OPERATIONAL SUPPORT

Protocol to measure COVID-19 vaccination impact among individuals aged 65 years and over

A Vaccine Effectiveness, Burden and Impact Study using electronic health records (VEBIS-EHR)

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

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Suggested citation: European Centre for Disease Prevention and Control. Protocol to measure COVID-19 vaccination impact among individuals aged 65 years and over. Stockholm: ECDC; 2026.

Stockholm, March 2026

ISBN: 978-92-9498-871-3
doi: 10.2900/1207009
Catalogue number: TQ-01-26-016-EN-N

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Abbreviations

COVID-19	Coronavirus disease 2019
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
HR	Hazard ratio
ICD	International Classification of Diseases
IPTW	Inverted probability of treatment weighting
IRR	Incidence rate ratio
RT-PCR	Reverse-Transcription Polymerase Chain Reaction
SARI	Severe Acute Respiratory Infection
SARS-CoV-2	Severe Acute Respiratory Syndrome– coronavirus 2
VE	Vaccine effectiveness
VEBIS	Vaccine Effectiveness, Burden and Impact Studies
VOC	Variant of concern
VOCs	Variants of concern
VPS	Vaccination propensity scores

Background

The Vaccine Effectiveness, Burden and Impact studies using electronic health records (VEBIS-EHR) project monitors the direct effect of each COVID-19 vaccination administered during the autumnal campaign every year, using monthly vaccine effectiveness (VE) estimates. This provides evidence on the level of protection conferred by the vaccine during each circulating wave of COVID-19 [1–4]. Additional VE estimates are obtained during specific periods of the year (e.g. periods when Omicron sub-lineages are predominant or during the summer) to answer specific research questions [5–7].

Although highly relevant, these measures of effectiveness do not consider the level of disease occurrence in the population (i.e. the baseline risk) or the proportion of the population which is vaccinated. Therefore they do not quantify the population-level benefit of vaccination in terms of the absolute decrease in the incidence of COVID-19, or the total number of severe events (cases, hospitalisations or deaths) averted by the autumn vaccination campaigns.

Population-level impact measures can be evaluated through the number of events prevented by the vaccine. This is an important component of vaccination campaign evaluation and key results can be communicated to support vaccination programmes and promote an increase in vaccination coverage.

Some studies have measured the impact of COVID-19 vaccination programmes in European Union/European Economic Area (EU/EEA) countries or regions [8–12]. These studies mainly focused on evaluating the impact of vaccination between the primary series and the second booster dose (from 2020 to 2022). To our knowledge, only one study [13] measured the impact of the new COVID-19 adapted vaccines (season 2023–24 season). This protocol proposes a common methodology to measure the impact of the COVID-19 autumn vaccination campaigns 2023 and 2024 in countries/regions participating in the ECDC VEBIS-EHR project.

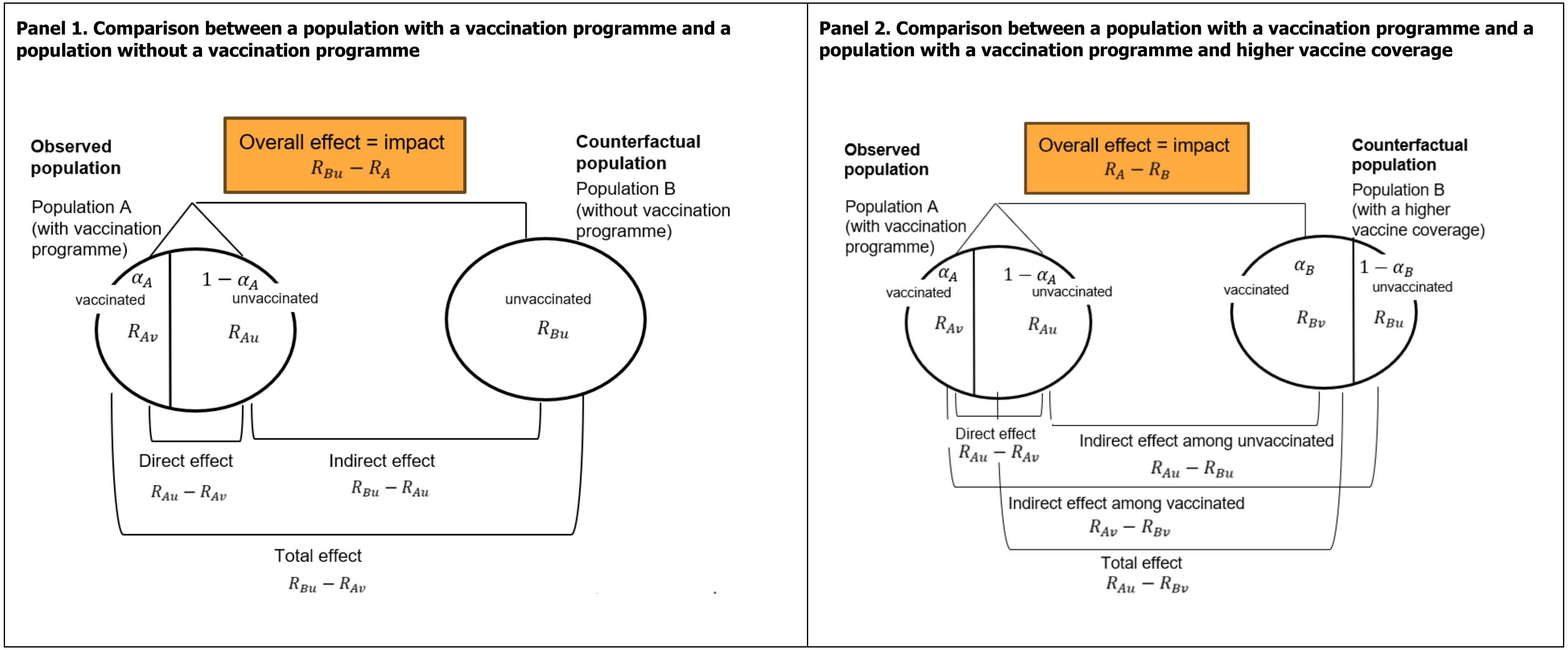
Definition of vaccine effects and parameters

