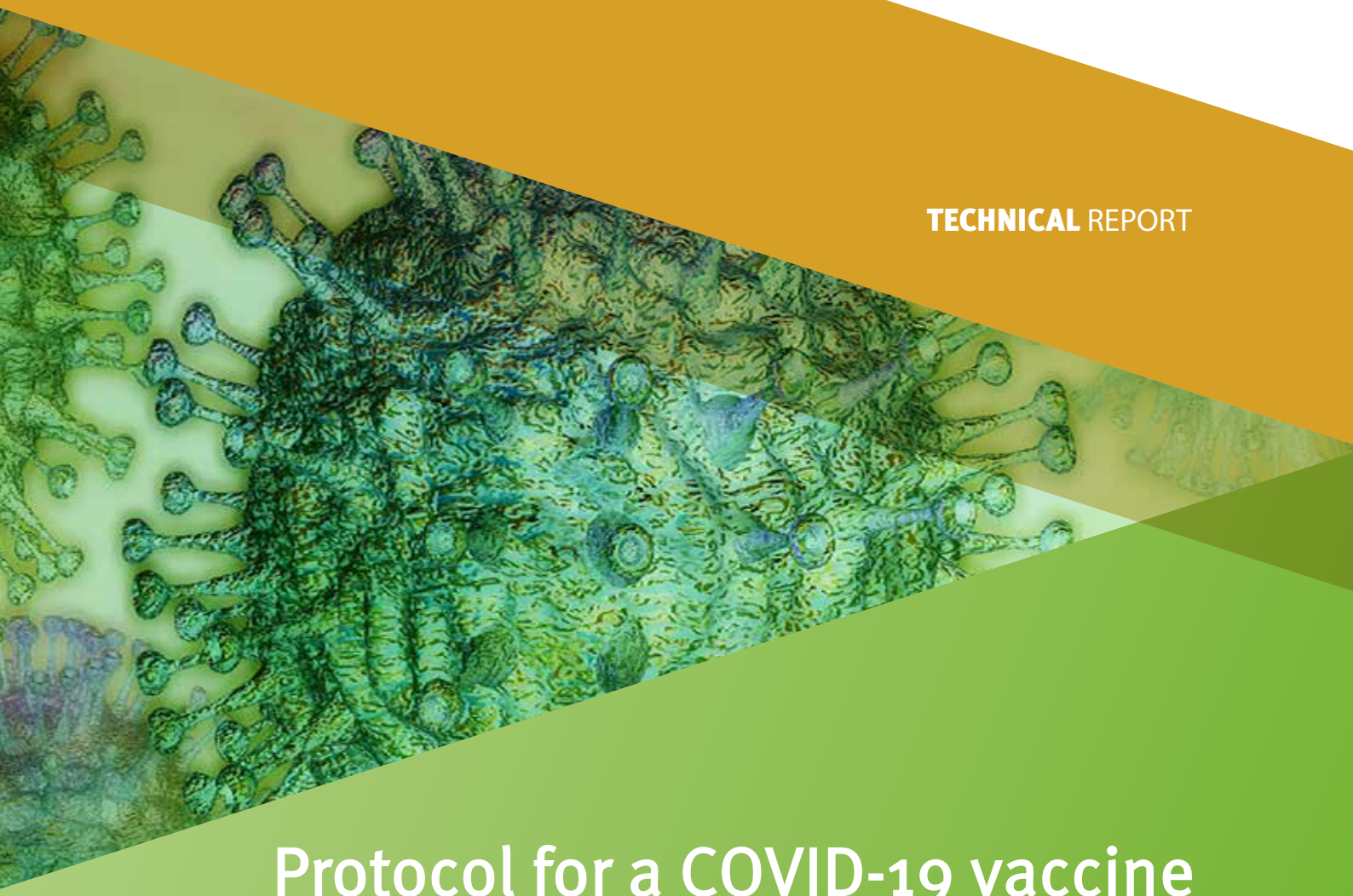

TECHNICAL REPORT

Protocol for a COVID-19 vaccine effectiveness estimation using health data registries, VEBIS multi-country study

Version 2.0

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ECDC TECHNICAL REPORT

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Abbreviations

BMI	Body Mass Index
COVID-19	Coronavirus disease 2019
CVE	COVID-19 vaccine effectiveness
EEA	European Economic Area
HER	Electronic Health Records
EMA	European Medicines Agency
EU	European Union
HR	Hazard Ratio
ICU	Intensive care Unit
PCV	Pneumococcal Conjugated Vaccine
PPV	Pneumococcal Polysaccharide Vaccine
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

Executive summary

This protocol presents a common updated methodology to estimate vaccine effectiveness (VE) for COVID-19, using established health data registries in participating European Union and European Economic Area (EU/EEA) countries.

This work is performed within the Vaccine Effectiveness, Burden and Impact Studies (VEBIS) project. The first objective of the study is to monitor COVID-19 VE in a prospective manner, with the production of VE monthly pooled estimates from up to eight countries, including Denmark, Spain (Navarre region only), Norway, Portugal, Belgium, and Luxembourg from October 2022, Italy from June 2023, and the Netherlands from October 2023, with retrospective contributions from the Netherlands and Italy since January and February 2023 respectively [1-5].

The present master protocol (version 2.0) intends to update the previously used methods [2] to monitor COVID-19 VE to reflect on the current SARS-CoV-2 testing strategies and 2023 autumn vaccination recommendations that now target specific age groups.

The proposed study design is a multicentre retrospective cohort design using data collected routinely from electronic health record (EHR) databases. The analysis included data from the resident community-dwelling population (i.e. excluding those living in nursing homes) ≥65 years of age and who belong to age-group for whom vaccination has been universally recommended at study enrolment (i.e. if vaccination with a booster was only recommended for individuals ≥80 years of age at a given month, VE corresponding to that month is only estimated in that group). Outcomes of interest include hospital admission due to COVID-19 and COVID-19-related death. Other data to be collected include socioeconomic (age, sex, socioeconomic status), clinical (comorbidities) and COVID-19 vaccination variables (brand, number, and dates of dose administration).

The protocol outlines the agreed methods for data analysis of national databases and includes a plan for the pooled analysis of all participating country VE estimates. With the vaccination campaign being first deployed between September and October 2023 in most countries, a first early estimate of VE will be performed in January 2024 covering the early phase of the rollout (October–November 2023) eight-week follow-up period (consolidated data available in January of the following year, 2024) followed by mid-year estimates in March, June, and September 2024.

This master protocol is primarily intended to guide the implementation of the ECDC-funded study in participating countries. However, ECDC encourages the conduct of VE studies, using this protocol as a basis, in countries that do not currently plan to participate in ECDC-funded studies. The use of common protocols will facilitate the comparability of results across studies, countries, sites, and time.

Background

The end of 2019 saw the emergence of a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19) with substantial disease burden [6]. As of October 2023, nine vaccines (Comirnaty, COVID-19 Vaccine Valneva, Nuvaxovid [previously Novavax], Spikevax [previously COVID-19 vaccine Moderna], Vaxzevria [previously AstraZeneca], Jcovden [previously Covid-19 Vaccine Janssen], VidPrevtyn Beta [from Sanofi], and Bimervax [previously COVID-19 Vaccine HIPRA]), Nuvaxovid (NVX-CoV2373), and six adapted vaccines (Comirnaty Original/Omicron BA.1, Spikevax bivalent Original/Omicron BA.1, Comirnaty Original/Omicron BA.4-5, Spikevax bivalent Original/Omicron BA.4-5, Comirnaty Omicron XBB.1.5, and Spikevax XBB.1.5) have been authorised by the European Commission based on the scientific opinion of the European Medicines Agency (EMA) for use in the European Union, and many others are under rolling review [7].

ECDC COVID-19 vaccine effectiveness studies

In 2020, the European Commission stressed the importance of continuously monitoring the safety and effectiveness of vaccines in the EU/EEA in the post-authorisation phase, with particular emphasis on COVID-19 vaccines in the context of the ongoing pandemic [8]. The 2018 Council Recommendation on Strengthened Cooperation against Vaccine-preventable Diseases asked ECDC and EMA to cooperate in ensuring the continued monitoring of vaccines and vaccination in use in EU/EEA vaccination programmes [9]. Such a request was subsequently formalised as part of the extended EMA regulatory mandate [10] and ECDC's newly amended mandate [11] which requested that the two Agencies develop a structured and independent post-authorisation Vaccine Monitoring Platform, initially prioritising COVID-19 vaccines. ECDC and EMA officially established and launched such a platform in May 2022, with the intention of bringing together public health and regulatory experts to discuss the studies needed to generate real-life evidence on the safety and effectiveness of vaccines in use in EU/EEA immunisation programmes [12].

