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EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

OPERATIONAL SUPPORT


# Protocol to measure COVID-19 XBB.1.5 vaccine effectiveness in the immunocompromised population during the 2023 autumn vaccination campaign

## A multi-centre cohort study using electronic health records in EU/EAA countries

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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', coordinated by Nathalie Nicolay. Production of the protocol was coordinated by Nathalie Nicolay and Kate Olsson.

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# Abbreviations

| | |
|---|---|
| ATC | Anatomical Therapeutic Chemical |
| COVID-19 | Coronavirus disease 2019 |
| EEA | European Economic Area |
| EHR | Electronic health record |
| EMA | European Medicines Agency |
| ESRD | End stage renal disease |
| EU | European Union |
| HR | Hazard Ratio |
| ICD | International Classification of Diseases |
| ICP | Immunocompromised person |
| ICPC | International Classification of Primary Care |
| RT-PCR | Reverse-transcription polymerase chain reaction |
| SARI | Severe acute respiratory infection |
| SARS-CoV-2 | Severe acute respiratory syndrome – coronavirus 2 |
| SES | Socioeconomic status |
| VE | Vaccine effectiveness |
| VEBIS | Vaccine Effectiveness, Burden and Impact Studies |
| VOC | Variant of Concern |
| WHO | World Health Organization |

# Executive summary

The European Centre for Disease Prevention and Control (ECDC) started several vaccine effectiveness (VE) studies in 2020. These were included in the Vaccine Effectiveness, Burden and Impact Studies (VEBIS) project in 2021 to monitor VE in different settings and using different methods, and to provide information on different outcomes (severe disease, moderate disease, infection, transmission, etc) (1–3). Within the VEBIS project, the protocol describes the methods to estimate the Coronavirus disease 2019 (COVID-19) XBB.1.5. monovalent-adapted VE in immunocompromised persons (ICP), against COVID-19 hospitalisations and deaths, using established health data registries across six participating European Union/European Economic Area (EU/EEA) countries. The protocol is aimed at implementing a specific question that has been identified as an area where additional scientific evidence is beneficial, in the context of the ECDC/EMA Vaccine Monitoring Platform research agenda (4), adding on the routine vaccine effectiveness monitoring performed across the six countries (5). This work is performed within the VEBIS Lot 4 framework contract.

The study design is a retrospective cohort study using data from ICPs eligible for COVID-19 vaccination at the start of the 2023 autumn vaccination campaign, collected routinely in electronic health record (EHR) databases. The study starts at the beginning of the vaccination campaign for each study site and ends 12 months after that. The study has two outcomes of interest: hospitalisations and deaths due to COVID-19. Data to be collected, besides the outcomes of interest, include sociodemographic (age, sex), clinical (ICP group) and COVID-19 vaccination history (brand, number of doses and dates of prior vaccine dose administration).

The protocol outlines the study design and methods for analysing the data at country level and includes a plan for the pooled analysis across countries. This protocol is primarily intended to guide the implementation of the ECDC-funded studies within the VEBIS project with a focus on specific objectives. Nevertheless, ECDC encourages the conduct of VE studies using this protocol and other VEBIS-related protocols as a basis in countries that do not currently plan to participate in ECDC-funded studies. Consistent protocols will facilitate the comparability of results across studies, countries, and sites.

# Background

On 11 March 2020, the World Health Organization (WHO) declared COVID-19 a pandemic (6). This pandemic would go on to cause a significant number of deaths, with close to seven million reported by August 2023 (7). More than three years after the start of the pandemic, in May 2023, WHO declared that COVID-19 was no longer a public health emergency of international concern (8). While the risk to human health has been drastically reduced due to high population immunity obtained through infection and vaccination against SARS-CoV-2, the risk remains high for severe COVID-19 in immunocompromised persons (ICPs)(9). In December 2020, the European Medicines Agency (EMA) authorised several vaccines against COVID-19 for use in the European Union (10). Since then, COVID-19 vaccines have been studied on their effectiveness for different at-risk groups, variants of concern (VOCs) and vaccination strategies (comparing primary vaccination and booster schedules). Since September 2022, the EMA has authorised the use of adapted/updated vaccines (2022 bivalent, 2023 XBB.1.5 and 2024 JN.1 monovalent vaccines) for use as booster doses/irrespective of previous vaccination or infection status (11).

Overall, current evidence suggests high vaccine effectiveness (VE) of COVID-19 vaccination against severe outcomes, such as hospitalisation and death (12). However, it has been shown that ICPs have a reduced response to COVID-19 vaccines compared to non-ICPs (9). Therefore, in 2021, the recommendation for ICPs was an extended primary vaccination course of three doses (13). Several studies estimated COVID-19 VE of booster doses (original composition) against hospitalisation and death in ICPs. However, few studies were focused on studying COVID-19 VE of different variant-adapted vaccines (bivalent or monovalent XBB) as booster doses in ICPs. Five studies analysing VE of adapted vaccines against COVID-19-related hospitalisation, ICU admission, and death were conducted in the United States of America (14–18), while only one was conducted in Europe (Denmark, Finland, and Sweden) (19). Studies measuring COVID-19 VE of the variant-adapted vaccines against severe outcomes focused on either: the bivalent Original/Omicron BA.1 or BA.4/5 vaccine, or the XBB.1.5 monovalent vaccine. Five of the studies measured VE in ICPs generally, while two studies measured VE in a population of end stage renal disease (ESRD) patients (17,18). All studies were conducted during Omicron dominant circulation period, with studies measuring VE during either: BA.4/5, BQ.1, XBB.1.5, EG.5.1, and/or BA.2.86/JN.1 Omicron sublineage periods.

Overall, VE of bivalent BA.1 or BA.4/5 booster moderately lowered the risk of COVID-19-related hospitalisations and death in ICPs. VE against hospitalisation varied between 25% and 67% (15,16); VE against ICU/death 28% (14); VE against death 58% (19); and VE against COVID-19-related thromboembolic hospitalisation in ESRD patients 60% (17). Two studies suggested that vaccination with XBB.1.5 booster provided moderate protection against hospitalisation (38% and 55%) (15,18). Several studies have also measured VE by time since vaccination, but the follow-up only lasted for a few months. Those that measured VE by time since vaccination found that protection against hospitalisation was between 11% and 47% after two to six months (14,15,18).

