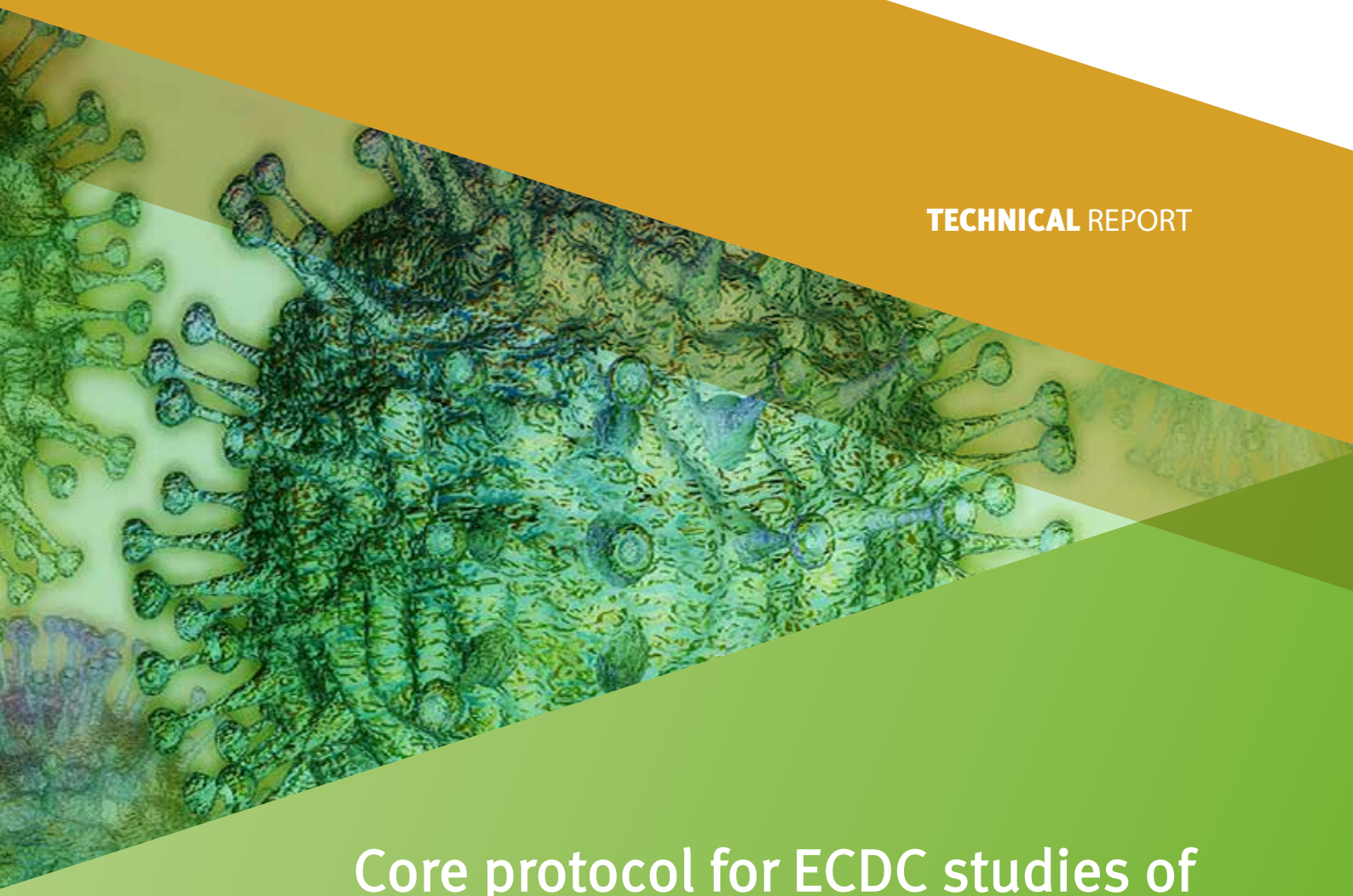

TECHNICAL REPORT

Core protocol for ECDC studies of vaccine effectiveness against hospitalisation with Severe Acute Respiratory Infection, laboratory-confirmed with SARS-CoV-2 or with seasonal influenza

Version 3.0

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This core protocol was commissioned by the European Centre for Disease Prevention and Control (ECDC), as part of the activities referring to Framework contract N. ECDC/2021/016 'Vaccine Effectiveness, Burden and Impact Studies (VEBIS) of COVID-19 and Influenza, Lot 1', and coordinated Nathalie Nicolay.

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The following ECDC staff provided substantial input during the production/revision of the document (alphabetical order): Nathalie Nicolay.