In 2020, utilising the lessons learned from other vaccine effectiveness (VE) studies, ECDC started the Vaccine Effectiveness, Burden and Impact Studies (VEBIS) project to monitor VE in different settings and different methods, and to provide information on different outcomes (severe disease, moderate disease, infection, transmission, etc) [13-20] (Annex 1). Within the VEBIS project, the present study aims to assess VE and the impact of COVID-19 vaccines through routinely collected vaccination status and outcome data using established electronic health records (EHR) across several study sites in the EU/EEA, in order to detect changes in VE over time and within population subgroups and inform public health strategies regarding COVID-19 vaccination.

The current protocol describes the updated methods to implement such studies. It is an adapted version of the first published protocol (version 1.0, published by ECDC in January 2023) [2] implemented in six countries in 2023 that aimed to monitor the COVID-19 VE in real time and in a prospective way [3-5]. However, the changes in vaccine recommendations targeting specific risk groups (elderly ≥60 or ≥65 years of age), the timing of rollout of vaccination campaigns, the low number and defined characteristics of unvaccinated individuals in target groups in most countries, and the reduced frequency of SARS-CoV-2 testing and increased focus on the monitoring of severe COVID-19, make it necessary to adapt the monitoring framework.

The present master protocol (version 2.0) intends to update the previously used methods to the current monitoring needs. A summary of changes from Protocol v.1.0 is outlined in Annex 2.

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 ≥65 years of age in EU/EEA countries to detect any variation in VE, so that public health vaccine recommendations may be adjusted accordingly. To achieve this aim, 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.

In the following sections, arrow marks with italicised text indicate the points that countries could further expand/detail when creating a country-specific protocol guided by the current ECDC master protocol.

Objectives

Principal objective

The principal objective is to estimate VE of the most recent COVID-19 vaccination dose, given as part of 2023 autumnal vaccination campaign, in community-dwelling resident populations aged ≥65 years, comparing the outcome incidence in the elderly individuals eligible for vaccination at the beginning of the campaign and who received a vaccine dose, compared to outcome incidence in elderly individuals who were eligible but have not (yet) received it at the time of vaccination status assessment, in EU/EEA countries. Outcomes of interest are:

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

The reference group for the outcome incidence comparison will be 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 will be stratified by age group: 65-79 years and ≥80 years.

Secondary objectives

To measure COVID-19 VE (if sample size allows):

1. By time since the COVID-19 vaccine booster dose: similar to the main analysis, stratifying the vaccinated group according to the number of days elapsed since the date of the most recent COVID-19 vaccine dose, administered as part of the 2023 autumnal vaccination campaign , to evaluate the decline in VE over time.
2. By number of booster doses: additional VE of the most recent COVID-19 vaccine dose, administered as part of the 2023 autumnal vaccination campaign , with the overall sample stratified by the total number of booster doses received prior to the start of the campaign (with alternative approaches if there are not sufficient events to allow stratification).
3. By vaccine product of the vaccine booster dose: similar to the main analysis, stratifying the vaccinated group by vaccine brand used as booster dose.

VE by time since the COVID-19 vaccine dose (secondary Objective #1) is included for the regular monitoring along with the principal objective. However, VE by number of booster vaccine doses (secondary Objective #2) is assessed ad hoc, once at the end of the respiratory disease season or more frequently if relevant for public health decision making. VE by vaccine product (secondary Objective #3) will be also assessed ad hoc, particularly when different vaccines are used simultaneously (not expected for the coming 2023/24 campaign).

Alternatives

- Study sites can contribute to all or only a subset of the established objectives (for example, only some outcomes or only to the secondary objectives).
- Additional objectives might be added as the situation evolves and new questions arise.

➢ *Study sites/countries to specify the study objectives.*

Methodology

Study design and setting

A retrospective cohort analysis using data collected routinely in EHR databases with a comparison of the risk of outcome occurrence between individuals with different vaccination status.

➢ *Study sites/countries to include more details on the areas covered by the study, its population, and its relative representativeness. Include brief information on the relevant vaccination rollout, including prioritised groups, and the dates on which different populations were incorporated into the vaccination programme.*

Study period

Estimates of VE are provided each month to allow the detection of variations over time. VE is estimated in study periods covering eight weeks of follow-up to allow the occurrence of sufficient number of events to produce VE estimates and the detection of changes in VE over time. The follow-up period may need to be increased ad hoc if, due to the evolving situation, the number of events is insufficient. The eight-week follow-up period is moved one month forward for each successive monthly estimate. A minimum of one month lagging period between the end of the follow-up period and the data extraction date is applied to allow consolidation of data in all EHR.

It is proposed that data extraction and analysis are performed at least four times per year (Table 1). With the 2023/24 vaccination campaign starting in September/October in most countries, a first early estimate of VE may be performed in January 2024 covering the early phase of the rollout (October–November 2023) eight-week follow-up period (consolidated data available in January of the following year, 2024) followed by mid-year estimates in March, June and September 2024.

A pre-campaign VE can also be estimated before the following vaccination campaign, looking at the VE of the previous vaccination campaign, waning of protection and residual effectiveness before a new dose is recommended; this pre-campaign VE could be drawn in September 2024 and cover the eight-week observation windows with consolidated data as of September, if SARS-CoV-2 was circulating (April–May 2024, May–June 2024, June–July 2024).

Table 1. Study periods for VE estimates for the 2023 autumnal vaccination campaign

Data analysis *	Eight-week follow up period
January 2024	• 1 October to 25 November 2023
March 2024	• 1 November to 26 December 2023 • 1 December 2023 to 25 January 2024
June 2024	• 1 January to 27 February 2024 • 1 February to 27 March 2024 • 1 March to 25 April 2024
September 2024	• 1 April to 26 May 2024 • 1 May to 25 June 2024 • 1 June to 26 July 2024

** The follow-up periods are assessed retrospectively. However, it is recommended that, for each period, the analysis is performed with a database that is extracted at about 30 days after the last day of that particular follow-up period, in order to have a homogeneous degree of data consolidation throughout the study. If that is not feasible, a single database may be extracted at the time of the analysis, to assess all follow-up periods in the same data; the date of data extraction will always need to be a minimum of 30 days after the last follow-up date in the study.*

Other time periods for follow-up and data extraction and analysis may be agreed if needed for decision-making purposes. In addition, this schedule may need to be adapted to the characteristics of the vaccination roll-out and SARS-CoV-2 circulation during the study period. For example, if the circulation of SARS-CoV-2 is low and events become scarce, wider analysis windows may need to be used in order to obtain VE estimates with sufficient precision. These time periods apply to the principal objective and the secondary objective of VE estimation by time since the COVID-19 vaccine dose, while the remaining secondary objectives will be addressed as needed and when feasible.

Study population

The study population includes community-dwelling individuals ≥65 years of age in national I databases. The study population should be eligible for COVID-19 vaccination during the 2023 autumnal vaccination campaign, including belonging to an age group for whom autumnal COVID-19 vaccination has been recommended in each site/country. Eligibility will be based on the following criteria as of the first day of the vaccination campaign, which may be adapted to match national recommendations:

- Aged between 65 and 110 years at the beginning of the vaccination campaign, or belonging to an age group over 65 years for which the vaccine dose being evaluated has been recommended, if different (it should be recommended for the entire age group). Birth year may be used instead of age in countries where vaccine recommendations are based on birth cohort, or where only year of birth is available.
- Permanent resident in the EU/EEA territory covered in the study (for each study site, according to the most recent information).

- 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 5-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], or; other criteria following the relevant national guidelines of each study site (for example, if autumnal vaccine is recommended at ≥180 days after the last dose).
- 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).

➢ *Study sites/countries should specify and describe the study population, in particular detailing any deviations (e.g. not possible to identify residents of nursing homes).*

Definitions

2023 autumnal vaccination campaign

Autumn 2023 dose vaccination is defined as any COVID-19 vaccine dose administered as part of the autumn 2023 vaccination recommendation (for a target age group, during specific dates between which the COVID-19 vaccination campaign is rolled out in a specific country or territory. Typically, a set of eligibility criteria are defined for the individuals that can receive this dose. Those eligibility criteria need to be aligned with the population eligible to contribute to this VE analysis.