Nevertheless, the implementation of VE studies among the ICPs has faced several challenges that could limit the interpretation of the results. One of these major challenges has been ensuring that those included in the study are currently immunocompromised and eligible for vaccination (14,15,19). The studies that use electronic health record (EHR) databases usually rely on ICD-10 diagnostic codes recorded in patient registries during their encounters with healthcare systems, drug prescriptions or via COVID-19 vaccination registries. There is substantial heterogeneity in ICPs (active cancer treatment, organ transplant, immunodeficiencies) and the state of immunosuppression can be short or long term, increasing the likelihood of misclassification of eligibles and potentially impacting the accuracy of VE estimates (14,15,19).

Given the high variability of reported VE estimations and in European countries' strategies regarding vaccinating ICPs, it is crucial to evaluate the effect of variant-adapted COVID-19 vaccines against severe outcomes in this high-risk group, which is generally not evaluated before authorisation. This need for additional knowledge is also reflected in the ECDC/EMA Vaccine Monitoring Platform research agenda that lists as a priority for the short-term to obtain estimates of the variant-adapted COVID-19 vaccines effectiveness among high risk groups, like immunocompromised persons (20).

ECDC started several VE studies in 2020 and these were included in the Vaccine Effectiveness, Burden and Impact Studies (VEBIS) project in 2021 to monitor VE in different settings and using different methods, and to provide information on different outcomes (severe disease, moderate disease, infection, transmission, etc) (1–3). As part of the VEBIS project, this protocol describes the methods to estimate monovalent XBB.1.5 VE against hospitalisation or death due to COVID-19 among ICPs, aged ≥18 years, during the 2023–2024 autumn/winter season, using routinely collected vaccination status, outcome data and other data sources through EHRs from six VEBIS-EHR network study sites. These methods have been previously used to monitor COVID-19 VE in adults in Europe with robust estimation (21–24).

# Objectives

## Principal objective

To estimate COVID-19 XBB.1.5. monovalent adapted VE delivered during the 2023 autumn vaccination campaign against COVID-19-related hospitalisations and deaths, overall and by time since vaccination, among immunocompromised persons, aged ≥18 years old, eligible for COVID-19 vaccinations, using information routinely collected in EHRs in the EU/EEA countries taking part in the study.

## Secondary objectives

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

1. By age group (18-64, 65+ years);
2. By subgroup of immunosuppressing conditions (Active Cancer treatment, Transplants, Immunodeficiencies, Immunosuppressive treatments, see below);
3. By vaccine product;
4. By SARS-CoV-2 Omicron sublineage dominant periods: XBB.1.5 versus BA.2.86/JN.1.

Study sites can contribute to all or only a subset of the established objectives.

# Methodology

## Study design

A retrospective cohort study will be implemented, at study site level, using data collected routinely in EHR databases. The study will include the adult (≥18 years of age) population eligible for the 2023 autumn vaccination belonging to one of the following ICP groups before the start of the autumn vaccine campaign: active cancer patients, organ transplant recipients, and patients who are otherwise immunodeficient or immunosuppressed. The risk of each outcome will be compared between people who received the XBB.1.5 monovalent adapted COVID-19 vaccine and those eligible but who have not yet received the vaccine. Overall vaccine effectiveness (VE) will be obtained by pooling study site level estimates.

We will use a fixed cohort approach, defining the eligible population by age at the vaccination campaign's start, per the age criteria described.

## Study period

The study period will begin at the start of the COVID-19 2023 autumn vaccination campaign in each study site and will end 12 months later (at the end of September 2024). The respective vaccine campaign start dates for each study site are reported in Annex 1.

## Study population

The study population will consist of ICPs, residents in one of the countries or regions covered by the VEBIS EHR study sites, and eligible for the 2023 autumn COVID-19 vaccination. In general, we will include people diagnosed or with one of the following conditions coded in the EHR at the start of the 2023 autumn vaccination campaign, according to the World Health Organisation (13): definition of ICPs (13):

- Active cancer treatment: active immunosuppressive treatment for a solid tumour or haematological malignancy (including leukaemia, lymphoma, and myeloma), or within 12 months of ending such treatment.
- Organ transplant recipients: received solid organ transplant and currently take immunosuppressive therapy. Receipt of stem cell transplant (within two years of transplantation or taking immunosuppressive therapy).
- Immunodeficiency diseases: severe primary immunodeficiency or chronic dialysis.
- Immunosuppressives: Active treatment causing significant immunosuppression, including high-dose corticosteroids, alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents, tumour-necrosis factor (TNF) blockers, or other highly immunosuppressive drugs, immunosuppressive chemotherapy or radiotherapy within the past six months.

To identify ICPs eligible for vaccination within the 2023 autumn campaign within the study sites' EHRs, a systematic approach in six steps will be implemented:

1. Request, from VEBIS EHR study sites, information on how to identify in the national health records ICPs the WHO definitions presented above (data sources and clinical codes vocabularies, and mapping).
2. Conduct an online technical meeting with all study site researchers to present results and agree on a strategy (held in May 2024). Results from the consultation (Table 1) showed heterogeneity in terms of data sources available and clinical vocabularies available (ICD-10, ICD-9, ICPC-2 and ATC). In this meeting, it was decided to further develop ICD-10 clinical vocabulary to define two harmonised definitions of the study population, one more specific with a low probability of including false positives and a second more sensitive to increase the probability of including all ICPs.
3. Collect, from the studies that measured variant-adapted COVID-19 VE among the ICPs, information about the methods used to identify and select from the EHR the ICP eligible for vaccination.
4. With the support of three clinical experts, map the ICD-10 codes needed to map the two ICP populations definitions.
5. Identification of the study population in each study site according to data sources and vocabularies available (Table 1).