This core protocol is an update of the 'Core protocol for ECDC studies of vaccine effectiveness against hospitalisation with Severe Acute Respiratory Infection, laboratory-confirmed with SARS-CoV-2 or with seasonal influenza, version 2.0', which was based on the initial core protocol (version 1.0) as well as scientific literature; I-MOVE generic influenza protocol for hospitalised older adults 2019–2020; I-MOVE-COVID-19 WP4 protocol for investigation into risk factors against severe COVID-19 among hospitalised patients; Guidance document from WHO Regional Office for Europe: COVID-19 VE against SARI hospitalisations associated with lab-confirmed SARS-CoV-1 version 5 (20 January 2021); first ECDC expert meeting on COVID-19 vaccine effectiveness studies (29 January 2021) SARI COVID-19 Vaccine Effectiveness questionnaire v7 from WHO Regional Office for Europe (3 February 2021); I-MOVE-COVID-19 protocol: European study of COVID-19 vaccine effectiveness against hospitalised SARI patients laboratory confirmed with SARS-CoV-2 (version 8 February 2021).

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Abbreviations

COVID-19	Coronavirus disease 2019
Ct	Cycle threshold
CVE	COVID-19 vaccine effectiveness
IVE	Influenza vaccine effectiveness
EEA	European Economic Area
EU	European Union
GP	General practitioner
HDU	High Dependency Unit
ICD	International classification of diseases
ICU	Intensive Care Unit
I-MOVE	Influenza – Monitoring Vaccine Effectiveness in Europe
OR	Odds ratio
PCV	Pneumococcal Conjugate Vaccine
PPV	Pneumococcal Polysaccharide Vaccine
RF	Risk factor
RSV	Respiratory Syncytial Virus
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

Executive summary

The end of 2019 saw the emergence of a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19). As of October 2023, almost 276 million cases and more than 2.2 million deaths had been reported in the WHO European Region [1]. As of October 2023, eight 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 [2].

Influenza viruses undergo frequent genetic and antigenic changes. The influenza vaccine is reformulated each year and annual re-vaccination is recommended. Observed influenza vaccine effectiveness (IVE) varies from year to year between population sub-groups (age groups, risk groups) and differs for the various influenza types, subtypes and genetic clades, and outcomes measured. Immunological correlates of protection are not well defined. In 2017, the EMA formally adopted new guidelines on influenza vaccines covering, inter alia, post-authorisation studies of vaccine effectiveness, including brand-specific IVE data [3].

The available vaccine products currently in use for EU/EEA immunisation programmes, the target groups for vaccination and the vaccination coverage all vary across countries. New vaccines are being developed for which limited or no effectiveness data are yet available in the EU. A comparison by vaccine type (adjuvanted vs non-adjuvanted, live attenuated vs inactivated, egg- vs cell-based, high vs standard dose), group (split virion, subunit, etc.) and product could provide essential information for vaccine recommendations and health economic assessments.

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 [4]. The 2018 'Council Recommendation on Strengthened Cooperation against Vaccine-preventable Diseases' already called on the European Centre for Disease Prevention and Control (ECDC) and EMA to cooperate to ensure the continued monitoring of vaccines and vaccination in use in EU/EEA vaccination programmes [5]. This request was subsequently formalised as part of the extended EMA regulatory mandate [6] and ECDC's newly amended mandate [7], requiring the two agencies to develop a structured and independent post-authorisation vaccine monitoring platform, initially prioritising COVID-19 vaccines. ECDC and EMA officially established and launched the 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.

From 2020, ECDC began building the infrastructure to perform COVID-19 vaccine effectiveness (CVE) studies, using the lessons learned from other vaccine effectiveness studies already conducted. One such study was the ECDC-funded I-MOVE (Influenza – Monitoring Vaccine Effectiveness in Europe) project, under which influenza vaccine effectiveness (IVE) has been measured in Europe using primary care sentinel surveillance systems since the 2007/08 influenza season [3,4]. The infrastructure will be used to build a system that regularly monitors vaccine effectiveness and performs studies, including impact and burden of disease studies, in different settings. Depending on the setting, information will be provided on different outcomes (severe disease, moderate disease, transmission, etc). The overall project is called VEBIS (Vaccine Effectiveness, Burden and Impact Studies) and it includes different networks of study sites/countries/infrastructures, where the multi-country studies are conducted.

This core protocol for ECDC studies of VE against hospitalisation with severe acute respiratory infection (SARI) laboratory-confirmed with SARS-CoV-2 or with influenza, version 3.0, represents an update to the main elements for a multi-country hospital-based study of COVID-19 vaccine effectiveness in patients hospitalised with SARI, initially published as version 1.0 [5], updated to version 2.0 [6]. This version includes updates on methodology for CVE pooled analyses The larger sample size achieved by combining data from multiple sites will provide more statistical power to meet more specific objectives. The protocol can be implemented for COVID-19 and/or influenza.