Vaccination status

The vaccination status is a time-changing variable, with people able to change vaccination status within the study period according to COVID-19 vaccine doses administered up to the date on which vaccination status is assessed, dynamically.

Definition of vaccination status for the principal objective

For the principal objective, the vaccination status is classified dynamically over time (i.e. vaccination status is defined as a time-changing variable). Among those eligible for the latest COVID-19 vaccine dose administered as part of a campaign, they will be 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 and up to the last date of that campaign. The status is achieved 14 days after the date of administration of the vaccine. The end of the autumn 2023 vaccination campaign will be decided by expert criterion at the national level, according to the specific rollout or, if no date can be identified, it will be set on 31st March.
- Reference group: all members of the population eligible for COVID-19 vaccination at the beginning of the country-specific autumn 2023 vaccination campaign of interest, 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), as well as events recorded during such time, will be dropped from the study. Any individual who receives an additional COVID-19 vaccine dose that results in a vaccination status not defined above will be 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, or any new vaccine dose in any individual after the last date of the campaign, as defined above).

In the event that a new vaccination campaign begins within one year of the previous one (e.g., spring vaccination campaign right after an autumn campaign for those ≥80 years), those individuals who get vaccinated as part of the new COVID-19 vaccination campaign will be censored from the study estimating the VE of the previous

campaign at the time they receive the new vaccine. A separate study may be set up for monitoring of the VE of the new campaign, applying its corresponding selection criteria and vaccination definitions. The two monitoring studies may be running in parallel, where the same individuals may contribute to one or both (for example, they may contribute to the vaccinated group for the first autumn campaign study, but to the reference group for the second spring campaign study).

Definition of vaccination status by time since the most recent (autumnal) COVID-19 vaccination

For the secondary objective of estimating the VE by time since the most recent (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) is broken down into three periods (other vaccination statuses remain 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).

Definition of vaccination status by number of booster doses

For the secondary objective of estimating the VE by number of booster vaccine doses, the study population will be classified into groups, according to the number of booster doses received at the beginning of the vaccination campaign. Among those eligible in each group, the VE of an additional dose during the autumnal campaign will be assessed.

Generically, vaccination statuses are defined as follows:

- Complete vaccination with primary series of COVID-19 vaccines: individuals who received the primary series of an EMA approved vaccine or any combination of vaccines, administered no less than 19 days apart (for vaccines requiring two doses for primary vaccination).
- Complete vaccination with first booster COVID-19 vaccine dose: individuals who received an additional dose of an EMA approved vaccine at least three months (90 days) after the date of complete primary series (as defined above).
- Complete vaccination with second booster COVID-19 vaccine dose: individuals who received an additional dose of an EMA approved vaccine at least 3 months (90 days) after the first booster COVID-19 vaccine dose (as defined above).
- Complete vaccination with third booster COVID-19 vaccine dose: individuals who received an additional dose of an EMA approved vaccine at least 3 months (90 days) after the second booster COVID- 19 vaccine dose (as defined above).
- Complete vaccination with a subsequent booster COVID-19 vaccine dose: individuals who received the subsequent dose of an EMA approved vaccine at least 3 months (90 days), or the elapsed time considered by national guidelines, after the most recent previous booster COVID- 19 vaccine dose.

Using these generic definitions, separate models are defined for the VE of the autumnal vaccination (the one being evaluated) depending on if it was used as a first, second, third or subsequent booster. The relevant comparisons for each option are defined as follows.

To estimate VE of the autumnal vaccination given as first booster we classify individuals (dynamically in time) as:

- Vaccinated with a first booster: Autumnal vaccination used as first booster dose, as defined above, at least 14 days ago.
- Reference group: Eligible for the autumnal vaccination with complete primary vaccination alone prior to the autumnal campaign (i.e. with no previous booster dose) but did not receive the 2023 autumnal dose (yet).

To estimate VE of the autumnal vaccination given as second booster we classify individuals (dynamically in time) as:

- Vaccinated with a second booster: Autumnal vaccination used as second booster dose, as defined above, at least 14 days ago.
- Reference group: Eligible for the autumnal vaccination with complete vaccination with a first booster (as defined above) prior to the autumnal campaign, but did not receive the 2023 autumnal dose dose (yet).

To estimate VE of the autumnal vaccination given as third booster we classify individuals (dynamically in time) as:

- Vaccinated with a third booster: Autumnal vaccination used as third booster dose, as defined above, at least 14 days ago.
- Reference group: Eligible for the autumnal vaccination with complete vaccination with a second booster (as defined above) prior to the autumnal campaign, but did not receive the 2023 autumnal dose (yet).

To estimate VE of the autumnal vaccination given as any subsequent booster we classify individuals (dynamically in time) as:

- Vaccinated with the subsequent booster: Autumnal vaccination used as subsequent booster dose, as defined above, at least 14 days ago.
- Reference group: Eligible for the autumnal vaccination with complete vaccination one less booster dose prior to the autumnal campaign, but did not receive the autumn 2023 dose (yet).

If the number of events is insufficient to allow stratified analyses, alternative approaches will be considered, such as constructing a unique reference group and categorising the group vaccinated with the autumnal vaccine according to the total number of doses achieved with the autumnal dose.

Definition of vaccination status by vaccine product

Vaccine product used in the most recent (autumnal) dose received by each individual will be categorised as follows:

Vaccine product – most recent dose received
• Pfizer (monovalent Wuhan) • Moderna (monovalent Wuhan) • Pfizer (bivalent original/BA.1) • Moderna (bivalent original/BA.1) • Pfizer (bivalent original/BA.4/BA.5) • Moderna (bivalent original/BA.4/BA.5) • Pfizer (monovalent XBB.1.5) • Moderna (monovalent XBB.1.5) • Novavax • Other (AZ, etc.) • Missing

The VE analysis will be performed by vaccine product. The vaccine product will be ascertained for all individuals in the sample for the most recent vaccine dose they received, either during the autumnal vaccination campaign or previously in case do not get vaccinated during the autumnal campaign.

For the analysis of VE by vaccine product, COVID-19 vaccination statuses defined above will be split by product received in the autumnal vaccination under monitoring. Vaccine products received by the reference group will be used for descriptive purposes.

Outcomes

Principal outcomes of interest are defined as:

- Hospital admission due to COVID-19:
  - admission to hospital in which COVID-19 is the main diagnosis in the discharge record (for example, based on International Classification of Diseases (ICD) coding or similar)
    OR
  - in which admission criteria are compatible with SARI - based on similar criteria as in SARI surveillance, ICD, codes or similar) AND with a laboratory-confirmed SARS-CoV-2 infection between up to 14 days before admission or 24 hours after.

Only the first hospitalisation episode after the beginning of the autumnal vaccination campaign will be considered an event.

- COVID-19-related death:
  - death for which 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 after a positive test.

For each outcome, its censoring date will be the earliest among the event dates (hospital admission or death) or of 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 will be the date of the sample or, if the sample date is not available, the date of laboratory result itself).

The aforementioned criteria indicate that fatalities and hospitalisations occurring beyond the eight-week follow-up period are included, provided that the positive test defining the event date falls within the eight-week follow-up period. Conversely, hospital admissions and deaths that occur within the follow-up study period must be excluded if the positive test defining the event date precedes the beginning of the observation period.

Alternatives

- Study sites may limit the study to some of those outcomes listed above.
- Sites not being able to identify hospitalisations due to COVID-19 (using the proposed or other similar definition) may provide hospitalisations with COVID-19 instead, provided this is well documented in the site- specific protocol and the reporting methods (Annex 5).

➢ *Study sites/countries to define the outcomes used and their definitions.*

Definition of covariates

Age group

Age will be calculated at the beginning of each study period using the date of birth and categorised into five-year group for use in model adjustment. For reporting stratified results by age group, the following groups will be used: 65–79 years, 80 years and above. Alternative age groups may be considered depending on requirements, for example, based on year of birth and birth cohorts.

Number of previous booster doses

The total number of booster doses received prior to the start of the vaccination campaign of 2023 autumn will be computed to be used as an adjustment variable, as well as a stratification variable for the secondary objective of estimating VE by previous number of booster doses (0, 1, 2, 3 etc).