Individuals will be considered as ICPs if they have at least one contact/registration in the specific data source used in the study site in the last three years before the start of the vaccination campaign.

The study population with a more sensitive definition will be used in our main analysis and applied to all study objectives (primary and secondary) when the sample size allows. For sensitivity analysis, all study objectives (primary and secondary) will be repeated for the second and more strict study population definition.

## Comparability of the study populations

With the objective of describing the correspondence between the ICP study population identified by each study site, and to detail the available data sources and clinical vocabularies, a descriptive analysis will be performed. This analysis will specifically aim to determine the number of people identifiable as belonging to any and each ICP group, and the respective population's vaccination histories. A data extraction plan has been developed for this purpose and is shared separately.

The results will be used to support the discussion on the limitations to pool the study population across study sites.

**Table 1. Clinical coding standards and data sources used by study sites**

| Study site | Information | Active cancer treatment | Organ transplant recipients | Immunodeficiency diseases | Immunosuppressives |
|---|---|---|---|---|---|
| **Belgium** | Data source | Cancer Register | Intermutualistic Agency (health insurance database) | Intermutualistic Agency (health insurance database) | Intermutualistic Agency (health insurance database) |
| | Clinical code standard | At least one Multidisciplinar Oncoloc Consult (MOC) or given chemo- or radiotherapy during the reference year (2021) | Pseudopathology groups are based on the delivery of medicines in community pharmacies using the ATC code during the reference year (2021) | Pseudopathology groups are based on the delivery of medicines in community pharmacies using the ATC codes during the reference year (2021) | Pseudopathology groups are based on the delivery of medicines in community pharmacies using the ATC codes during the reference year (2021) |
| **Denmark** | Data source | National Patients Registry | National Patients Registry | National Patients Registry | National Patients Registry |
| | Clinical code standard | ICD-10 (at least one primary or two secondary diagnoses in the last 3 years) | ICD-10 (at least one encounter) | ICD-10 (at least one encounter in the last 3 years) | ICD-10 (at least one encounter in the last 3 years) |
| **Italy** | Data source | Vaccination registry | Vaccination registry | Vaccination registry | Vaccination registry |
| | Clinical code standard | ICD-9 (Any self-reported condition at the time of COVID-19 vaccination since 2020) | ICD-9 (Any self-reported condition at the time of COVID-19 vaccination since 2020) | ICD-9 (Any self-reported condition at the time of COVID-19 vaccination since 2020) | ICD-9 (Any self-reported condition at the time of COVID-19 vaccination since 2020) |
| **Navarre (Spain)** | Data source | Primary Care Information System | Primary Care Information System | Primary Care Information System | Primary Care Information System |
| | Clinical code standard | ICPC - 2 (Cancer diagnosis at the beginning of the study period and year of diagnosis. We separate haematological and non-haematological cancer, reviewed October 2023) | ICPC - 2 (all people with a history of transplant, reviewed October 2023) | ICPC - 2 (HIV infection, congenital immunodeficiency, asplenia at the beginning of the study period and year of diagnosis, reviewed October 2023) | ICPC - 2 (Illness with possible immunosuppressive treatment: rheumatological illness, chronic inflammatory bowel illness, haematological cancer, reviewed October 2023) |
| **Portugal** | Data source | Primary Care Information System | Primary Care Information System | Primary Care Information System | Primary Care Information System |
| | Clinical code standard | ICPC - 2 (at least one encounter in the last 3 years) | ICPC - 2 (at least one encounter in the last 3 years) | ICPC - 2 (at least one encounter in the last 3 years) | ICPC - 2 (at least one encounter in the last 3 years) |
| **Sweden** | Data source | National Patients Registry | National Patients Registry | National Patients Registry | National Patients Registry |
| | Clinical code standard | ICD-10 (at least one primary or two secondary diagnoses in the last 3 years) | ICD-10 (at least one encounter) | ICD-10 (at least one encounter in the last 3 years) | ICD-10 (at least one encounter in the last 3 years) |

**Table 2. Set of codes that define ICP study populations for each ICP group and clinical codes used at study site level**

| ICP group | Specific definition (sensitivity analysis) | Sensitive definition (main analysis) |
|---|---|---|
| | ICD-10 | ICD-10 |
| Active cancer treatment | C00, C01, C02, C03, C04, C05, C06, C07, C08, C09, C10, C11, C12, C13, C14, C15, C16, C17, C18, C19, C20, C21, C22, C23, C24, C25, C26, C30, C31, C32, C33, C34, C37, C38, C39, C40, C41, C43, C45, C46, C47, C48, C49, C50, C51, C52, C53, C54, C55, C56, C57, C58, C60, C61, C62, C63, C64, C65, C66, C67, C68, C69, C70, C71, C72, C73, C74, C75, C76, C77, C78, C79, C80, C81, C82, C83, C84, C85, C86, C88, C90, C91, C92, C93, C94, C95, C96, C97, C4A, C7A, C7B, Z51.0, Z51.1 | All codes included in 'Specific' in addition to: C44, D37, D38, D39, D40, D41, D42, D43, D44, D45, D46, D47, D48, D60, D61.0, D61.8, D61.9, D70, D71, D76, Z51.2 |
| Organ transplant recipients | T86, Z94 | Specific codes plus: Z98.85, D47.Z1, Z48.2 |
| Immunodeficiency diseases: | D61, D80, D81, D82, D83, D84, D84.89, D89, E31.0, K70 (excluding K70.9), N04, R18, Z99.2, Q90 | Specific codes plus: D72.8, D72.89, K71, K72, K73, K74.4, K74.5, K74.6 (excluding K74.60 and K74.69), G61.0, G70, G71, F72, F73, F84.0, F84.1, Q05 |
| Immunosuppressives | D86, E85, G35, L40, L93, L94, M05, M06, M07, M08, M30, M32, M33, M34, M45, M46, K50, K51 | Specific codes plus: J67.9, M09, M13, M31, M35, M94.1 |

## Inclusion criteria

Besides the ICP definition, the study population includes the adult reference population registries fulfilling the following criteria during the study period:

- Aged between 18 and 110 years at the beginning of the vaccination campaign. 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;
- Received their final COVID-19 vaccine dose in the complete primary series (*with or without extended series dose recommended to those identified as ICP*) at least 180 days before the start of the 2023 autumn vaccination campaign;
- Resident in any of the participating EU/EEA countries covered in the study.