The proposed method is a case-control study using a test negative design. The study population consists of individuals of all ages, belonging to the target group for COVID-19 or influenza vaccination, hospitalised with SARI symptoms and no contra-indication for being vaccinated with the vaccine of interest. It would be beneficial if countries test for all other respiratory viruses (as appropriate depending on time of year).

This core protocol is primarily intended to guide the implementation of ECDC-funded studies. However, ECDC encourages using this protocol as a basis to conduct vaccine effectiveness studies in countries not currently planning to participate in ECDC-funded studies. The use of consistent protocols will facilitate the comparability of study results across studies, countries and study sites.

1. Background

1.1 COVID-19

The end of 2019 saw the emergence of a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19). As of October 2023, almost 276 million cases and more than 2.2 million deaths had been reported in the WHO European Region [1]. As of October 2023, eight 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 [authorised 1 September 2022], Spikevax bivalent Original/Omicron BA.1 [1 September 2022], Comirnaty Original/Omicron BA.4-5 [12 September 2022], Spikevax bivalent Original/Omicron BA.4-5 [20 October 2022], Comirnaty Omicron XBB.1.5 [31 August 2023] and Spikevax XBB.1.5 [15 September 2023]) 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 [2]. Comirnaty and Spikevax vaccines of three different valencies have now been approved: a monovalent vaccine based on the original SARS-CoV-2 strain, a bivalent vaccine based on the original strain and the Omicron BA.1 lineage, and a bivalent vaccine based on the original strain and the Omicron BA.4-BA.5 lineages, and an adapted vaccine based on Omicron XBB.1.5. [2]. Some EU/European Economic Area (EEA) countries have also used other vaccines, such as Sputnik V and Sinopharm in Hungary.

By January 2021, all 30 EU/EEA countries had started COVID-19 vaccination campaigns, and different COVID-19 vaccine products have been gradually introduced as they have become available through the EU Vaccines Strategy [8]. In addition to healthcare workers and residents of long-term care facilities, the vaccination strategy in the general population had an age-based staggered approach prioritising older individuals over younger ones. Most of the vaccines used so far, including booster vaccines, have been mRNA vaccines [9].

1.2 Influenza

Despite a recommendation in 2009 by the Council of Ministers that all EU Member States achieve an influenza vaccination coverage of 75% in all risk groups by the winter season 2014–15, a survey by ECDC at the end of 2018 showed that very few had reached this goal in the specific risk groups [10]. Risk groups are defined as children aged 6–59 months, pregnant women, healthcare workers, individuals 60 or 65 years and older, and people with a range of underlying medical conditions [11,12].

Influenza viruses undergo frequent genetic and antigenic changes and vaccine-induced immunity only lasts between 6–12 months (sometimes less). Therefore, the influenza vaccine is evaluated each year and annual re-vaccination is recommended. Available seasonal influenza vaccines are only moderately effective and influenza vaccine effectiveness (IVE) may vary depending on the vaccine product, the time since last vaccination and previous influenza infection and influenza vaccine history. Observed IVE varies from year to year among population sub-groups (age groups, risk groups) and differs for the various influenza types, subtypes, antigenic groups and outcomes measured.

Conducting annual IVE estimates at the European level right at the beginning of a seasonal influenza epidemic/pandemic may provide critical evidence for public health recommendations. For example, the recommended target groups for the current season's vaccine can be expanded/amended if circulating strains are causing severe illness, but there are good/high early IVE estimates. Alternatively, very low early IVE estimates can prompt recommendations to use other non-pharmaceutical interventions (such as use of face masks or physical distancing), or antivirals as an additional preventative measure. Lacking early season IVE results could also result in a failure to use alternative measures, leading to increased disease burden and increased costs.

Monitoring of the IVE along the course of the epidemic/pandemic allows more precise estimates of the impact of current vaccination strategies on the burden of disease to support vaccination campaigns, and may trigger further investigations on seasonal and pandemic vaccines (improve composition, use of adjuvants, different doses, or the need for booster doses). Additionally, IVE studies can counterbalance the reports of adverse events following immunisation by providing elements for adequate risk benefit and cost-effectiveness analysis.

Early-season IVE by product and influenza type/subtype is also critical for the WHO vaccine composition meeting discussions, in which the vaccine selections for the subsequent season are decided.