Socioeconomic

- Sex;
- Individual level socioeconomic status: Educational level, occupation, income, as available in registries;
- Area level socioeconomic condition (postal code, municipality or other): income per capita, Gross Domestic Product per capita, inequality or deprivation index [22], unemployment rate, as available in registries;
- Others (e.g. crowding).

Comorbidities and healthcare-seeking behaviours

Several variables may be used to account for comorbidities. For homogenisation purposes, it is recommended to include comorbidities as a three-level variable:

- 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.

Examples of comorbidities that can be considered in each category are provided in Annex 3.

Additionally, based on which variables are considered relevant confounders (and available) at study-site level, other adjusting variables can be considered:

- Number of consultations in primary care over the last 12 months, or another relevant timeframe (0, 1, 2, ≥3 consultations);
- Hospitalisation in the previous year, or other relevant timeframe (yes, no);
- Others (e.g. frailty index).

➢ *Study sites/countries to specify the covariates analysed in the study, and the definitions used for each.*

Data sources

The study uses routinely collected data from various population health registries available at national or subnational level. Each database should contain a unique identifier for any individual to allow data linkage between EHR databases.

Sources of information on the reference population

- The reference population database (for example, census database, health coverage database, etc.) with individual records of the target population;
- It should contain variables that allow the identification of non- residents, or temporary residents;
- In any of the databases it is desirable that identification of specific populations, such as those living in nursing homes or other institutions, is possible.

Sources of information on vaccination status

- Vaccination registry or vaccination record databases that record each individual vaccinated, the dates of COVID-19 vaccination, and vaccine product.

➢ *Study sites/countries to specify and describe sources of information on the vaccination status, their potential limitations, and/or unique characteristics.*

Sources of information on outcomes

Data will be extracted from different EHR databases:

- Databases including COVID-19 laboratory-confirmed infection;
- Epidemiological surveillance databases (for notifiable diseases);
- Primary healthcare consultation;
- Hospital admission/discharge;
- Death or mortality registers which record the cause of death.

Alternative

Study sites may aim/wish to only contribute with estimations for some but not all outcomes. Therefore, sources of data will be included according to which outcomes will be included in the site-specific study protocol.

➢ *Study sites/countries to specify and describe sources of information for each outcome, including their potential limitations and or/unique characteristics.*

Sources of information on covariates

- EHR databases recording comorbidities, including but not limited to primary healthcare records, databases containing medicine and healthcare product prescribing data, or any other population-based data source that can provide information on comorbidities for all cohort individuals;
- EHR databases recording healthcare-seeking behaviours, including but not limited to healthcare administrative databases (i.e. to derive number of consultations), laboratory records (i.e. number of tests performed).

➢ *Study sites/countries to specify and describe sources of information for each effect modifier/confounding factor, and the potential limitations and/or unique characteristics of the source used.*

Construction of the cohort

Identification of individuals and start of follow-up

The reference population database will be linked with the EHR databases on vaccination, comorbidities and healthcare registries using the unique identifier and deterministic data linkage (i.e. with no probabilistic component in the linkage procedure).

The start date of follow-up for each follow-up period is the latest date between:

- The start of the eight-week follow-up period;
- The start of the autumnal vaccination campaign (for the campaign being evaluated) +14 days.

To construct a cohort with time-varying vaccination status we will split each individual in the dataset into as many records (rows in the dataset) as vaccination statuses apply to that individual during the study follow-up period.

People will enter the study in their corresponding group of vaccination status based on the data available in the vaccination registry as of the start of follow-up, and will change their vaccination status during the follow-up period should they receive a new vaccine dose (or as increasing time elapses since the vaccine dose, for analysis of time since vaccination). Individuals that change vaccination status during the follow-up period will be censored without event in the group that they leave and are recorded as a delayed entry in the group which they are newly classified into (as in the Example Tables 2 and 3, where individual 12345 is in the reference group at the start of follow-up, but then receives a autumnal vaccine dose on day 16 after the start, with the following 13 days after the booster – corresponding to the induction period – not contributing to any vaccination status category, and later has the event on day 50).

This process will be different for each model, depending on the objective of the study. Thus, one data set is normally created for each model. An example dataset is shown in Table 2, for an individual that received the 2023 autumnal vaccine dose on day 15 after the start of the follow-up period.

Variables to be measured at baseline include age, sex, region (if relevant), comorbidities, and other socioeconomic or healthcare-seeking behaviour variables that will be used to adjust the models.

Table 2. Example of implementation of time-dependent variables

Individual ID	Start day	End day	Vaccination status	Time since booster dose	Other variables classified at baseline (e.g., age, sex, comorbidities)
12345	0	15	Eligible for autumnal vaccine dose (reference)	-	Constant
12345	16	29	-	-	Constant
12345	30	56	2023 autumnal dose	≥14 days and <3 months	Constant

➢ *Study sites/countries to specify the data linkage method used and the criteria used to determine the start of follow up into the study, in particular recording reasons for significant deviations from the protocol.*

Identification of outcomes during follow-up and censoring events

Outcome classification for each individual will be assessed from the study follow-up start date (t0) and up to the administrative censoring date (eight weeks later).

Table 3. Example of dataset with information on the outcome

Individual ID	Start day	End day	Vaccination status	Time since booster dose	Event
12345	0	15	Eligible for autumnal vaccine dose	-	0
12345	16	29	-	-	0
12345	30	50	Autumnal vaccine dose	<12 weeks	1

All individuals will be followed from the start of the follow-up period until the earliest between:

- Date of the event of interest, as defined previously.
- Death of any cause (on the date of death).
- Discontinuation in the administrative database (i.e. emigration).
- Administration of any additional vaccine dose in individuals that already received the autumnal vaccine.
- Administration of any additional vaccine dose after the end of the vaccination campaign, as defined above (for example, this would include doses administered as part of a possible spring vaccine dose after the previous autumnal vaccination campaign).
- Administrative censoring (eight weeks after the start of the follow-up period).

End of follow-up will be established at the time of occurrence of any reason for censoring and will be marked as event=1 if the reason for censoring is the event of interest, or event=0 otherwise. Table 3 shows the example of individual with ID 12345 who experienced the event of interest on day 50 after the start of the follow-up period.

Analysis plan

Description of the data extraction and sample selection

The total number of individuals in each of the databases fulfilling the inclusion criteria will be collected at least once a year, along with basic meta information relating to the data extraction itself (Table 4). The number and proportion of individuals excluded after each selection criteria is applied will be recorded in a flowchart by each site and country.

It is recommended that sites perform an analysis of the time required to complete data consolidation. They may do this by comparing the number of events in the same fixed follow-up period, but measured in different data extractions. Then, the time needed for data consolidation will be defined as the number of days from the end of the follow-up period to the date of the data extraction needed to have a considerable proportion (i.e. around >80%) of events recorded in the final evaluated data extraction.

Table 4. Description of data extraction and number of individuals in the source data

	Source 1	Source 2	Source 3	Source 4
Name of database				
Date of extraction				
Last date in the dataset				
Number of individuals (before selection)				

Description of the study population

Data regarding the number of individuals in the unvaccinated and vaccinated groups at the end of follow-up (for each follow-up period), the cumulative person-time of follow-up contributed by each individual to the unvaccinated and vaccinated group throughout the follow-up period, and the count of events in each group will be gathered for both outcomes (hospitalisation and death), and for all models. This information, stratified by vaccination status and age group, will be collected and explored on a monthly basis, although only with reference to the model constructed for the principal objective and the COVID-19 hospitalisation outcome in accordance with the format specified for periodic reporting of VE results (Annex 4).

Study-site background information will also be collected, and can include the incidence rate, the distribution of vaccination coverage, and the proportion of variant circulation at different points in time. This information will be extracted from ECDC data repositories on case notifications, vaccine coverage, and variant circulation.

Information on dates in which the different age groups entered the vaccination programme for first vaccine dose, first booster dose, or successive doses will be collected as part of the background information on the study setting (see 'Study setting' section in this protocol). The proportion of missing data will be used to determine if each specific variable can be included in the model and how (e.g. missing could eventually be included as a covariate in the model). Data imputation for missing data in order to improve quality is not planned but will be encouraged where suitable, the methodology for which will be recorded and presented with results.

Finally, it is recommended that sites look at the distribution of events throughout the follow-up period for each outcome, age-group, and by vaccination statuses, to assess any systematic difference in the vaccination status groups which are being compared.