## Exclusion criteria

- People identified as testing positive for or hospitalised with COVID-19 in the 90 days before the start of the 2023 autumn vaccination campaign (or according to national recommendations as defined by study sites);
- People who received a COVID-19 vaccine dose, irrespective of the number of doses, in the last 90 days before the start of the 2023 autumn vaccination campaign (or according to National recommendations as defined by study sites);
- People with inconsistent or missing data on vaccination (vaccination status unknown, any vaccination date unknown, any vaccine brand unknown, and number of doses unknown);
- People vaccinated with a number of doses higher than the total number recommended for their group (ICP and age group);
- People who received any vaccine brand not authorised for use in the EU by the European Commission and or those for which the combination of vaccine brands received is not possible when following the recommended schedule for their group (may vary by age group) will be excluded;
- People resident in a nursing home/long term care facility before or during the study period (according to the most recent information available).

# Definitions

## 2023 autumn vaccination campaign

The autumn 2023 vaccination campaign is defined as the period of COVID-19 vaccine dose administration for a target group, during specific dates between which the COVID-19 vaccination campaign is rolled out in a specific country or study site.

## 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 XBB.1.5 vaccine doses administered.

### *Vaccination status – Overall vaccinated*

Among those ICP eligible for the latest COVID-19 vaccine dose administered as part of the 2023 autumn vaccination campaign, they will be classified into:

- **Vaccinated with XBB.1.5 monovalent adapted COVID-19 vaccine:** ICP received a vaccine dose of an EMA-approved XBB.1.5 monovalent COVID-19 vaccine, administered on or after the date of initiation of the country-specific COVID-19 autumn 2023 vaccination campaign and up to the last date of that campaign. The status is achieved 14 days after the vaccine's administration date. 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 2024.
- **Reference group:** all ICP 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) and events recorded during such time will be excluded. Any individual who receives a COVID-19 vaccine dose different from the monovalent XBB.1.5 vaccine or 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 dose administration (for example, a COVID-19 vaccine different from the monovalent XBB.1.5 vaccine, or a subsequent vaccine dose in an individual already vaccinated with the 2023 autumn 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. the spring 2024 vaccination campaign right after a 2023 autumn campaign for those ≥80 years), those people who get vaccinated as part of the new COVID-19 vaccination campaign will be censored from the study at the time they receive the new vaccine, thereby estimating the VE of the original/previous campaign.

### *Vaccination status – by time since the most recent (autumn) COVID-19 vaccination*

To estimate COVID-19 VE by time since the most recent (autumn) COVID-19 vaccination, the reference group will also be those ICP eligible to receive the 2023 autumn vaccine but who have not received it yet. 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 <2 months (i.e. ≥14-59 days ago);
- Dose administered ≥2 months and <4 months (i.e. 60-119 days ago);
- Dose administered ≥4 months & <6 months (i.e. 120–179 days ago);
- Dose administered ≥6 months & ≤ 12 months (i.e. 180-365 days ago).

### *Definition of vaccination status by vaccine product*

Vaccine product used in the most recent (autumn) 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 (monovalent XBB.1.5) |
| • Other (AZ, others...) |
| • Missing |

Vaccine products will be ascertained for everyone in the sample for the most recent vaccine dose they received, either during the 2023 autumn vaccination campaign or previously in case they were not vaccinated during the 2023 autumn campaign.

To estimate VE by vaccine product we will only consider the COVID-19 XBB.1.5 monovalent adapted vaccines (Pfizer - Comirnaty Omicron XBB.1.5 (adapted), Moderna - Spikevax XBB.1.5 (adapted) or Novavax - Nuvaxovid XBB.1.5 (adapted) highlighted in bold in the table above) as exposures of interest.

The COVID-19 vaccination statuses defined above will be split by the product received in the autumn 2023 vaccination campaign. Vaccine products received by the reference group before the start of the study period 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 Severe Acute Respiratory Infection (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 2023 autumn vaccination campaign will be considered as 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 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 the laboratory result itself.

The study outcomes (COVID-19 hospitalisations or deaths) will be possibly combined to increase the statistical power.

## Stratification variables

The XBB.1.5 monovalent COVID-19 overall VE will be stratified by the following variables.

### *Age group (secondary objective 1)*

Estimates of XBB.1.5 VE will be obtained for each age group independently. Age will be calculated at the beginning of the study period using the date of birth and categorised into two age groups: 18 to 64 and 65 years or more.

### *Immunocompromised group (secondary objective 2)*

For the study sites that can collect information on the ICP that each individual belongs to, and if sample size allows, the overall XBB.1.5 monovalent COVID-19 VE will be estimated within each of the ICP groups: active cancer treatment, organ transplant recipients, immunodeficiency diseases, and immunosuppressives.

### *SARS-CoV-2 Omicron sublineage periods (secondary objective 4)*

Estimates of XBB.1.5 VE will be presented with study time stratified by Omicron sublineage predominance. This study will consider the XBB and BA.2.86/JN.1 dominance periods. A period of Omicron sublineage dominance is defined by the set of weeks starting with the first week where the proportion of SARS-CoV-2 cases that belong to the specific sublineage of interest is higher or equal to 80% and ends with the last week where the VOC prevalence is higher or equal to 80%. The methods used to define the XBB and BA.2.86 sublineages dominance period and the predominance periods per study site will proceed according to similar analyses conducted previously (25).

## Potential confounding variables for adjustment

### *Age group*

Age will be calculated at the beginning of the study using the date of birth and categorised into five-year age groups for use in model adjustment.