Furthermore, new vaccines are being developed for which limited or no effectiveness data are yet available in the EU. In the event of an influenza pandemic, an established EU platform to rapidly measure IVE by vaccine type and product will allow the evaluation of any pandemic vaccine and the adaptation of preventive and control strategies.

Besides measuring IVE by influenza (sub)type early and late in the season and by vaccine type, these IVE studies can be used to help answer further research questions, such as the effect of previous influenza vaccination on current season influenza infection, to what extent IVE may decline within the season, the effect of first influenza infection on subsequent IVE and the measurement of IVE against different influenza clades or genetic variants.

Long-term multi-centre studies may provide adequate sample size and data quality to answer some of these questions.

1.3. Integrated respiratory surveillance

It is recommended that surveillance for respiratory pathogens (including both influenza and SARS-CoV-2) should be integrated across Europe [13,14]. Effective integrated respiratory surveillance systems should provide data sufficient for monitoring the spread and intensity of respiratory viruses to guide control measures and mitigate their impact. These systems will also be important in the event of future pandemics. In this context, well-designed, representative sentinel surveillance systems in primary and secondary care should remain the central surveillance method for acute respiratory infections. Sentinel systems provide robust epidemiological data that are routinely collected using common syndromic case definitions with reliable denominators and integral microbiological testing that can be extended to multiple viruses. This makes them ideal as the basis of integrated impact assessment of influenza, COVID-19, and potentially other respiratory virus infections. Monitoring systems should be sensitive enough to detect virus variants, accurately follow virus-specific disease incidence by age/location/level of severity and to assess vaccine effectiveness.

1.4 ECDC COVID-19 and influenza vaccine effectiveness studies

In 2018, the Council 'Recommendation on Strengthened Cooperation against Vaccine-preventable Diseases' (2018/C 466/01) called on the European Commission to work with the Member States, with the support of EMA and in cooperation with ECDC, to '… continuously monitor the benefits and risks of vaccines and vaccinations at EU level, including through post-marketing authorisation 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 [15]. This was subsequently formalised as part of the extended EMA regulatory mandate [16] and ECDC's newly amended mandate [17], requiring the two Agencies to develop a structured and independent post-authorisation vaccine monitoring platform, initially prioritising COVID-19 vaccines. ECDC and EMA officially established and launched 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 for EU/EEA immunisation programmes.

ECDC began building infrastructure to perform COVID-19 vaccine effectiveness (CVE) studies in 2020, using the lessons learned from other vaccine effectiveness studies (Table 1). The infrastructure is being used to build a system that regularly monitors CVE and performs studies in different settings. Depending on the setting, information will be provided on different outcomes (severe disease, moderate disease, transmission, etc). At the start of 2022, ECDC expanded this infrastructure to include IVE monitoring. The multi-country approach of effectiveness studies is one of the key features, and other countries are foreseen to be included over time.

Table 1. Type of studies and settings within the VEBIS infrastructure, as of November 2023

Setting	Type of study	Main outcome	References
Hospitals	Test negative design	Severe disease; influenza and COVID-19	[5,6,18–22]
Healthcare workers cohort	Cohort study	Infection, COVID-19	23,24]
Electronic healthcare databases	Cohort study	Hospitalisation, death, COVID-19	[25]
Primary care	Test negative design	Moderate disease (~ARI/ILI), influenza and COVID-19	[26,27]

One of the first studies implemented, and for which the core ECDC protocol version 1.0 was published in October 2021 [8], was a multi-country study to estimate CVE against severe disease, by assessing it in individuals hospitalised for SARI. The second update is presented in this document as version 3.0.

1.5 Aim of the core protocol

This core protocol for ECDC studies of CVE and IVE against hospitalisation with SARI laboratory-confirmed with SARS-CoV-2, and SARI laboratory-confirmed with influenza, version 3.0, presents the main elements for a multi-centre (multi-country) hospital-based study of CVE/IVE in patients hospitalised with SARI. It outlines the agreed methods for collecting data related to SARS-CoV-2, COVID-19 and influenza virus and disease at country level, and includes a plan for the pooled analysis. The combination of data from multiple sites will facilitate studies with more statistical power in order to meet more specific objectives.

ECDC has worked closely with EU Member States with to implement a system for the regular monitoring of vaccine effectiveness among hospitalised SARI patients, taking advantage of parallel efforts to enhance SARI surveillance in the EU/EEA and countries of the Western Balkan region[1]. Hospitals that can apply the core protocol and contribute to EU-level monitoring of CVE and ultimately IVE have been recruited through a process involving ECDC's relevant National Coordinator[2].