Estimation of vaccine effectiveness

Several different models are built to provide estimates for the principal and secondary objectives. Each model corresponds to a section in the reporting template (Annex 5), so it is possible to clearly define the reference and exposure categories for each one separately.

Estimation of VE for the principal objective

Generically, two models need to be built: one for the outcome of hospitalisation due to COVID-19 and another one for COVID-19-related death. In each model, there will be only one vaccinated category, as defined previously (see 'Definitions' section, 'Vaccination status' subsection). Incidence of each outcome in those vaccinated with the autumnal COVID-19 vaccine will be compared to incidence in those eligible but who have not received it yet (as time-changing, see above).

Estimation of VE by time since the most recent (autumnal) COVID-19 vaccine dose

For the secondary objective of VE by time since the most recent (autumnal) COVID-19 vaccine dose, also two models need to be built: one for the outcome of hospitalisation due to COVID-19 and another one for COVID-19 related death. In each model, there will be a maximum of three categories of vaccination status, depending on the time elapsed since autumnal vaccination (see 'Definitions' section, 'Vaccination status' subsection). Incidence of each outcome in those vaccinated with the autumnal COVID-19 vaccine 14-89 days, 90-179 days or ≥6 months will be compared to incidence in those eligible but who have not received it yet (as time-changing, see above).

Estimation of VE by number of booster doses

The secondary objective of VE by number of COVID-19 vaccine booster doses will not be monitored routinely, but will be assessed ad hoc, at minimum at the end of each autumnal vaccination campaign. Several models need to be built, depending on the number of booster doses that have been administered at the time of the autumnal campaign. One model will be fit for each group defined by the number of booster doses received at the beginning of the autumn 2023 campaign (i.e. completed primary vaccination alone with no booster, vaccinated with a first booster, with a second booster and so forth, see 'Definitions' section, 'Vaccination status' subsection), with each of these groups being the reference for their corresponding model. Exposure will be thereafter defined as receiving one additional dose (as time-changing, see above), resulting in the following comparisons:

- Incidence of each outcome in those vaccinated with the 2023 autumnal COVID-19 vaccine as a first booster will be compared to incidence in those who completed primary vaccination alone and eligible for the first booster but who have not received it yet (as time-changing, see above).
- Incidence of each outcome in those vaccinated with the 2023 autumnal COVID-19 vaccine as a second booster will be compared to incidence in those vaccinated with a first booster and eligible for the second booster but who have not received it yet (as time-changing, see above).
- Incidence of each outcome in those vaccinated with the autumnal COVID-19 vaccine as a third booster will be compared to incidence in those vaccinated with a second booster and eligible for the third booster but who have not received it yet (as time-changing, see above).

And so forth.

This analysis may be further split by time since the 2023 autumnal dose, in the same manner as described above. Importantly, each number of doses will be assessed only for the age groups in which that number of doses has already been recommended.

As addressed above, other approaches may be explored if the number of events is insufficient to support the stratified analysis. For instance, to use the overall population not vaccinated with the autumnal vaccine as reference group for any number of booster doses, an ordinal variable could be created with value 0 for those not vaccinated for the autumnal vaccine, and increasing indicator numbers for increasing number of total booster doses for those who received the autumnal vaccines. Within these categorical variables, the difference across individuals with different number of vaccines doses could also be assessed, with increased statistical power.

Estimation of VE by vaccine product

The secondary objective of estimating VE by vaccine product will be assessed in the event that multiple vaccine products are used simultaneously during the vaccination campaign, which is currently not planned in the study sites for the 2023/24 campaign. For addressing this objective, the vaccinated groups may be further split according to the product used for the autumnal COVID-19 vaccination (see 'Definitions' section, 'Vaccination status' subsection). Incidence of each outcome in those vaccinated with each product for the autumnal COVID-19 vaccine will be compared to incidence in those eligible but who have not received any vaccine yet (as time-changing, see above). The vaccine brand of vaccine doses received prior to the vaccination campaign will not be assessed. Each comparison will be restricted to the countries that have used the vaccine brands of interest. Direct comparisons of incidence of each outcome in groups who received different vaccine products as autumnal vaccination may also be considered.

Crude hazard ratio

The crude hazard ratio (HR) of the defined outcome will be estimated using survival Cox regression models with calendar time as the underlying time scale, thus assigning time 0 to the first day of the follow-up period.

➢ *Study sites to define the analytical approach.*

Adjusted hazard ratio and vaccine effectiveness

The regression analysis to estimate HR will be adjusted for confounders, as appropriate, and as previously defined. First, partially adjusted HR will be estimated, adjusting by age group (5 year-bins), sex and region in the country, if appropriate. Second, a fully adjusted HR (aHR) estimate will be produced adjusting by variables related to socioeconomic status, comorbidities and healthcare-seeking behaviour, total number of COVID-19 vaccine doses up to the start of the autumnal vaccination campaign, and/or others, as relevant at each study site.

The adjustment variables have been selected based on their availability (though this may vary between the different study sites) and their role in a possible confounding bias given the assumptions on the cause-effect relationships reflected in the causal graphic representation on Annex 5. To select additional variables for adjustment of the models at each study site, it is recommended to analyse their possible role within the overall assumed causal-effect relationships in Annex 5, and fit models with and without them, to assess the effect that they have on the estimate of the adjusted HR.

Finally, when the best possible valid aHR has been estimated, VE will be calculated as:

VE = (1-aHR) x 100

Methods for pooling estimates

Country-specific adjusted HRs and standard errors for the effect of COVID-19 vaccination obtained from the study sites are combined in a model using meta-analysis techniques [23]. Study sites will not report VE estimates for which the number of events *in the reference group* is less than five, and they will not be included in the pooled estimates. The number of events in the exposed group will not be set to a minimum, since for very effective interventions accurate effect estimates can be obtained with a low number of events in the exposed. However, study-sites may need to apply this threshold of a minimum of five events, or even a higher threshold, if needed for data protection compliance at the country level. Pooled estimates will be produced when the total number of events *in the reference group* (across all sites contributing to that model) is 15 or more.

First, as a main approach, a random-effects meta-analysis is used. Conceptually, it is possible that VE is different depending on measured or unmeasured site-specific factors. To account for the two sources of variability (intra-study and inter-study), the marginal variance is divided into two components: the individual study-specific variances and the variance of the random study effects (τ^2). I^2 represents the proportion of the total variance that is attributable to the random study effects, i.e. the percentage of the variability between the effect estimates that is due to between studies heterogeneity rather than chance. τ^2 and I^2 are used to report between-studies statistical heterogeneity, along with the p-value of the heterogeneity test.

As a sensitivity analysis, a fixed-effects approach may be used, by computing a simple weighted average across studies. To do this, the site-specific vaccination status-disease effects (HRs) will be weighted by the inverse of their marginal variances (generic inverse variance method). This will give the pooled HRs and a standard error. Confidence intervals around the pooled effect (the range of values that contain the true average HR with 95% certainty) are then calculated.

Potential factors or specific study sites characteristics that could be the source of qualitative heterogeneity will be described, as covered in the descriptive part of the data analysis in this protocol.

The country-specific HR and their confidence intervals, along with the pooled HRs, are presented graphically in a forest plot. The crude effect, the partially adjusted effect (age, sex, region), and the fully-adjusted effect (adding the rest of available covariates) are then compared to assess the degree of confounding by different factors and to guide the interpretation of inter-site variability.

Sensitivity analyses are conducted for pooled estimates obtained while excluding some study participants for whom variables were collected, defined or managed differently, or who have differences in the study setting that could affect the estimates (e.g. different SARS-CoV-2 genetic predominant variants) or for whom estimates significantly differ across sites (i.e. site confidence intervals do not overlap with the pooled estimate confidence interval), particularly if the I^2 estimate is >50%.

Data checking and validation

The following data checking and data validation are undertaken before analysis at the study site level:

- Identification of inconsistencies (e.g. earlier dates for second doses than for first doses).
- Unusual values and outliers.
- Inclusion/exclusion criteria adherence.
- Missing values, missing clinical details, missing laboratory results.
- Duplicate cases and multiple admissions.

- Consistency of dates (onset, admission, discharge, swabbing), and plausibility of durations between them (e.g., too long a delay between the date of symptom onset to lab specimen collection date).
- Proportions of records excluded due to missing data that relate to essential variables.