### *Number of previous booster doses*

The total number of booster doses received prior to the start of the 2023 autumn vaccination campaign will be used as an adjustment variable.

### *Sociodemographic*

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

### *Comorbidities and healthcare-seeking behaviours*

Several variables may be used to account for comorbidities. For the purpose of harmonisation, it is recommended to use the ICP groups defined above: active cancer treatment, organ transplant recipients, immunodeficiency diseases, and immunosuppressives.

In addition, 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).

## Data sources

The study uses routinely collected data from various population EHRs 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*

Annex 4 contains the reference population database (census database, health coverage database, etc.) with individual records of the target study population for each study site, including the description of the data sources used to identify the ICP groups.

### *Sources of information on the vaccination status*

Vaccination registry or vaccination record databases with records of ICPs, including dates of COVID-19 vaccination and vaccine brand. Annexes 4 and 5 summarise the data sources and linkage used by each study site.

### *Sources of information on the outcomes*

Data will be extracted from different EHR databases (Annex 4)

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

### *Sources of information on confounders*

- 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.

## Construction of the cohort

### *Identification of individuals and characteristics at baseline*

After restriction to the ICP group according to the rules presented in the Study Population section, the source population database will be linked with the EHR databases on vaccination, comorbidities and healthcare registries using the unique identifier and deterministic data linkage. The start date of follow-up will correspond to the beginning of the 2023 autumn vaccination campaign plus 14 days and will end 12 months later.

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.

ICP will enter the study 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 the XBB.1.5 monovalent vaccine dose (or as increasing time elapses since the vaccine dose, for analysis of time since vaccination). People who change vaccination status during the follow-up period will be censored without an 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 Table 3, where individual 12345 is in the reference group at the start of follow-up, but then receives the XBB.1.5. 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).

**Table 3. 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) | Event |
|---|---|---|---|---|---|---|
| 12345 | 0 | 15 | Eligible for seasonal vaccine dose (reference) | - | Constant | 0 |
| 12345 | 16 | 29 | - | - | Constant | 0 |
| 12345 | 30 | 50 | 2023 autumn dose | ≥14 days and <3 months | Constant | **1** |

This process will be different for each model, depending on the study's objective. Thus, one data set is normally created for each model.

Variables to be measured at baseline include ICP subgroup (more or less strictly defined), age, sex, region (if relevant), and other socioeconomic and healthcare-seeking variables that will be used to adjust for confounding.

# 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 (end of study 12 months after).

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 vaccine dose different from the monovalent XBB.1.5. vaccine during the study period.

Administration of any additional vaccine dose in people who already received the monovalent XBB.1.5. vaccine.

Administration of any vaccine dose after the end of the 2023 autumn vaccination campaign, as defined above.

Censoring the entire group of specific ICPs if they are targeted for a spring vaccination campaign on the date of the vaccination campaign start.

Administrative censoring (at the end 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.

# Analysis plan

## Description of the sample selection

The total number of ICP fulfilling the inclusion criteria at the study baseline will be calculated for each database. The number and proportion of ICP excluded after applying each selection criteria will be recorded.

## Description of the study population

Data regarding the number of people in the unvaccinated and vaccinated groups at the end of follow-up, the cumulative person-months of follow-up contributed by each individual to the unvaccinated and vaccinated group throughout the follow-up period will be described by baseline variables (sex, age group, immunocompromised condition group and previous number of vaccine booster doses). The count of events by each vaccine status group will be gathered for both outcomes (hospitalisation and death) together with person-months follow-up. Descriptive mock-up tables are presented in Annex 6.

## Estimation of vaccine effectiveness

### *Groups to be compared and subgroup analysis*

Overall, VE will be estimated by comparing the hazard rate of the outcome in the study population with autumn 2023 XBB.1.5 vaccination (exposed group) with the hazard rate of the outcome in those belonging to the same group but yet to receive the XBB.1.5 monovalent vaccination (reference group).

In the analysis of VE by time since vaccination, VE will be estimated by comparing the hazard rate of the outcome in the study population with autumn 2023 XBB.1.5 vaccination for each class of the time since vaccination: 14 to 89, 90 to 179 and ≥180 days (exposed group) compared with the outcome hazard rate in those yet to receive the autumn XBB.1.5 vaccination belonging to the study population (reference group).

For secondary objectives 1, 2, and 4, overall, VE will be stratified respectively by age group (18–64 and 65 years or more), by ICP subgroup (active cancer treatment, organ transplant recipients, immunodeficiency diseases, and immunosuppressives), and by Omicron sublineage predominance group XBB and BA.2.86/JN.1.

### *Crude hazard ratio*

We will use Cox proportional hazards regression models to estimate the hazard ratio (HR), considering the event as the first hospitalisation or death due to COVID-19, the exposure as the vaccination status and calendar time as the time. The crude HR of vaccinated versus unvaccinated will be estimated for each outcome of interest during the study period at each study site, without adjusting for other factors or covariates.

### *Vaccine effectiveness*

The regression analysis to estimate HR will be adjusted for confounders, as appropriate, and as previously defined. Firstly, partially adjusted HR will be estimated, adjusting by age group (five-year bins), sex and region in the country,

if appropriate. Secondly, a fully adjusted HR (aHR) estimate will be produced adjusting by variables related to socioeconomic conditions, ICP group and healthcare-seeking behaviour, total number of previous COVID-19 vaccine doses up to the start of the autumnal vaccination campaign, and/or others, as relevant at each study site.

The potential adjustment variables were selected based on their availability (although this may vary between the different study sites) and their role as possible sources of confounding bias. A list of the variables per study site can be found in Annex 3.

Finally, VE will be calculated as: VE = (1-aHR) x 100

### *Methods for pooling estimates*

Country-specific adjusted log HRs and standard errors for the effect of COVID-19 vaccination obtained from the study sites will be combined in a model using meta-analysis techniques (26). Study sites with less than five people in the reference group will not report HR estimates, nor will they 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 at least three study sites estimates are available.

