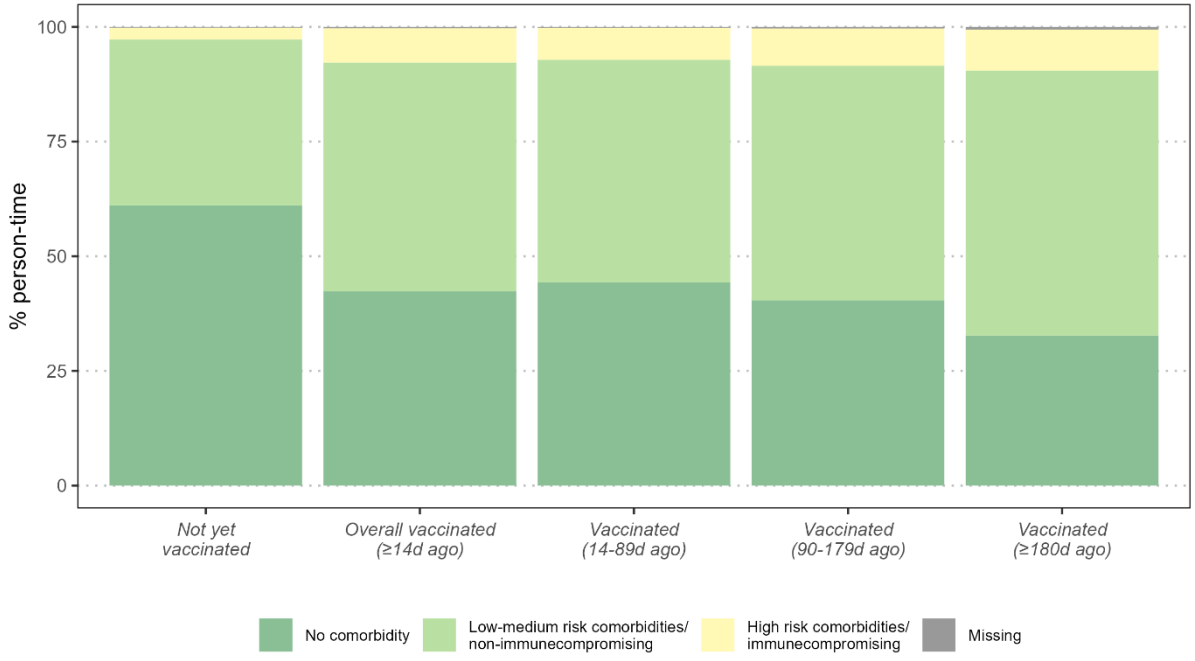




Distribution (%) by sex and vaccination status



Distribution (%) by comorbidities and vaccination status



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