One particularity of transmissible infectious diseases is that the risk of infection is not an independent occurrence, given that it depends on the point prevalence of infectious individuals in the population and their contact patterns [14]. This is relevant when measuring the effect of vaccination, as the reduction in infection risk among those vaccinated can indirectly benefit unvaccinated individuals. According to Halloran and Struchiner [14], several vaccine effects can be measured by comparing a population with a vaccination programme against a counterfactual population without a vaccination programme (vaccine coverage=0%).

Direct, indirect and total effect

In vaccine research, the most common effect measured is **the direct effect** of the vaccine, either efficacy or effectiveness, obtained by comparing the risk of infection between vaccinated and unvaccinated individuals within populations served by vaccination programmes (Figure 1). This parameter can also be interpreted as the fraction of disease prevented among vaccinated individuals [15]. This effect can be measured on an additive risk scale ($R_{Au} - R_{Av,}$, where R_{Au} and R_{Av} are, respectively, the risk of the disease among the unvaccinated and vaccinated individuals) or a relative risk scale ($VE = 1 - \frac{R_{Av}}{R_{Au}}$, this being the more frequently used formula). From this direct effect, it is also possible to measure the number of individuals requiring immunisation in order to prevent one disease event, computed as $NNV = \frac{1}{R_{Au} - R_{Av}}$ or, as a function of VE, $NNV = \frac{1}{R_{Au}VE}$.

Figure 1. Conceptual design of the vaccine effects by comparing a population with a vaccination programme (vaccine coverage α_A) against a population without a vaccination programme (panel 1, left) and by comparing the same population with a population with higher vaccine coverage $\alpha_B > \alpha_A$ (panel 2, right)



Adapted from Halloran ME and Struchiner CJ. [14] and from Jia et al. [27].

R_{Av}: *risk of disease among those vaccinated in a population with a vaccine programme;*
R_{Au}: *risk of disease among those unvaccinated in a population with a vaccine programme;*
R_{Bu}: *risk of disease among those unvaccinated in a population without a vaccine programme in Panel 1 and among a population with higher vaccine coverage in Panel 2.*
R_{Bv}: *risk of disease among those vaccinated in a population with higher vaccine coverage in Panel 2.*

A counterfactual population (population B in Figure 1), without a vaccination programme, serves as a control against which we can compare populations with vaccine programmes (population A in Figure 1), allowing us to measure the indirect and total effects of the vaccine.

Thus, the **indirect effect** of the vaccine is obtained by comparing the risk of disease between the two unvaccinated groups in each population, with and without a vaccination programme. Any difference in risk may reflect the indirect protection conferred to unvaccinated individuals by living in a population with widespread vaccine coverage. Usually, the indirect effect of vaccines is difficult to measure, given that it is necessary to have a measure of the disease risk among the unvaccinated individuals living in populations with and without vaccination programmes. One approach to capturing this is to compare unvaccinated individuals before and after the introduction of a vaccination programme, or if regions in a country introduce the vaccination programme at different times [2,3].

The total effect is obtained by comparing the risk of disease among vaccinated individuals (population A) with those unvaccinated in the population without a vaccination programme (population B), measuring this as the maximum potential benefit of the vaccine, which is equal to the sum of the direct and indirect effects.

Impact or overall effect

Number of averted events due to the vaccination programme

To estimate the population-level impact of a vaccination programme, or the overall effect, the overall disease risk in a population with the programme (Population A) is compared to that in a population without a programme (Population B; see Figure 1). This difference reflects the population-prevented fraction of disease. This parameter can be interpreted as the population-prevented fraction of disease [15].

This measure of vaccination programme impact can be written estimated as $\alpha_A(R_{Au} - R_{Av}) + (R_{Bu} - R_{Au})$, where α_A represents the proportion of individuals vaccinated in population A with a programme, and R_{Au} and R_{Av} represent, respectively, the risk of disease among unvaccinated and vaccinated individuals in the population with a vaccination programme, and R_{Bu} represents the risk of disease in population B (Figire 1) without a vaccination programme. To estimate the total number of cases prevented by the vaccination programme, we multiply the size of the population by the calculated impact (absolute risk difference) $N\ \alpha_A(R_{Au} - R_{Av}) + (R_{Bu} - R_{Au})$. This measure can also be interpreted as the total number of disease events averted by the vaccination programme.