First, as a main approach, a random-effects meta-analysis will be used. Conceptually, VE may be different depending on measured or unmeasured site-specific factors. To account for the two sources of variability (intra- and inter-study), the marginal variance will be divided into two components: the individual study-specific variances and the variance of the random study effects ($\tau^2$). $I^2$ 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. $\tau^2$ 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) will then be calculated.

Potential factors or specific study site 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, will be 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) will be compared to assess the degree of confounding by different factors and to guide the interpretation of inter-site variability.

### *Exploration of heterogeneity and its effect on the pooled estimates*

Sensitivity analyses will be conducted for pooled estimates obtained while excluding some study sites 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 I2 estimate is >50%.

The interpretation of the pooled estimates can be difficult in a context with potentially high heterogeneity across study sites. The likely incorporation of a random effect would imply that the pooled estimates would not reflect a "true" effect but an average effect over several different, but related, effect sizes. (27). This heterogeneity can reflect both real differences in effect size, VE here, that can be due to a lot of country specific factors, including the nature and uptake of the public health interventions implemented or the variant distribution during the study period across study sites, or varying biases due to the different nature of the EHRs and their related sensitivity/specificity of the ICP definition and/or the identification of the events. Hence, providing an analysis on the underlying heterogeneity and its influence on the pooled estimates would help nuance the interpretation.

We will perform a meta-regression analysis with log aHR as outcomes and covariates at study site level as explanatory variables with inverse variance weighting (28). The explanatory variables will attempt to characterise the most likely sources of heterogeneity: covariates reflecting differential biases or sources of actual differences in VE. Covariates potentially reflecting differential biases could include the main features of the EHRs to explore their differing ability to identify ICPs and/or events accurately. Covariates potentially reflecting sources of "real" differences in VE could include ICP population characteristics such as the age distribution, some markers of the public health situation such as the vaccine coverage at population level (a proxy for indirect protection), or variant distribution.

The meta-regression will investigate the association with the covariates individually and with two covariates simultaneously at most due the low number of study sites. The coefficients, their 95% confidence intervals, and their p-value will be presented in a table and figures if it is judged relevant. This additional analysis will only be exploratory. The very small sample size, there will be as many data points as the number of study sites, will severely

limit our ability to make valid inferences and only allow us to explore tentative associations between the effect size and site level covariates.

### Feasibility analysis

We will conduct a feasibility analysis prior to performing the main analysis to assess if every objective is achievable given the expected heterogeneity in ICP identification across study sites and if the pooled analysis can detect minimum values of VE, with at least 80% of statistical power, that are in a plausible range. The feasibility analysis will also allow us to improve comparability across sites by identifying and harmonising identified discrepancies in ICP identification whenever possible.

Study sites will provide population-level data from their EHRs focusing on individuals aged 18 years and over identified as ICP or non-ICP during the 2023–2024 autumn/winter period including vaccination records and COVID-19 related outcomes. We will compare the proportions of ICP and ICP subgroups across sites to assess if ICP identification is comparable across sites, and assess if some ICP subgroups are harder to identify consistently.

The distribution of the number of events, the event rate among vaccinated and unvaccinated ICP, and the vaccine coverage for the autumnal booster will allow us to calculate the minimum detectable VE at site level (29). Some study sites may not be able to contribute to a pooled estimate for every outcome and in every ICP subgroup if the number of events is low. If less than 5 events are reported among unvaccinated ICP, we expect a high uncertainty around the VE estimate and will not include it to produce the pooled estimate. We will produce pooled estimates of the minimum detectable VE if at least 3 sites can provide a VE estimate assuming various levels of heterogeneity (30) to assess if plausible values can be detected.

Based on the feasibility analysis, primary and secondary objectives will be classified based on their feasibility and this information will be used to adjust and conduct the final version of the statistical analysis.

## 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.

## 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 to national and EU ethical and data protection requirements.

## Potential biases and limitations

- Identification of those who are immunocompromised, and which subgroups should be included within this category, has not yet been standardised to EU/EEA populations for COVID-19 – leading to a heterogeneity in data sources, terminology, classification and the clinical codes used by each of the study sites.
- Study sites do not use a single clinical coding standard, e.g. ICD-10 diagnosis coding, and so any attempt to harmonise coding across study sites relies on best-matching across standards with methodology used for harmonisation described in full where necessary (i.e. between ICPC, ICD-9 and ATC to ICD-10 codes).
- The definition of ICP in active treatment using ICD or ICPC codes presents limitations given that its only possible to know if a person as or not the disease diagnose, but it's not possible to know if the person was under treatment in the last 12 months given that this information is not available in the patient's registry.
- The coding frameworks with less granularity than ICD-10 codes will limit the number of sites that can identify ICPs with a specific definition. The corresponding sensitivity analysis will then be restricted to a smaller number of sites, limiting its value.

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# Annex 1. Vaccination campaign start dates

**Table 1.1. Vaccination campaign rollout by country**

| Study site | Start of campaign |
|---|---|
| Belgium | 11 September 2023 |
| Denmark | 1 October 2023 |
| Italy | 1 October 2023 |
| Sweden | 1 September 2023 |
| Navarre (Spain) | 16 October 2023 |
| Portugal | 29 September 2023 |

# 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 hospitalization up till 24 hours after hospitalisation. |
| Denmark | Laboratory-confirmed infection 24 hours after hospital admission or 3 weeks before admission, lasting for a minimum of 24 hours and in which 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 confirmed infection through RT-PCR or antigenic test and clinical manifestations of the respiratory tract or other organs directly associated with SARS-CoV-2 infection |
| Navarre (Spain) | Hospital admission with laboratory-confirmed COVID-19 infection by 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 3 weeks before admission. The COVID-19-related ICD-10 code as primary diagnosis. |

# Annex 3. Confounding variables for adjustment

**Table 3.1. Indicators of socioeconomic status**

| Study site | Indicators of socioeconomic status |
|---|---|
| Belgium | Household income |
| Denmark | Not available |
| Italy | Deprivation Index at the municipality level provided by the Italian Institute of Statistics (Istat) |
| Navarre (Spain) | Household income |
| Portugal | European Deprivation Index at the municipality-level |
| Sweden | Individual education, marital status |

In addition, study sites can adjust for variables that translate to different healthcare-seeking behaviour. Portugal will also consider the number of SARS-CoV-2 tests performed during the previous year (0, 1, 2 to 4, ≥5).