This core protocol is therefore primarily intended to guide the implementation of ECDC-funded studies. However, ECDC encourages using this protocol in countries not currently planning to participate in ECDC-funded studies.as a basis to conduct VE studies , as the use of consistent protocols will facilitate the comparability of study results across studies, countries, and study sites.

This document presents version 3.0 of the core protocol. Version 2.0 has already been implemented at country level. This document will be updated and revised on a regular basis.

This core protocol is complemented by a questionnaire, a list of variables to be collected and their coding, all of which are available upon request at vpd.vpd@ecdc.europa.eu (the list of variables and coding also appear in Annex 1).

Under each paragraph, arrow marks indicate the points that countries/hospitals/study sites could further expand/detail when creating a country-specific protocol using the core ECDC protocol.

[1] Western Balkans, i.e. Albania, Bosnia and Herzegovina, Montenegro, Serbia, North Macedonia, and Kosovo (this designation is without prejudice to positions on status, and is in line with UNSCR 1244/1999 and the ICJ Opinion on the Kosovo declaration of independence).

[2] https://www.ecdc.europa.eu/sites/portal/files/media/en/aboutus/governance/competent-bodies/Documents/coordinating-competent-bodies-structures-terms-of-reference-and-interactions-w-Annexes.pdf

2. Objectives

2.1 Primary objective

The primary objective of this protocol is for it to be used to measure the direct effect (effectiveness) of overall and product-specific COVID-19 and influenza vaccines against SARI due to laboratory-confirmed SARS-CoV-2 and/or influenza in hospitalised patients, within each European country/site participating in both CVE and IVE and in a pooled, multi-country analysis. This will provide up-to-date information on the ability of COVID-19 and influenza vaccines to prevent severe disease under real conditions of use.

2.2 Secondary objectives

The secondary objectives are among SARI patients requiring hospitalisation:

- to measure overall and product-specific CVE and IVE against SARI due to laboratory-confirmed SARS-CoV-2 or influenza in hospitalised patients by participating study country, risk group (e.g. specific chronic conditions), age group, COVID-19 or influenza vaccination target group, time since vaccination, calendar time and vaccine doses when applicable;
- to measure overall and product-specific CVE and IVE against specific genetic variant(s) of laboratory-confirmed SARS-CoV-2, type, subtype/lineage and specific clades of influenza (where possible), and more severe outcomes (ICU admission, invasive ventilation, in-hospital mortality);
- to identify potential factors that may modify CVE or IVE: prior SARS-CoV-2/influenza infection, chronic conditions, the role of influenza/COVID-19 vaccination, etc.

The aim of these three secondary objectives is to understand the duration of vaccine protection and identify any differences in CVE/IVE among each of these strata, potential target groups for vaccination, and key SARS-CoV-2 or influenza virus phenotypic or genotypic evolutions that could affect vaccine performance.

2.3 Specific objectives for COVID-19 vaccine effectiveness

The estimation of CVE has evolved compared to the VE when COVID-19 vaccination was first introduced. There has been much variation in the scientific literature in the past two to three years in the definitions of vaccination and reference groups used. In this protocol, we focus on an analysis of CVE for a specific seasonal vaccination campaign, similar to IVE. Here we compare the group vaccinated during the seasonal COVID-19 vaccination campaign of interest with a group not vaccinated during the vaccination campaign of interest. This provides information on the performance of the current season's vaccine(s), not taking prior vaccination history into account and providing, for the exposed group, a potentially similar exposure in a context of constantly changing variants. COVID-19 is still a novel virus, and our approach to analyse CVE will evolve over time, with several reference groups currently relevant. We propose other analysis types alongside the main analysis. More details can be found in Sections 3.8 Exposure (vaccination) and 3.13 Analysis.

- Each study site/country to specify primary objectives of their study as measuring CVE only or CVE and IVE.
- Each study site/country to specify the (additional) secondary objectives of their study.

3. Methods

3.1 Study design

The following study design is applied:

At country level: a hospital-based, test-negative, case-control study at each participating hospital.

- At EU/EEA level: a multi-centre hospital-based, test-negative, case-control study, using pooled data from several countries/regions.

In addition to the test-negative controls, some sites/countries may be able to recruit a second additional control group (e.g. non-SARI hospitalised patients matched to cases by date of admission; see Section 3.5.5).

- ➢ Each study site/country to specify if, in addition to the test-negative controls, other control groups are selected.

3.2 Study population

This study is intended to be conducted primarily in countries with pre-existing SARI surveillance systems, to recruit patients for hospital-based CVE/IVE studies. The study population for the CVE/IVE study will therefore consist of individuals of all ages hospitalised with SARI symptoms in one of the participating hospitals/services, with no contra-indication for COVID-19 vaccination (for CVE studies) or for influenza vaccination (for IVE studies).