➢ *Study sites/countries to list data checking and validation items and, if possible, to provide the methodology (scripts, excel templates) used during data checking.*

Ethical requirements

Approval by an ethics committee is a requirement. A statement that ethical approval is not necessary according to a country's legislation, should that be the case, is also valid. All sites must conform with national and EU ethical and data protection requirements.

➢ *Study sites to provide information on ethical approval.*

Potential biases and limitations

- Input data: The availability and granularity of the study variables may be constrained by the information documented in registries that were originally created for purposes other than conducting this investigation. Furthermore, the possibility of registry errors cannot be ruled out. Finally, significant variability in the way the different variables are defined and categorised between countries is anticipated, which may complicate the interpretation of aggregated results as a unified estimation.
- Because of the discontinuation of systematic SARS-CoV-2 testing in most European countries after January 2022, previous infection is mostly unknown to the health registries. Moreover, the widespread use of self-applied rapid antigenic testing for SARS-CoV-2 implies that individuals may be making decisions based on information on previous infections not collected in the databases. Lack of available information on previous infection poses different problems:
  - On one hand, it can create confounding, as it will influence the probability that an individual seeks vaccination and also influences both the risk of a subsequent infection and the probability that it results in hospitalisation or death (Annex 5, note that the arrow from previous infection <90 days to COVID-19 hospitalisation has been omitted for simplicity, but this does not change the assessment for potential confounding). Reported SARS-CoV-2 infection in <90 days before the start of the campaign is used as a proxy but the probability that the adjustment is incomplete is very high, plus it creates additional threats by creating associations dependant on testing behaviour. Unfortunately, there is no information available to achieve a good adjustment by previous infection.
  - On the other hand, if VE is different in people depending on their previous infection history, the VE estimates that do not account for previous infection will represent an average effect of the vaccine in a population with a given (and mostly unknown) proportion of previously infected individuals. External validity will be compromised, and results will not be transportable to countries with different proportion of individuals with previous infection. This can also be a source of heterogeneity among the different study sites implementing this protocol.
- Control for confounding depends in the ability of available data to completely account for differences in comorbidities, healthcare-seeking behaviour and socioeconomic variables related to both the exposure and the outcome (Annex 5, note that the arrow from these variables to SARS-CoV-2 infection during the season has been omitted for simplicity, but this does not change the assessment for potential confounding).
- Due to the staggered and differential roll-out of COVID-19 vaccination campaigns in the different countries the reference group, those eligible to receive a subsequent vaccine dose during a population campaign, will be comprised of people with varying numbers of previous vaccine doses. For example, for the vaccination campaign in the autumn of 2023, eligible individuals may have up to four doses in countries who only administered up to two boosters (with autumn campaigns alone), or up to six doses if the country also performed spring vaccination in 2022 and 2023. As before, this is a pragmatic approach with accurate interpretation at the national level, but with limitations in the generalisability of results. The secondary objective of estimating VE by number of vaccine doses aims to overcome this limitation and provide complementary results.
- The discontinuation of systematic SARS-CoV-2 testing in individuals hospitalised with severe acute respiratory infection in some countries may also challenge the generalisability of results if, for example, only more severe cases are tested in one country but not in other. As long as testing is not dependent on vaccination status, a severe bias is not expected as a result of this change in testing policy.

➢ *Study sites to describe the main limitations of their study and how those can affect the results, including aspects detailed in the protocol that were unachievable in their study.*

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Annex 1. Type of studies and study settings within the VEBIS infrastructure as of November 2022

Setting	Type of study	Main outcome	References
Hospitals	Test negative design	Severe disease; influenza and COVID-19	[12-16]
Healthcare workers cohort	Cohort study	Infection, COVID-19 and Influenza	[18,19]
Electronic healthcare databases	Cohort study	Hospitalisation and other severe outcomes, COVID-19	[3-5]
Primary care	Test negative design	Moderate disease (~ARI/ILI), Influenza and COVID-19	[19]

Annex 2. Summary of changes from Protocol v.1.0

This Protocol incorporates lessons learned from one and a half years of prospective monitoring of COVID-19 VE based on electronic health records, and updates the methods to the current situation regarding epidemiology of SARS-CoV-2, testing strategies and booster doses rollout in the EU/EEA countries. The changes form version 1.0 of the protocol [2] include:

1. The background has been updated to include information on current SARS-CoV-2 epidemiology, vaccine product availability, and to reflect the current stage of the project, including the justification for this updated protocol.
2. The study population has been restricted to those aged ≥65 years (changes implemented in the 'Objectives' and 'Study population' sections)
3. The description of the outcome 'Death due to COVID-19' has been changed to 'COVID-19-related death' to reflect that it is not possible to ensure that deaths with a positive SARS-CoV-2 test in the previous 30 days are caused by COVID-19 (changes implemented in the 'Objectives' and 'Outcomes' sections)
4. The outcomes 'Hospital admission due to COVID-19 with laboratory-confirmed SARS-CoV-2 infection' and 'Death due to COVID-19 with laboratory-confirmed SARS-CoV-2 infection' have been updated to remove 'with laboratory-confirmed SARS-CoV-2 infection', because a positive test is not always required (changes implemented in the 'Objectives' section).
5. The principal objective has been changed to reflect the comparison of the most recent vaccine dose, given as part of autumnal vaccination campaigns, with the entire eligible population who did not receive it, under a pragmatic approach (changes implemented in the 'Objective' section and 'Vaccination status' subsection). The aim of this change is to adapt the protocol to the current public health strategy regarding COVID-19, and to better inform policies in the future.
6. The objective of estimating VE by number of vaccine doses has become a secondary objective, and only relative VE of the most recent (autumnal) vaccine dose will be monitored (removing comparisons with unvaccinated individuals, or the comparisons of second and subsequent booster doses with complete primary vaccination alone) (changes implemented in the 'Objectives' and 'Vaccination status' sections).
7. The secondary objective of measuring VE against ICU admission as an outcome has been removed (changes implemented in the 'Objectives' section).
8. Estimation of VE by number of doses and by vaccine product have been changed as ad hoc analyses (changes implemented in the 'Objectives' section).
9. Headings 'study design' and 'study setting' have been merged into 'Study design and setting'
10. The 'study period' has been re-written to reflect the quarterly monitoring, vs. the monthly monitoring implemented before.
11. Selection criteria have been modified to reflect eligibility for booster vaccination (changes implemented in the 'Study population' section).
12. A note of dynamic implementation of selection criteria to enter into the study has been added, since some criteria change with time (changes implemented in the 'Construction of the cohort' section, 'Identification of individuals and start of follow-up' subsection).
13. Definition of vaccination statuses and reference groups has been modified to reflect changes to Objectives (changes implemented in the 'Vaccination status' subsection).
14. For clarity, the induction times have been removed from the generic classification of vaccination statuses by number of doses, and particular vaccine brands used as booster doses have been substituted by a broader term such as 'EMA approved vaccine' (changes implemented in the 'Vaccination status' subsection).
15. A generic 'subsequent booster COVID-19 vaccine dose' has been defined, to make the protocol more flexible to future approvals of more booster doses (changes implemented in the 'Secondary objectives' and 'Vaccination status' subsections).
16. For the 'time since vaccination' variable, time since the vaccine is now counted from the day of the vaccine administration regardless of the induction time (changes implemented in the 'Secondary objectives' and 'Vaccination status' subsections). Cut-offs are now set at 90 and 180 days, for better homogeneity with other studies.