**Table 3.2. Factors used to adjust for confounding in each study site**

| Confounder | Belgium | Denmark | Italy | Navarre (Spain) | Portugal | Sweden |
|---|---|---|---|---|---|---|
| **Age group** | X | X | X | X | X | X |
| **ICP group** | X | X | X | X | X | X |
| **Previous booster doses** | X | X | X | X | X | X |
| **Sex** | X | X | X | X | X | X |
| **Region** | X | X | X | | X | X |
| **Socioeconomic status** | X | | | | X | X |
| **Country of birth** | | | X | X | | |
| **Dependence** | | | | X | | |

# Annex 4. Data sources on reference population, vaccination, outcome and confounders

**Table 4.1. Source of information on the reference population**

| Study site | Source of information | Residency definition |
|---|---|---|
| Belgium | The Belgian national registry | Every person registered in the Belgian national register. |
| Denmark | The Danish Civil Registration System (CPR) | Residency is defined as an individual who is registered as currently living in the country (as the main country of residency). It is impossible to live in Denmark for a prolonged period without being registered as a resident. |
| Italy | National Vaccination Registry (MoH) | The database includes records for all individuals who have received at least one vaccine dose in Italy. The database contains variables that allow the identification of those residing in Italy, i.e. people, of Italian and foreign citizenship, having habitual residence in the national territory even if temporarily absent. |
| Navarre (Spain) | Administrative database | Residents covered by the Navarra Health Service. This Service covers 98% of the population in the region, with an unbiased distribution by sex and geographical areas.<br>The database contains variables that allow the identification of non-residents or temporary residents. |
| Portugal | National Health Service User (NHSU) dataset | Residents in mainland Portugal who had contact with the healthcare system in the previous three years. |
| Sweden | Register of the Total Population | Residency is defined as an individual who is registered as currently living in the country (as the main country of residency). Other additional requirements could be added in the future based on national guidelines – e.g. have to have been living in SE for three years before study start. |

**Table 4.2. Source of information and limitations on vaccination, outcome and confounders**

| Type of variables | Study variable | | Study site | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Belgium | Denmark | Italy | Navarre (Spain) | Norway* | Portugal | Sweden |
| Outcomes | Hospital admission due to COVID-19 | Clinical Hospital Survey database | Danish National Patient Register (DNPR) | National Integrated COVID-19 Surveillance Databases | Enhanced COVID-19 surveillance with individual revision of events | Norwegian Patient Register (NPR) | National Hospital Discharge database (BIMH) | Swedish National Patient Register |
| | Death due to COVID-19 | Not applicable | MiBA and Danish Civil Registration system (CPR) | National Integrated COVID-19 Surveillance Databases | Administrative database of deaths and individual revision of events | Norwegian Death Registry (DÅR) | National Death Registry (SICO) and National Health Service User databa (NHSU). Cause of death is from SICO, death status and date of death from NHSU. | Swedish Cause of Death register and Register of the Total Population Register on surveillance of notifiable communicable diseases |
| Exposures | Vaccination status | National vaccine registry (VACCINNET) | Danish Vaccination Registry (DVR) | National Vaccination Registry | Vaccination register | The National Immunisation Register (SYSVAK) | The National Vaccination Register (VACINAS) | Swedish National Vaccination Register |
| Variables for adjustment or stratification | Age | The national population register | CPR | National Vaccination Registry | Administrative database | The National Population Register (Folkeregisteret) | National Health Service User database (NHSU) | Register of the Total Population |
| | Sex | national population register | CPR | National Vaccination Registry | Administrative database | The National Population Register (Folkeregisteret) | National Health Service User database (NHSU) | Register of the Total Population |
| | Health Region | Province of residence: national population register | CPR | Region where vaccination took place National Vaccination Registry | Not applicable | County of residence at end of study period: The National Population Register (Folkeregisteret) | Region of residence: National Health Service User database (NHSU) | Register of the Total Population |
| | ICP group | Intermutualistic Agency database | DNPR | National Vaccination Registry | Primary Care clinical record | Risk groups / Comorbidities: Based on Norwegian Patient Registry (NPR) | Primary Care Information System (SIM@SNS). | Swedish National Patient Register |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Previous booster doses** | National vaccine registry (VACCINNET) | Danish Vaccination Registry (DVR) | National Vaccination Registry | Vaccination register | The National Immunisation Register (SYSVAK) | The National Vaccination Register (VACINAS) | Swedish National Vaccination Register |
| | **Others specific to the study site** | Household income (according to tax records) categorised as low (lowest 40%), mid (middle 30%), and high (highest 30%): STATBEL database | Not applicable | Country of birth National Vaccination Registry | Country of birth and high functional dependence: Administrative database | 1. Conditions of living – Crowding: Statistics Norway (SSB). Most recent data from 2019 – separate level for missing data<br>2. *County of birth:* Folkeregisteret | Conditions of living – Deprivation at the municipality level: Most recent data from Census 2011 | Marital status, educational level, country of birth The Longitudinal integrated database for health insurance and labour market studies |