- ➢ Each study site/country to describe the setting (number of hospitals included, number of beds, number and type of wards/specialties/services included).
- ➢ Each study site/country to describe the existing SARI surveillance system in place.
- ➢ Each study site/country to describe the study population for IVE and for CVE.
- ➢ Each study site/country to describe target group(s) for vaccination and order/timeline of vaccination by group (if known).
- ➢ Each study site/country to describe the epidemiological situation (incidence, number of COVID-19 or influenza hospitalisations, mortality).

3.3 Study period

The study period for CVE starts with the availability of COVID-19 vaccine(s) and a SARS-CoV-2 variant of concern circulating in the participating country. In order to determine SARS-Cov-2 variant dominance, ECDC surveillance data on variants of concern can be used. In the context of vaccination campaign performed in autumn 2023 to which this protocol refers, and with possible spring campaigns for selected groups, the study period for CVE can be more adapted to the IVE methods, with the study period starting at the initiation of the relevant COVID-19 vaccination campaign within a country/region. As COVID-19 and vaccination campaigns evolve, the study period can be adjusted accordingly. The study period for IVE begins when the seasonal influenza vaccine for the corresponding season becomes available and the influenza season begins in the country/region. The study period finishes at the end of the influenza period which could be defined as the last week in which there was a hospitalised SARI patient positive for influenza, or week 20, depending on which is earliest. Cases and controls are included from the week of onset of the season's first influenza-positive case in each country-specific study.

Participating hospitals carry out the CVE study throughout the year.

- ➢ Each study site/country to define the beginning of the CVE study period (day/month/year).
- ➢ Each study site/country to define the beginning and end of the IVE study period (day/month/year) and criteria for defining the IVE study period in their country.
- ➢ Each study site/country to specify the start date of their COVID-19 and influenza vaccination campaign, by target group and for the general population, for primary course vaccination. For COVID-19, each site/country should additionally specify dates for each booster dose, by target group (if applicable) and for the general population.

3.4 Outcomes

COVID-19 vaccine effectiveness studies

The outcome of interest for the primary analysis is SARS-CoV-2 infection in patients of all ages hospitalised with SARI symptoms, laboratory-confirmed by PCR, documented either on admission to hospital or in the 14 days before admission.

Secondary outcomes of interest, in the same patient group, are laboratory-confirmed infections with genetic variants of SARS-CoV-2 and confirmed SARS-CoV-2 patients with severe outcomes (ICU admission, invasive ventilation or death).

Influenza vaccine effectiveness studies

The outcome of interest is laboratory-confirmed influenza in patients of all ages, hospitalised with SARI symptoms.

More specifically, this will be:

- subtype-specific laboratory-confirmed influenza A;
- laboratory-confirmed influenza B overall and, if available, by lineage (B Victoria/B Yamagata);
- laboratory-confirmed influenza by clade (where possible);
- laboratory-confirmed influenza co-infected with SARS-CoV-2 (where possible).

3.5 Definitions

3.5.1 Hospitalised patient

A hospitalised patient is one who has been admitted to one of the participating hospitals during the study period and has not been discharged to their home or home equivalent, or died within 24 hours.

3.5.2 SARI patient

A SARI patient is defined as a hospitalised person with at least one of the following symptoms:

- cough;
- fever;
- shortness of breath;
- sudden onset of anosmia, ageusia or dysgeusia.

SARI patients with onset of symptoms in the 14 days prior to hospital admission will be included in the study. Note that hospitals already participating in SARI surveillance systems should not modify the SARI inclusion criteria for surveillance. However, for the CVE analysis, only those patients with onset of symptoms in the 14 days prior to hospital admission will be included.

In a later protocol version, a cut-off for days between onset of symptoms and swabbing may be decided (if appropriate).

A SARI patient is defined using ECDC's clinical case definition for a hospitalised possible COVID-19 case[3]. Compared with the World Health Organization (WHO) SARI case definition[4] (an acute respiratory infection with a history of fever or measured fever of ≥38 C° and cough, onset within the last 10 days and requiring hospitalisation), ECDC's possible COVID-19 case definition is more sensitive. Each study site/country will report individual SARI symptoms separately to allow sensitivity analyses comparing CVE and IVE estimates, based on alternative SARI case definitions and depending on the pathogen.

3.5.3 SARI patients confirmed as COVID-19

A confirmed COVID-19 case will be defined as a hospitalised patient fulfilling the SARI case definition, with a respiratory sample positive for SARS-CoV-2 by PCR, [29] either on admission to hospital or documented in the 14 days prior to hospital admission.