Number of avertable events due to an increase in vaccination coverage

In addition to the impact of the vaccination programme represented in Figure 1, Panel 1, where we compare a population with a vaccination programme to a population without one, it is also possible to compare the risk of disease between two populations with a vaccination programme (Figure 1, Panel 2). Comparing the observed population (Population A) with one that has higher vaccine coverage ($\alpha_B > \alpha_A$) provides an estimate of the additional number of disease cases that could be prevented by increasing coverage. This can be obtained by $N\big((\alpha_B - \alpha_A)(R_{Au} - R_{Av}) + \alpha_B(R_{Av} - R_{Bv}) + (1 - \alpha_B)(R_{Au} - R_{Bu})\big)$, where α_B represents the proportion of vaccinated individuals in a population with a higher vaccine coverage, and R_{Bu} and R_{Bv} represent respectively the risk of disease among unvaccinated and vaccinated individuals in a population with a vaccination programme that has higher vaccine coverage. This measure can also be interpreted as the total number of disease events which can be averted by a vaccination programme with a higher vaccine coverage (vaccine coverage increase of $(\alpha_B - \alpha_A)$).

Ignoring the indirect effect

In most scenarios, the indirect effects of the vaccines are very difficult to estimate, and even more so if we were to include the indirect effects resulting from the reduction in the healthcare burden. In the case of SARS-CoV-2, evidence on the effect of the COVID-19 vaccines in transmission, and in the prevalence of infectious individuals as a consequence, is scarce and mainly available for the Omicron phase [17] which is covered by this protocol/study.

Given this difficulty in estimating the indirect effect of the COVID-19 vaccine, we propose simplifying the formulae of the number of averted events and avertable events, respectively to $N\ \alpha_A(R_{Au} - R_{Av})$ and $N\big((\alpha_B - \alpha_A)(R_{Au} - R_{Av})\big)$, where $\alpha_B - \alpha_A$ represents the increase in the vaccine coverage.

These measures of impact can also be expressed as a function of the vaccine effectiveness, the direct vaccine effect in a relative risk scale ($VE = 1 - \frac{R_{Av}}{R_{Au}}$): $R_{Au}N\alpha_A VE$ for the number of averted disease events and $R_{Au}N(\alpha_B - \alpha_A)VE$ for the number of avertable events by an increase of $\alpha_B - \alpha_A$, or by $R_A N\frac{\alpha VE}{(1-\alpha VE)}$ and $R_A N\frac{(\alpha_B-\alpha_A)VE}{(1-(\alpha_B-\alpha_A)VE)}$ respectively.

These formulae have several advantages because they can be applied when only the measures of the direct vaccine effect in a relative risk scale are available (which is the most common scenario). In addition, the second formula can be simplified even further to $e_A\frac{\alpha VE}{(1-\alpha VE)}$ and $e_A\frac{(\alpha_B-\alpha_A)VE}{(1-(\alpha_B-\alpha_A)VE)}$, where e_A is the total number of events in the population.

In this protocol, we propose using the impact measure estimator based on the vaccine effectiveness using the relative risk scale, given that this is the measure estimated in the context of the VEBIS-EHR project.

Objectives

Principal objective

The principal objective was to estimate the impact of the 2023 and 2024 autumn vaccination campaigns by measuring the number of COVID-19 hospitalisations and COVID-19-related deaths averted by vaccination among the population aged 65–79 years and 80 years or over, living in Belgium, Denmark, Italy, Navarre (Spain), Norway, Portugal and Sweden, in each country/region, overall and stratified by week (2023–Week 40 to 2025–Week 39).

Secondary objectives

1. To estimate the number of COVID-19 hospitalisations and COVID-19 related deaths avertable by increasing the COVID-19 2023–24 and 2024–25 autumn vaccine coverage by 10% increments up to 90%, overall and stratified by week (2023–Week 40 to 2025–Week 39), in each country/region, overall and stratified by week (2023–Week 40 to 2025–Week 39).
2. To estimate the number of individuals to vaccinate to avert a hospitalisation due to COVID-19 and a COVID-19-related death, during the 2023–24 and 2024–25 autumn vaccination campaigns, overall and stratified by week (2023–Week 40 to 2025–Week 39), in each country/region, overall and stratified by week (2023–Week 40 to 2025–Week 39).

Methodology

Study design

To obtain estimates for the impact of the 2023–24 and 2024–25 autumn vaccination campaigns, we will apply an adapted version of the method used previously to measure the impact of influenza vaccination [18,19], which was also recently applied to estimate the impact of the COVID-19 vaccination programme [8–13]. The rationale for this approach was described in more detail in the previous section.

We will estimate the number of COVID-19 hospitalisations averted (NAE) by the vaccination programme in week t by $NAE_t = e_{A(t)} \frac{VC_t VE_t}{(1 - VC_t VE_t)}$, with the week defined from Monday to Sunday, and the study period will start at 2023–Week 40 to 2024–Week 39 for the 2023–24 season, and 2024–Week 40 to 2025–Week 39 for the 2024–25 season.