17. Within each specific model to estimate VE, individuals with vaccination statuses not included have been removed (changes implemented in the 'Definition of vaccination status for the secondary objectives' subsection).
18. A redundant paragraph relating to selection criteria has been removed from the Vaccination Status Definition section (changes implemented in the 'Vaccination status' subsection).
19. Definition of the outcomes has been re-ordered for better clarity with no change in the criteria. The date of the outcome has been modified so as to be the earliest among the date of the outcome event (hospital admission or death) or the date of the laboratory diagnosis. A definition for 'date of laboratory diagnosis' has been added. Some examples relaying the process of inclusion/exclusion of outcomes have also been added (changes implemented in the 'Outcomes' subsection).
20. The section on definitions of vaccine products has been simplified. The section on 'stratification variables' has been removed and 'Potential confounding variables for adjustment' has been renamed to 'Definition of covariates' (changes implemented in the 'Definitions' section, 'Definition of covariates' subsection).
21. Previous infection is no longer included as a covariate in the model, therefore its definition has been removed from the protocol (changes implemented in the 'Definitions of covariates' subsection).
22. 'Sociodemographic covariates' has been renamed 'Socioeconomic covariates', and the Age Group variable has been removed to avoid duplication (changes implemented in the 'Definitions of covariates' subsection).
23. 'Medium-low risk comorbidities' have been renamed 'Medium risk comorbidities' since they correspond to conditions for which COVID-19 vaccination was nationally recommended (changes implemented in the 'Comorbidities and healthcare-seeking behaviours' subsection).
24. The 'Construction of the cohort' section has been updated to reflect additional eligibility criteria and dynamic entry into the study. An explicit list of criteria to determine the start and end date of follow-up has been added (changes implemented in the 'Construction of the cohort' section).
25. Distribution of persons and person-months by key variables, stratified by vaccination status and age group, will be collected and explored only with reference to the model constructed for the main objective and the hospitalisation outcome ('Analysis plan' section, 'Description of the study population' subsection).
26. The subsection 'Groups to be compared' has been removed from the 'Estimation of vaccine effectiveness' section, because it has been incorporated into the 'Definitions' section, within the 'Vaccination status' subsection. The 'Estimation of vaccine effectiveness' section has been split into one sub-section for each main or secondary objective (changes implemented in the 'Estimation of vaccine effectiveness' subsection).
27. Mentions of time-changing confounders have been removed, since they are no longer analysed (changes implemented in the 'Construction of the cohort' section).
28. A criterion was added to 'Method for Pooling estimates': pooled estimates will be produced when the total number of events (across all sites contributing to that model) is 15 or greater (changes implemented in the 'Methods for pooling estimates' subsection).
29. The main method for pooling estimates was changed and now uses random effects (changes implemented in the 'Methods for pooling estimates' subsection).
30. Potential biases and limitations section has been re-written to reflect the challenges in the new context and with the revised methods.
31. Reporting templates have been adapted to the new protocol.
32. A Directed Acyclic Graph (DAG) has been added as Annex 5 to help identify sources of confounding bias.

Annex 3. Data dictionary (example)

Individual characteristics

	Variable	Type	Coding	Definition
Operational	Extract date	Date	dd/mm/yyyy	Database extraction date
Patient characteristics	Sex	Numeric	0 = female	Sex of patient
			1 = male	
			3 = other	
			8 = do not know	
	dob	Date	dd/mm/yyyy	Date of birth (only if no age; once age calculated from dob this will be dropped)
	postcode	Numeric		Postcode of residence
	residence	Numeric	0 = at home, not dependent on home support/care	Patient residence at time of event onset. Whether patient was living at home or was institutionalised, or had pre-hospital dependence on home support/care
			1 = at home, but dependent on home support/care	
			2 = institutionalised	
			3 = Do not know	

Outcome

	Variable	Type	Coding	Definition
COVID-19 case	swabdate	Date	dd/mm/yyyy	Respiratory specimen collection date
	lab_covtest	Numeric (categorical)	0 = No	Tested for SARS-CoV-2
			1 = Yes	
			8 = Do not know	
	lab_covtesttype	Numeric (categorical)	1 = RT-PCR	Type of lab test used
			2 = Serology	
			3 = Rapid test	
			4 = Other	
			8 = Do not know	
	lab_covtesttype_sp	Text		Specify other type of lab test
	lab_covid	Numeric (categorical)	0 = Negative	Laboratory result: virus type SARS-CoV-2
			1 = Positive	
			8 = Do not know	
			1 = Positive	
			8 = Do not know	
Hospital/ward information	prevhosp	Numeric (categorical)	0 = No	Prior admission to hospital (at least once in previous 12 months)
			1 = Yes	
			8 = Do not know	
	admitdate	Date	dd/mm/yyyy	Date of hospital admission
	hospitalward	Text		Ward
	dischargedate	Date	dd/mm/yyyy	Date of hospital discharge
COVID_icu	icu		0 = No	Admission to intensive care unit (ICU)
			1 = Yes	
			8 = Do not know	
	icuadmitdate	Date	dd/mm/yyyy	Date first admitted ICU
	icudisdate	Date	dd/mm/yyyy	Date last discharged from ICU
Death	death	Numeric (categorical)	0 = No	Person is deceased
			1 = Yes	
			8 = Do not know	
	deathdate	Date	dd/mm/yyyy	Date of death
	deathcause	Numeric (categorical)	1 = died from COVID-19	Cause of death
			2 = died other cause	
			8 = died unknown cause	

Vaccination status

	Variable	Type	Coding	Definition
COVID-19 vaccination	panvaccany	Numeric (categorical)	0 = No	Received at least one dose of COVID-19 vaccine
			1 = Yes	
			8 = Do not know	
	Panvaccdate_i	Date	dd/mm/yyyy	Vaccination date (for each dose, i)
	Panvacctype_i	Text		Type of vaccine (for each dose, i)
	panvaccdose	Numeric	0, 1, 2	Number of doses received

Comorbidities

	Variable	Type	Coding	Definition
Underlying chronic conditions	Anaemia	Numeric (categorical)	0 = No	Anaemia/chronic haematologic disease
			1 = Yes	
			8 = Do not know	
	Asplenia	Numeric (categorical)	0 = No	Asplenia (absence of/damage to spleen)
			1 = Yes	
			8 = Do not know	
	Asthma	Numeric (categorical)	0 = No	Asthma
			1 = Yes	
			8 = Do not know	
	Cancer	Numeric (categorical)	0 = No	Cancer (any)
			1 = Yes	
			8 = Do not know	
	Hypert	Numeric (categorical)	0 = No	Hypertension
			1 = Yes	
			8 = Do not know	
	Demente	Numeric (categorical)	0 = No	Dementia
			1 = Yes	
			8 = Do not know	
	Diabetes	Numeric (categorical)	0 = No	Diabetes
			1 = Yes	
			8 = Do not know	
	Heartdis	Numeric (categorical)	0 = No	Heart / cardiac disease (excluding hypertension)
			1 = Yes	
			8 = Do not know	
	Immuno	Numeric (categorical)	0 = No	HIV or other immunodeficiency or organ transplantation
			1 = Yes	
			8 = Do not know	
	Liverdis	Numeric (categorical)	0 = No	Chronic liver disease (excluding cancer)
			1 = Yes	
			8 = Do not know	
	Lungdis	Numeric (categorical)	0 = No	Lung disease (excluding asthma)
			1 = Yes	
			8 = Do not know	
	Neuromusc	Numeric (categorical)	0 = No	Neuromuscular disorder
			1 = Yes	
			8 = Do not know	
	Height	Numeric (integer)		Height of patient in metres
	Weight	Numeric (integer)		Weight of patient in kg
	BMI	Numeric (1 d.p)		BMI of patient (calculated using data collected on height and weight)
	Obese	Numeric (categorical)	0 = No	Obesity (only if height, weight and BMI not collected; can be calculated)
			1 = Yes	
			8 = Do not know	
	Rendis	Numeric (categorical)	0 = No	Renal disease (excluding cancer and acute renal failure)
			1 = Yes	
			8 = Do not know	
			0 = No	

	Variable	Type	Coding	Definition
	Rheumat	Numeric (categorical)	1 = Yes 8 = Do not know	Rheumatologic disease

	Variable	Type	Coding	Definition
	Stroke	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Stroke
	Tuberc	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Tuberculosis

Other confounding variables

	Variable	Type	Coding	Definition
Patient characteristics	Frailty	Numeric (categorical)	To be updated with coding depending on score used	Clinical frailty score at admission (where possible) or Barthel Index
Pre-symptomatic treatment/interve ntio n: vaccination	flu_vacc	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Received current autumnal influenza vaccination
	flu_vaccdate	Date	dd/mm/yyyy	Date of last influenza vaccination
	ppv_vacc	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Received PPV23 vaccination
	ppv_vaccdate	Date	dd/mm/yyyy	Date of last PPV23 vaccination
	pcv_vacc	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Received PCV7/10 or 13 vaccination
	pcv_vaccdate	Date	dd/mm/yyyy	Date of last PCV7/10 or 13 vaccination
	bcg_vacc	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Received BCG vaccination
	bcg_vaccyear	Numeric	yyyy	Year of BCG vaccination

Annex 4. Characteristics of study population collected through the monthly reporting template (one per country/site)