3.5.4 SARI patients confirmed as influenza

A confirmed influenza case will be defined as a hospitalised patient fulfilling the SARI case definition, with a respiratory sample PCR-positive for influenza[5].

[3] ECDC possible COVID-19 case definition: https://www.ecdc.europa.eu/en/covid-19/surveillance/case-definition

[4] WHO SARI case definition: https://www.who.int/teams/global-influenza-programme/surveillance-and-monitoring/case-definitions-for-ili-and-sari

[5] No requirement for the dates of the test. There are additional requirements in the exclusion criteria relating to test date and symptom onset.

3.5.5 SARI patients testing negative for SARS-CoV-2/influenza (test-negative controls)

A control will be defined as a hospitalised patient fulfilling the SARI case definition, with a respiratory sample negative for SARS-CoV-2 by PCR (for CVE) or a respiratory sample negative for influenza (for IVE) on admission to hospital.

It is advised that all sites test for both SARS-CoV-2 and influenza during the influenza season, as well as for all other respiratory viruses (as appropriate, depending on time of year), even if they are not participating in IVE. If this is not feasible, then during influenza season all samples that are negative for SARS-CoV-2 should also be tested for influenza (if not already tested at primary care level).

Controls that are negative by PCR but have Ct results suggestive of COVID-19[6], and those with prior SARS-CoV-2 infection in the three months before admission, may be excluded as controls in sensitivity analyses (see Section 3.5.7 'Exclusion criteria').

- A study site/country measuring only CVE should indicate which testing strategy they will use (testing all samples for both SARS-CoV-2 and influenza, or only testing for influenza in those negative for SARS-CoV-2).
- Each study site/country to indicate whether they can test for other respiratory viruses, only SARS-CoV-2 and influenza, or only SARS-CoV-2.

Other control groups (optional)

During periods when respiratory viruses are in low circulation, the number of SARI patients testing negative for SARS-CoV-2/influenza may be limited. Some sites may therefore wish to include other control groups, either in addition to SARI controls or as an alternative, and these must be recruited throughout the whole study period.

Examples of other control groups include:

- Patients testing PCR-negative to all respiratory viruses;
- Patients testing PCR-positive to respiratory viruses other than influenza (if IVE) or SARS-CoV-2, e.g. rhinovirus, respiratory syncytial virus (RSV), etc.; noting that patients with seasonal coronaviruses are excluded for CVE;
- Patients hospitalised with non-SARI related symptoms matched by time, age group and, if possible, underlying conditions:
  - Example source of hospitalised non-SARI cases: hospital wards admitting patients without COVID-19.
- Primary care: selection of GP patients belonging to the hospital catchment area and vaccination target group matched by time and age group:
  - Example source of GP patients: contact the GP for the case and select patients from his/her list (matching by GP).
- Community controls:
  - Random selection of community controls belonging to the vaccination target group, matched by time and age group (e.g. vaccine registry, telephone random survey, other planned survey);
  - Vaccination coverage in cases will be compared to vaccination coverage in the vaccination target population (screening method). Vaccination coverage should be available by time, age group and comorbidities;
  - Vaccination coverage among GP patients in the hospital catchment area: a random sample of GPs in the hospital catchment area can be used to compute the proportion of GP patients who are vaccinated
  - Vaccination coverage using vaccination centres in the hospital catchment area: the vaccination; coverage can be computed by dividing the number of individuals vaccinated (by age group, target group) by the number of individuals eligible for vaccination in the hospital catchment area (by age group, target group). Several methods can be used to estimate the population in the hospital catchment area.

All control groups should represent the vaccination coverage of the population giving rise to the cases. As the circulation of SARS-CoV-2/influenza and vaccination coverage changes over time, it is recommended that cases and controls be matched by time (e.g. onset of SARI symptoms) or adjusted by time in the analysis.

- Each study site/country including other control groups should define the control group, how controls will be selected, representativeness (vaccination coverage in the population giving rise to the cases) and potential limitations.

[6] https://www.who.int/publications/i/item/diagnostic-testing-for-sars-cov-2

3.5.6 Exclusion criteria

The patient will not be enrolled in the study if she/he:

- is unwilling to participate or unable to communicate and give consent (the consent may also be given by her/his legal representative, or by specific consent procedures, acceptable according to the local ethical review process);
- has a contraindication for the COVID-19 (for CVE) or influenza (for IVE) vaccination;
- cannot be swabbed due to severe septum deviation, obstruction or other conditions that contra-indicate swabbing;
- has a history of hospitalisation within the 14 days immediately prior to this admission (including transfers from another hospital);
- had his/her SARI onset ≥ 48 hours after admission to the hospital (for IVE) or ≥ 7 days after admission to the hospital (for CVE);
- was institutionalised at the time of symptom onset (lives at a care-home/residence for people who require continual nursing care and have difficulty with the required activities of daily living);
- had a respiratory specimen taken ≥ 8 days after SARI symptom onset (for IVE) or ≥ 10 days after SARI symptom onset (for CVE);
- had a respiratory sample taken ≤ 3 days before SARI symptom onset (for CVE)
- tested positive for any influenza virus in the current season before the onset of symptoms leading to the current hospitalisation (IVE).