Estimates of COVID-19 hospitalisation among the population $e_{A(t)}$, vaccine coverage VC_t and the vaccine effectiveness VE_t at week t will all be extracted from the study site-specific VEBIS-EHR cohorts at all study sites, with the exception of Belgium, where COVID-19 hospitalisations will be extracted from the SARI surveillance system. All parameters will be estimated weekly, except for the VE. To obtain weekly VE estimates, we will apply interpolation methods to the eight-week rolling period VE estimates obtained previously, according to Versions 2.0 [20] and 3.0 [21] of the VEBIS-EHR scientific protocol.

Study population

The study population will consist of all individuals aged 65–79 years and 80 years or over, living in one of the VEBIS-EHR study sites and eligible for the 2023–24 or 2024–25 autumn vaccination campaign, at the start of the campaign, at each study site. More details on the definition of the study population can be found in the VEBIS-EHR scientific protocol [20,21].

Outcomes

Following the VEBIS-EHR scientific protocol [20,21], the principal outcomes of interest are defined as:

- hospital admission due to COVID-19:
  - admission to hospital where COVID-19 is the main diagnosis in the discharge record (for example, based on International Classification of Diseases (ICD) coding or similar), OR
  - where admission criteria are compatible with SARI - based on similar criteria to SARI surveillance, ICD, codes or similar), AND with a laboratory-confirmed SARS-CoV-2 infection from up to 14 days before admission to 24 hours after;
  - only the first hospitalisation episode after the beginning of the seasonal vaccination campaign will be considered an event.
- COVID-19 related death:
  - where COVID-19 is recorded as the main cause of death, OR
  - if cause of death is not available, laboratory-confirmed SARS-CoV-2 infection, with death in the 30 days following a positive test.

To estimate the vaccination programme impact, we will use the number of COVID-19 hospitalisations and COVID-19-related deaths among the eligible population by week t obtained from the cohort studies. Given the risk of underreporting of COVID-19 hospitalisation and COVID-19 related deaths at study site level, each study should evaluate this risk and propose measures to mitigate this bias. To account for underreporting, we propose to extract the data with a time interval that reduces the probability of underreporting due to delays in updating hospital data, or apply weights where the surveillance system used to identify COVID-19 hospitalisations only covered a fraction of the national cases.

Vaccine coverage

Vaccine coverage, or the proportion of immunised individuals among those eligible and at-risk will be estimated on a weekly basis from the VEBIS-EHR study site level cohorts. The proportion of individuals vaccinated in week t will be estimated by $VC_t = \frac{v_{t-2}}{N}$, where N is the number of individuals eligible for vaccination at the start of the vaccination campaign and v_{t-2} is the cumulative number of vaccinated individuals up to week t-2 (two weeks – 14 days before to allow individuals to gain immunity after vaccination) among the individuals eligible for the vaccine at the start of the campaign.

For secondary objective 1, we will assume a span of possible vaccine coverage increases at study site level from the observed vaccine coverage at the end of the vaccination campaign up to 90% in 10% increments.

To adjust the weekly vaccine coverages to a defined increase α_{inc} in the final vaccine coverage VC_T where T=2024–Week 39 or 2025–Week39, we will compute new cumulative vaccine coverage as $VC_t(\alpha_{inc}) = \sum_{i=1}^{t}(VC_t - VC_{t-1})\left(1 + \frac{\alpha_{inc}}{VC_T}\right)$, $VC_0 = 0$ (week before the start of the study).

Measures of vaccine effectiveness

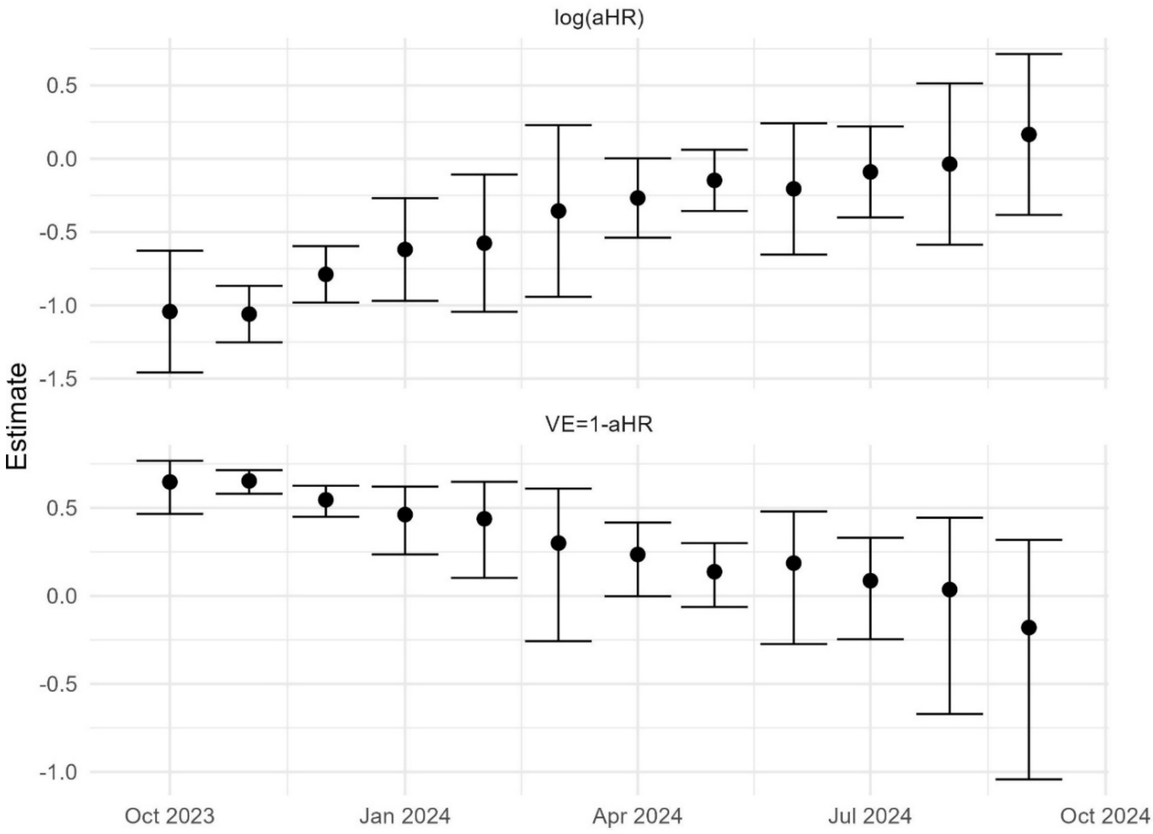
VE effectiveness estimates will be obtained from the monthly monitoring VE estimates obtained in the VEBIS-EHR project for the periods from 2023–Week 40 to 2024–Week 39 and from 2024–Week 40 to 2025–Week 39, using the eight-week rolling period VE estimates. Details on the methods used to estimate the VE at study site level and pooled level can be found in the VEBIS-EHR masters protocols Versions 2.0 and 3.0.