(Example, the full periodic reporting tables are available in excel format upon request to ECDC)

	Not vaccinated during the seasonal campaign	Vaccinated during the seasonal campaign (≥14 days ago)	Vaccinated during the seasonal campaign (≥14 and ≤89 days ago)	Vaccinated during the seasonal campaign (90–179 days ago)	Vaccinated during the seasonal campaign (≥180 days ago)
	n*	***n****	***n****	***n****	***n****
Site					
Total individuals	***#N/A***	***#N/A***	***#N/A***	***#N/A***	***#N/A***
Sex					
Male	***#N/A***	***#N/A***	***#N/A***	***#N/A***	***#N/A***
Female	***#N/A***	***#N/A***	***#N/A***	***#N/A***	***#N/A***
Missing	***#N/A***	***#N/A***	***#N/A***	***#N/A***	***#N/A***
Number of booster doses received prior to the seasonal campaign					
0	#N/A	#N/A	#N/A	#N/A	#N/A
1	#N/A	#N/A	#N/A	#N/A	#N/A
2	#N/A	#N/A	#N/A	#N/A	#N/A
3	#N/A	#N/A	#N/A	#N/A	#N/A
4	#N/A	#N/A	#N/A	#N/A	#N/A
5	#N/A	#N/A	#N/A	#N/A	#N/A
Country of birth					
native	#N/A	#N/A	#N/A	#N/A	#N/A
non-native	#N/A	#N/A	#N/A	#N/A	#N/A
missing	#N/A	#N/A	#N/A	#N/A	#N/A
Nationality					
national	#N/A	#N/A	#N/A	#N/A	#N/A
non-national	#N/A	#N/A	#N/A	#N/A	#N/A

	Not vaccinated during the seasonal campaign	Vaccinated during the seasonal campaign (≥14 days ago)	Vaccinated during the seasonal campaign (≥14 and ≤89 days ago)	Vaccinated during the seasonal campaign (90–179 days ago)	Vaccinated during the seasonal campaign (≥180 days ago)
missing	#N/A	#N/A	#N/A	#N/A	#N/A
Vaccine product - third booster (only including individual who received the third booster before end of study period)					
Pfizer (monovalent)	#N/A	#N/A	#N/A	#N/A	#N/A
Moderna (monovalent)	#N/A	#N/A	#N/A	#N/A	#N/A
Pfizer (bivalent original/BA.1)	#N/A	#N/A	#N/A	#N/A	#N/A
Moderna (bivalent original/BA.1)	#N/A	#N/A	#N/A	#N/A	#N/A
Pfizer (bivalent original/BA.4/BA.5)	#N/A	#N/A	#N/A	#N/A	#N/A
Moderna (bivalent original/BA.4/BA.5)	#N/A	#N/A	#N/A	#N/A	#N/A
Pfizer (XBB.1.5)	#N/A	#N/A	#N/A	#N/A	#N/A
Moderna (XBB.1.5)	#N/A	#N/A	#N/A	#N/A	#N/A
Novavax	#N/A	#N/A	#N/A	#N/A	#N/A
Other (AZ, others...)	#N/A	#N/A	#N/A	#N/A	#N/A
Missing	#N/A	#N/A	#N/A	#N/A	#N/A
Comorbiditites					
No comorbidity	#N/A	#N/A	#N/A	#N/A	#N/A
Medium risk comorbidities /non-immunecompromising	#N/A	#N/A	#N/A	#N/A	#N/A
High risk comorbidities/ immunecompromising	#N/A	#N/A	#N/A	#N/A	#N/A
Missing	#N/A	#N/A	#N/A	#N/A	#N/A

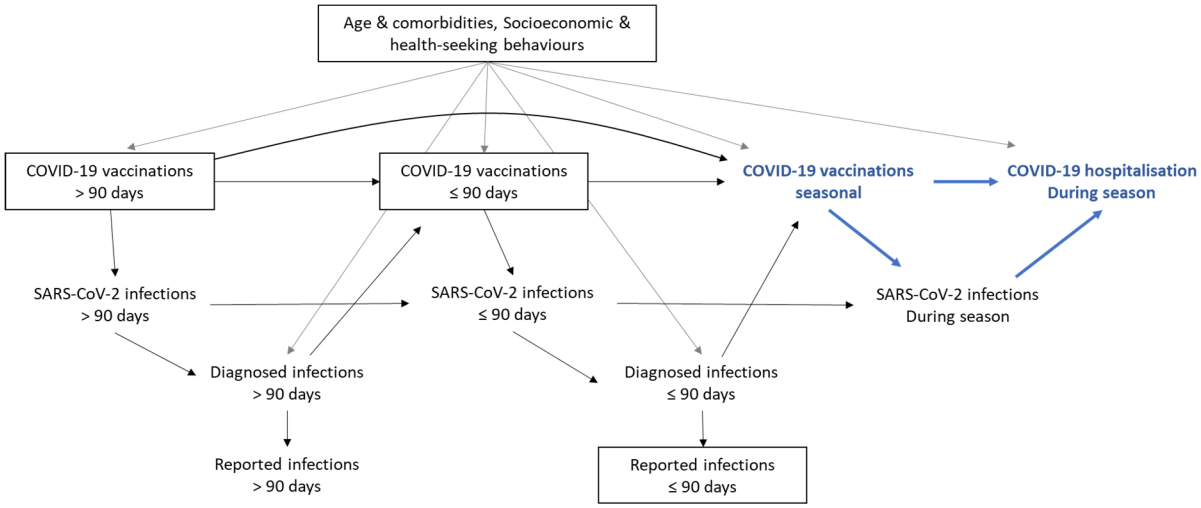
** Total number of individuals classified in the vaccination status by the end of the follow-up period.*

(Example, the full periodic reporting tables are available in excel format upon request to ECDC)

Exposure categories	N*	person-days	Events	HR crude			HR adjusted1**			HR adjusted2***		
				Estimate	95%CI low	95%CI high	Estimate	95%CI low	95%CI high	Estimate	95%CI low	95%CI high
Not vaccinated during the seasonal campaign	#N/A	#N/A	#N/A	REF	REF	REF	REF	REF	REF	REF	REF	REF
Vaccinated (≥14 days ago; overall)	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
Vaccinated (≥14 and ≤89 days ago)	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
Vaccinated (90–179 days ago)	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
Vaccinated (≥180 days ago)	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A

** Number of individuals contributing to each group. Because exposure is time changing, the sum of N in all categories will be greater than the total sample size in the study.*
*** HR adjusted1: Adjusted by age (5-year bins), sex and region according to country-specific protocol.*
**** HR adjusted2: Additionally adjusted by the rest of confounding variables according to country-specific protocol.*

Annex 5. Directed Acyclic Graph (DAG) for the estimation of the effect of autumnal vaccination on COVID-19 hospitalisation



This DAG depicts the relationship between variables through arrows that go from causes to effects, as assumed in this protocol. The blue variables and arrows correspond to the exposure and outcome variables to be evaluated and the causal pathways that aim to be estimated, i.e. the paths through which both variables are linked always following the direction of the arrows. Variables that have a square around them are controlled for in the analysis, and thus any path that goes through them is blocked.

Relevant assumptions in this DAG: 1) The arrow from previous infection ≤90 days to COVID-19 hospitalisation (assuming a previous infection can influence the possibility that a subsequent infection is severe) has been omitted for simplicity, with no change in conclusions. 2) For simplicity and better visualisation of the DAG, we have omitted the arrows from age, comorbidities, socioeconomic variables and healthcare-seeking behaviours to SARS-CoV-2 infection (with no change in the overall bias ascertainment). We assume we have controlled for these variables, though it is very possible that residual confounding can exist since the amount and quality of these variables in the electronic heath records may not be optimal. If the adjustment is incomplete, any non-causal paths (linking variables in a direction opposed to the arrow) that pass through these variables will not be completely blocked and thus residual confounding exist. 3) Reported infections ≤90 days is used as a proxy of SARS-CoV-2 infections ≤90 days. Because this will be an incomplete adjustment, it is possible that residual confounding exists following the reverse pathway: COVID-19 vaccination autumnal – SARS-CoV-2 infections ≤90 days – SARS-CoV-2 infections During season – COVID-19 hospitalisation During season. Due to the low current diagnosis rates, it is impossible to control for this in our study. The assumed DAG is assumed to be similar for COVID-19 related death.

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