# Annex 5. Data linkage methods

**Table 5.1. Data linkage method used in each study site**

| Study site | Data linkage method |
|---|---|
| Belgium | Each individual registered in the LINK-VACC environment is assigned a unique identifier based on their social identification number, enabling linkage between the databases within the system. |
| Denmark | The reference population database will be linked with the electronic databases on vaccination, comorbidity and/or healthcare-seeking behaviours registries using the unique identifier and a deterministic data linkage procedure (no random component in the linkage procedure). The CPR-number from the Danish Civil Registration System (CPR) is used as a unique identifier and linkage between registries. |
| Italy | Deterministic record linkage through the individual tax code (unique individual identifier), or through the municipality code (for the deprivation index measured at municipality level) |
| Navarre (Spain) | A unique individual identifier is used for linkage of all information of each person.<br>All datasets used in the analyses are anonymised. |
| Portugal | Each of the registries considered contains a unique individual's identifier (NHS), allowing deterministic data linkage between registries.<br>Data extraction and linkage is performed monthly by the Shared Services of the Ministry of Health in accordance with national legal requirements. All data are anonymised prior to transfer to INSA research team for analysis. |
| Sweden | The reference population database will be linked with the national registers on vaccination, healthcare services use (in-patient and specialised out-patient care (not primary care)), prescribed drugs, sociodemographic data using the unique personal identifier and a deterministic data linkage procedure (no random component in the linkage procedure). |

# Annex 6. Reporting templates

**Table 6.1. Dummy table describing the distribution of the total number of persons or person-time during the follow-up period by sociodemographic and clinical characteristics of the study population included by vaccination status (one table per study site – principal objective, secondary objective 1 and 4)**

| | Unvaccinated | Vaccinated (≥14d ago) | Vaccinated (14-89d ago) | Vaccinated (90-179d ago) | Vaccinated (≥180d ago) |
|---|---|---|---|---|---|
| | *N (total number of persons)*<br>*or*<br>*PY (total number of person-years)* | | | | |
| **Sex** | | | | | |
| Male | | | | | |
| Female | | | | | |
| Missing | | | | | |
| **Age-group** | | | | | |
| 18-64 | | | | | |
| 65+ | | | | | |
| **Country of birth** | | | | | |
| Native | | | | | |
| Non-native | | | | | |
| Missing | | | | | |
| **Nationality** | | | | | |
| National | | | | | |
| Non-national | | | | | |
| Missing | | | | | |
| **Vaccine product (only including individuals who achieved full vaccination before end of study period)** | | | | | |
| Pfizer – Comirnaty XBB.1.5 (adapted) | NA | | | | |
| Moderna – Spikevax XBB.1.5 (adapted) | NA | | | | |
| Novavax – Nuvaxovid XBB.1.5 (adapted) | | | | | |
| Other | NA | | | | |

| | Unvaccinated | Vaccinated (≥14d ago) | Vaccinated (14-89d ago) | Vaccinated (90-179d ago) | Vaccinated (≥180d ago) |
|---|---|---|---|---|---|
| Missing | NA | | | | |
| **ICP group** | | | | | |
| Active/Solid cancers | | | | | |
| Transplant recipients | | | | | |
| Immunodeficient | | | | | |
| Immunosuppressed | | | | | |

**Table 6.2. Dummy table (one table per study site – principal objective)**

| **Age group** | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **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** |
| Unvaccinated | | | | REF | REF | REF | REF | REF | REF | REF | REF | REF |
| Vaccinated (≥14 days) | | | | | | | | | | | | |
| Unvaccinated | | | | REF | REF | REF | REF | REF | REF | REF | REF | REF |
| Vaccinated (14-89 days) | | | | | | | | | | | | |
| Vaccinated (90-179 days) | | | | | | | | | | | | |
| Vaccinated (180-270 days) | | | | | | | | | | | | |

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

**Table 6.3. Dummy table (one table per study site – secondary objective 1)**

| **Age group** | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **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** |
| **18-64 age group** | | | | | | | | | | | | |
| Unvaccinated | | | | REF | REF | REF | REF | REF | REF | REF | REF | REF |
| Vaccinated (≥14 days) | | | | | | | | | | | | |
| **≥65 age group** | | | | | | | | | | | | |
| Unvaccinated | | | | REF | REF | REF | REF | REF | REF | REF | REF | REF |
| Vaccinated (≥14 days) | | | | | | | | | | | | |

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

**Table 6.4. Dummy table (one table per study site – secondary objective 2)**

| Age group | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **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** |
| **Active cancer** | | | | | | | | | | | | |
| Unvaccinated | | | | REF | REF | REF | REF | REF | REF | REF | REF | REF |
| Vaccinated (≥14 days) | | | | | | | | | | | | |
| **Organ transplant recipients** | | | | | | | | | | | | |
| Unvaccinated | | | | REF | REF | REF | REF | REF | REF | REF | REF | REF |
| Vaccinated (≥14 days) | | | | | | | | | | | | |
| **Immunodeficiencies** | | | | | | | | | | | | |
| Unvaccinated | | | | REF | REF | REF | REF | REF | REF | REF | REF | REF |
| Vaccinated (≥14 days) | | | | | | | | | | | | |
| **Immunosuppressed** | | | | | | | | | | | | |
| Unvaccinated | | | | REF | REF | REF | REF | REF | REF | REF | REF | REF |
| Vaccinated (≥14 days) | | | | | | | | | | | | |

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

**Table 6.5. Dummy table (one table per study site – secondary objective 3)**

| **Age group** | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **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** |
| Unvaccinated | | | | REF | REF | REF | REF | REF | REF | REF | REF | REF |
| Vaccinated **Comirnaty XBB.1.5** (≥14 days) | | | | | | | | | | | | |
| **Spikevax XBB.1.5** (≥14 days) | | | | | | | | | | | | |
| **Nuvaxovid XBB.1.5** (≥14 days) | | | | | | | | | | | | |

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

**Table 6.6. Dummy table (one table per study site – secondary objective 4)**

| Age group | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **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** |
| **XBB predominance** | | | | | | | | | | | | |
| Unvaccinated | | | | REF | REF | REF | REF | REF | REF | REF | REF | REF |
| Vaccinated (≥14 days) | | | | | | | | | | | | |
| **BA.2.86/JN1 predominance** | | | | | | | | | | | | |
| Unvaccinated | | | | REF | REF | REF | REF | REF | REF | REF | REF | REF |
| Vaccinated (≥14 days) | | | | | | | | | | | | |

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

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