Table 1. Definition of the eight-week periods for which VE against hospitalisation was estimated at study site level and the corresponding weeks covered by the VE estimates

2023-2024 autumn vaccination campaign		2024-2025 autumn vaccination campaign	
Eight-week follow up period	**Weeks covered**	**Eight-week follow up period**	**Weeks covered**
1 October to 25 November 2023	2023-W40 to 2023-W47	1 October to 25 November 2024	2024-W40 to 2024-W48
1 November to 26 December 2023	2023-W44 to 2023-W51	1 November to 26 December 2024	2024-W44 to 2024-W52
1 December 2023 to 25 January 2024	2023-W49 to 2024-W04	1 December 2024 to 25 January 2025	2024-W48 to 2025-W04
1 January to 25 February 2024	2024-W01 to 2024-W08	1 January to 25 February 2025	2025-W01 to 2025-W09
1 February to 27 March 2024	2024-W05 to 2024-W13	1 February to 27 March 2025	2025-W05 to 2025-W13
1 March to 25 April 2024	2024-W09 to 2024-W17	1 March to 25 April 2025	2025-W09 to 2025-W17
1 April to 26 May 2024	2024-W14 to 2024-W22	1 April to 26 May 2025	2025-W14 to 2025-W22
1 May to 25 June 2024	2024-W18 to 2024-W26	1 May to 25 June 2025	2025-W18 to 2025-W26
1 June to 26 July 2024	2024-W22 to 2024-W30	1 June to 26 July 2025	2025-W22 to 2025-W30
1 July to 25 August 2024	2024-W27 to 2024-W35	1 July to 25 August 2025	2025-W27 to 2025-W35
1 August to 25 September 2024	2024-W31 to 2024-W39	1 August to 25 September 2025	2025-W31 to 2025-W39
1 September to 26 October 2024	2024-W36 to 2024-W43	1 September to 26 October 2025	2025-W36 to 2025-W43

We will use the eight-week VE estimates to estimate VE at the weekly level using an interpolation method. The eight-week VE will be modelled by either an exponential or a logistic decay function, allowing for a slower early decay and more flexibility overall, depending on which one provides the best fit, as assessed by the Akaike information criterion (AIC) and the Bayesian information criterion (BIC) (see Annex 5). The exponential function is a decay function commonly used to model protection waning [22,23]. It is often used because it is relatively simple, has a small number of parameters, and is the implicit assumption made by traditional, compartmental Susceptible-Infected-Recovered models. Alternative decay functions have also been explored, including the Weibull function [24], the gamma function [25], or the logistic function [26]. The model fit will be assessed on the (log(1-VE)) (or log aHR) scale because it is the scale at which the estimates and their standard errors are primarily calculated (Figure 2).

Figure 2. Illustration of vaccine effectiveness estimates (VE), their 95% confidence intervals (the error bars), and their corresponding values on the original scale of log(aHR) using 2023–24 pooled estimates



An exponential decay function is as follows: $VE_t = VE_{t=0} \times e^{-b \times t}$ where t is an indicator for the week and $b > 0$ is the decay rate. A logistic decay function is as follows: $VE_t = \frac{VE_{t=0}}{1+a \times e^{b \times t}}$ where t is an indicator for the week, a is constant, related to the initial conditions and $b > 0$ is the decay rate.

We will fit both decay functions to our estimates, produced monthly over rolling eight-week (Table 1) periods on the log(aHR) scale through non-linear regression technique with the inverse variance of the estimates as weighting by minimising the weighted squared residuals (see Annex 4).

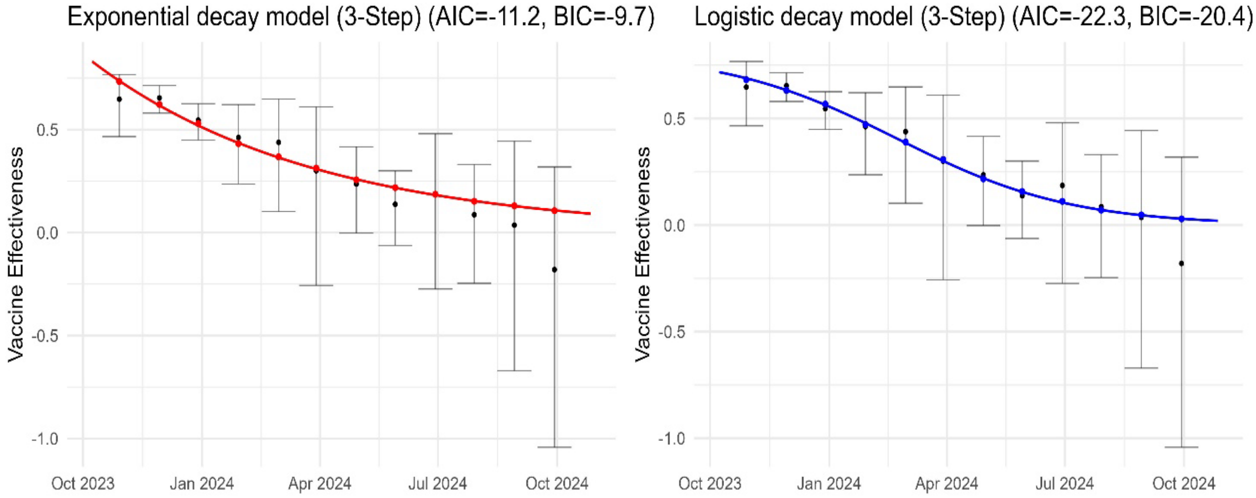
The decay functions, rearranged on the log(aHR) before applying non-linear regression techniques with the inverse variance of the aHR estimates as weights (see Annex 4), are as follows:

- Exponential decay $log(aHR_t) = log(1 - VE_{t=0} \times e^{-b \times t})$
- Logistic decay: $log(aHR_t) = log(1 - \frac{VE_{t=0}}{1+a \times e^{b \times t}})$

Models will then be fitted using the average values of $log(aHR_t)$ over the same eight-week periods as our estimates and will be assessed using the Akaike information criterion (AIC) and the Bayesian information criterion (BIC).

The predicted values on the log(aHR) scale will then be transformed to the VE scale to provide weekly estimates. Figure 3 shows an example of this approach.

Figure 3. Example of model fit of the exponential and logistic decay functions to vaccine effectiveness (VE) estimates using 2023–2024 pooled estimates (logistic model had a lower AIC and BIC in this example)



The predicted values of the decay functions are on the weekly scale and the values used to fit the decay functions are on the same timescale as the VE estimates (eight-week moving window). The black dots and the error bars indicate the VE estimates and their 95% confidence intervals. The red and blue dots indicate the predicted values from the exponential and logistic decay functions, averaged over the same eight-week periods as those used to estimate the VE.

Source of the vaccine effectiveness estimates

We will use both the pooled VE estimates and the study-site-specific estimates for every site as a sensitivity analysis. Certain study sites could not produce some of the VE estimates due to a low number of events and we will therefore only use the pooled VE estimates for them.

Analysis and parameters estimate

Events averted by vaccination

The number of weekly (*t*) COVID-19 hospitalisations averted by the 2023 and 2024 vaccination campaigns in the study site *k* will be estimated as follows:

$NAE_{tk} = e_{A(t)k}\frac{VC_{tk}VE_{tk}}{(1-VC_{tk}VE_{tk})}$, were $e_{A(t)k}$, VC_{tk} and VE_{tk} will be estimated from the study site cohorts as described before.

Events avertable by increasing the vaccination coverage

The number of weekly (*t*) COVID-19 hospitalisations avertable by the 2023–24 and 2024–25 vaccination campaigns in the study site *k* will be estimated as follows:

$NAbE_{tk}(\alpha) = e_{A(t)k}\frac{VC(\alpha)_{tk}VE_{tk}}{(1-VC(\alpha)_{tk}VE_{tk})}$, where $e_{A(t)k}$, $VC_{tk}(\alpha)$ and VE_{tk} will be estimated from the study site cohorts, as described before.

Number of vaccinations required to prevent one COVID-19 related hospitalisation

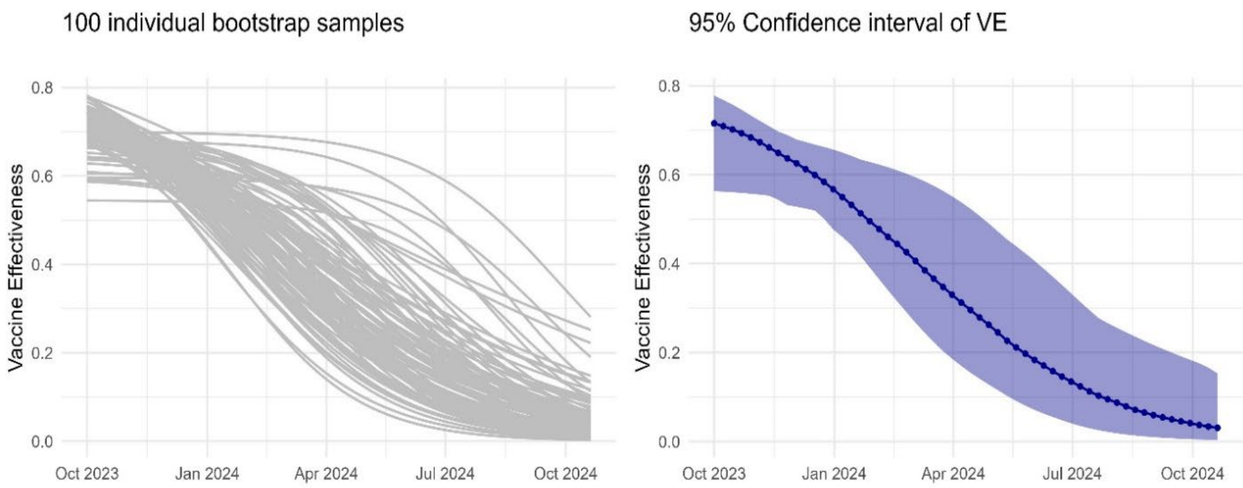
The number of weekly (*t*) individuals to be vaccinated to avert COVID-19 hospitalisation during the 2023–24 and 2024–25 vaccination campaigns at the study site *k* will be estimated as follows:

$NNV_{tk} = \frac{1}{R_{B(t)k}\,VE_{tk}}$ where $R_{B(t)k} = \frac{e_{A(t)k}+NAE_{tk}}{N_{tk}}$ and VE_{tk} will be estimated from the study site cohorts, as described before.

Uncertainty measures

We will assume that the weekly number of events ($e_{A(t)k}$) and vaccine coverage (VC_{tk}) and size of the population are known (N_{tk}). To account for the uncertainty in VE estimates, we will apply a parametric bootstrap and estimate the covariance matrix of the decay function parameters (on the log(aHR) scale). This will allow us to assess the uncertainty around the weekly VE, by drawing a random sample from the multivariate normal distribution of the decay function parameters using the covariance matrix estimated in the step before. The sets of weekly VE derived from the sample of parameters will produce a 95% quantile confidence interval (Figure 4). This uncertainty around our weekly VE will then be translated to the number of averted and avertable events.

Figure 4. Illustration of the method to estimate uncertainty around weekly vaccine effectiveness interpolated values with 100 bootstrap samples for the logistic decay function (left) and the resulting 95% confidence interval ribbon around the logistic decay function (right)



Strategies to prevent sparse data problems and imprecise estimates

In this study we anticipate high standard errors in estimates of weekly disease rates both among those who are unvaccinated and vaccinated. This may affect effectiveness estimates, mainly at study sites with smaller populations and/or during periods of low disease incidence.

When the number of weekly events in the population is lower than five, we will increase the analysis periods to four-week intervals, with the aim of increasing disease rate precision by including more events in each period.

Sensitivity analysis

To evaluate the impact of using weekly VE interpolated values, we will repeat the analysis using eight-week rolling period VE estimates, COVID-19 hospitalisation rates and vaccine coverage.

Limitations

Conceptual

In this study we intend to measure the impact of the 2023 and 2024 autumn COVID-19 vaccination campaigns considering only the direct effect of the vaccines. The indirect effects of the vaccine were not measured and so will not be considered as part of this study. In principle, we could assume that estimates of the number of averted COVID-19 hospitalisations are lower than the true number of averted hospitalisations. Nevertheless, a recent study [27] claims that these assumptions cannot be verified if the risk of severe disease outcomes, the transmission probability, or the VE changes considerably over time during the study period. This would suggest that our estimates will be more reliable at the start of the vaccination campaign than during the later periods occurring closer to summer. These concerns will be taken into consideration during the results discussion, in light of the potential presence of time changes affecting the risk of severe disease, transmission and VE.

Data sources and their limitations

To calculate the impact of the vaccination campaigns we will use parameters estimated during routine VEBIS-EHR cohort study analyses. The validity of these estimates depends on the presence of selection or measurement bias in parameters such as population size, vaccine coverage and risk of COVID-19 hospitalisations among the unvaccinated. For measures of VE, in addition to the potential presence of selection and measurement bias, we should also consider the presence of residual and/or unmeasured confounding bias. In Table 2, we list the study parameters used, the potential bias presence, the studies conducted to evaluate their validity and possible measures for correction.

Table 2. Study parameters, potential bias, evaluation and possible correction measures

Parameter	Potential bias	Evaluation and correction measures
Size of the population eligible for vaccination and at risk of disease N_{tk}.	Selection bias: the study cohorts do not cover all of the eligible population in the country or region of the study site.	This bias was evaluated in the VEBIS-EHR evaluation study [28]. In the case of underreported coverage, a weighting procedure can be applied to correct the size of the country/region population.
Vaccine coverage: proportion of individuals eligible for vaccination and still at risk who are vaccinated.	Measurement bias: underreporting of vaccinated individuals.	This bias was evaluated in the VEBIS-EHR evaluation study [28] by comparing vaccine coverage in the cohort with official national estimates. In the event of the VC being underestimated, a weighting procedure can be applied to correct the VC.
Risk of COVID-19 hospitalisations.	Measurement bias: underreporting of COVID-19 hospitalisations.	The risk of this bias will be evaluated at study site level. Measures to correct this bias could be extraction of data with a time interval that reduces the probability of underreporting due to delays in updates of hospital data, or applying weights if the surveillance system used to identify COVID-19 hospitalisations only covers a fraction of the national cases.
Vaccine effectiveness.	Measurement and confounding bias: measurement error in the exposure and outcome and the presence of residual and unmeasured confounding.	This bias was evaluated in the VEBIS-EHR evaluation study [28]. The conclusions were that measurement bias due to delayed data extraction will be small at most study sites. However, the presence of residual and unmeasured confounding bias cannot be excluded, which can potentially overestimate VE. This problem will be taken into consideration in the discussion. At study sites with underreporting of events due to extraction delays, a longer period of data extraction will be recommended.

Ethical requirements

Each study site received ethical approval and conformed to national and EU ethical and data protection requirements.

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Annexes

Annex 1. Vaccination campaign start dates

Table 1.1 Vaccination campaign roll-out by country

Study site	Start of 2023 campaign	Start of 2024 campaign
Belgium	11 September 2023	23 September 2024
Denmark	1 October 2023	1 October 2024
Italy	1 October 2023	18 September 2024
Sweden	1 September 2023	15 October 2024
Navarre (Spain)	16 October 2023	14 October 2024
Portugal	29 September 2023	20 September 2024

Annex 2. Outcome definition by study site

Table 2.1 Outcome definition by site

Study site	Outcome definition
Belgium	Hospital admission due to COVID-19 symptoms for which COVID-19 infection has been confirmed via PCR, antigen test, or rapid antigen test during the period from 14 days before hospitalisation to 24 hours after hospitalisation.
Denmark	Laboratory-confirmed infection 24 hours after hospital admission or three weeks before admission, lasting for a minimum of 24 hours and where admission is classified with ICD-10 codes B342 and B972 or one of the sub-codes under these. The COVID-19-related ICD-10 codes have to be both primary diagnosis and action code.
Italy	Hospital admission with SARS-CoV-2 infection confirmed through RT-PCR or antigenic test, and clinical manifestations of the respiratory tract or other organs directly associated with SARS-CoV-2 infection.
Norway	
Navarre (Spain)	Hospital admission with l COVID-19 infection laboratory-confirmed using RT-PCR, reviewed by a medical doctor who concluded that the hospitalisation was due to COVID-19.
Portugal	COVID-19 is the main diagnosis in the discharge record.
Sweden	Laboratory-confirmed infection 24 hours after hospital admission or three weeks before admission. The COVID-19-related ICD-10 code as primary diagnosis.

Annex 3. Dummy tables for the results

Table 3.1 Number of averted COVID-19 hospitalisations and number of people to be vaccinated to prevent one COVID-19 hospitalisation by country and age group x during season y (one table for each age group 65-79 years and 80+ years, and season 2023–24 and 2024–25)

	Belgium	Denmark	Italy	Norway	Navarre (Spain)	Portugal	Sweden
Observed number of events							
Averted number of events by vaccination (95% UL)							
Averted number of events by vaccination (95% UL) per 100 000 people.							

Table 3.2 Number of avertable COVID-19 hospitalisations by increasing vaccine coverage to 50%, 75% and 90%, by country and age group (65–79 years and 80+ years) during season 2023–24

Number of avertable COVID-19 hospitalisations (95% UL)							
	Belgium	Denmark	Italy	Norway	Navarre (Spain)	Portugal	Sweden
50% vaccine coverage							
60% vaccine coverage							
70% vaccine coverage							
80% vaccine coverage							
90% vaccine coverage							

Annex 4. Methods used to fit weekly VE

We will fit both exponential and logistic decay functions to our estimates, produced over rolling eight-week periods by minimising the weighted squared residuals (wsr). The wsr will be calculated on the log(1-VE) scale using the average of the predicted values over the same eight-week periods (the same timescale as our VE estimates) and using the inverse of the variance as weights to account for the uncertainty around them.

$$wsr = \frac{\sum_{i=1}^{t} \frac{1}{{\sigma_i}^2} \times (\log(1 - VE_i) - \mathrm{logpred}_i)^2}{\sum_{i=1}^{t} \frac{1}{{\sigma_i}^2}}$$

With i a time interval for producing our VE estimates (rolling eight-week periods), $\mathrm{logpred}_i$ the average of the predicted values over the period used to produce our VE estimates ($logpred_{i=1} = \frac{\sum_{w=1}^{8} \log(1-\widehat{VE_w})}{8}$, with $\widehat{VE_w}$ the weekly prediction value of the decay function in the eight-week period of interest), and ${\sigma_i}^2$ the variance of our VE estimates on the log(1-VE) scale.

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