Information will be collected on these and other potential exclusion factors and patients will be excluded from primary analyses according to available evidence on these factors (not all available at time of writing).

In sensitivity analyses, the CVE/IVE will be estimated:

- with different cut-offs for numbers of days between onset and swabbing, onset and hospitalisation, and between vaccination and onset of symptoms;
- excluding those positive for seasonal coronaviruses (e.g. HCoV-NL63, HCoV-229E, HCoV-OC43 and HCoV-HKU1);
- excluding those who are current controls (SARS-CoV-2 negative for CVE; influenza negative for IVE) but were positive by PCR in the previous year before the current hospitalisation, or reported clinically confirmed COVID-19, so as to determine the best cut-off period for having had a previous positive test during the preceding year versus 'any previous positive test' irrespective of date;
- using results from rapid antigen tests (RATs) when PCR information unavailable;
- dropping SARS-CoV-2-positive controls from IVE analysis and dropping influenza-positive controls from CVE analysis;
- excluding those who have received antivirals ≤14 days prior to swabbing (to avoid false negatives; the exact cut-off and types of antivirals will be determined as more research becomes available).

Please see Annex 2 for further analysis.

➢ The study site/country should define how they obtain informed consent from those who are too unwell at time of recruitment (e.g. oral consent with witness for those in isolation, until written consent possible, and/or consent of next of kin by telephone, etc).

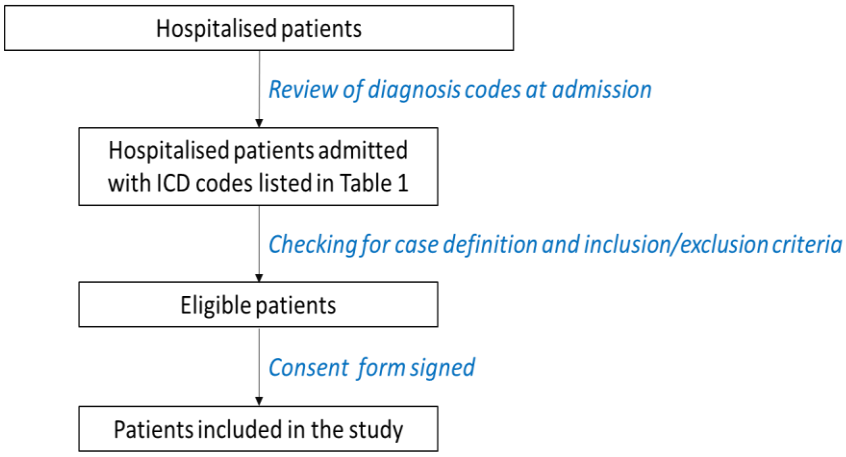
3.6 SARI patient identification – algorithm for patient inclusion

SARI patients are identified from among patients hospitalised for at least 24 hours in one of the participating hospitals. SARI patients should be enrolled and swabbed within 48 hours of hospital admission.

3.6.1 Recruitment strategies

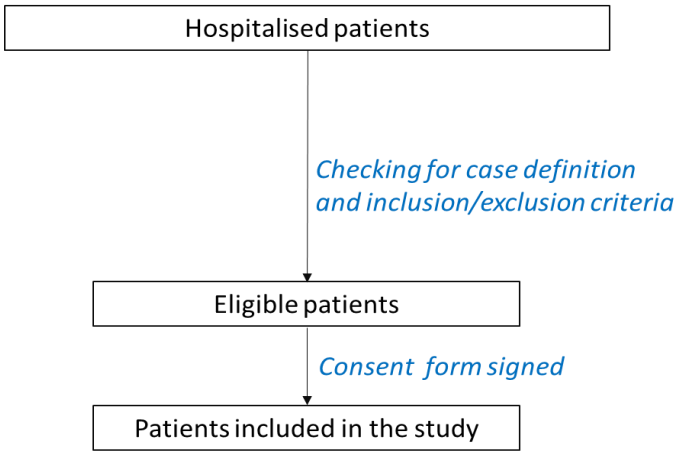
For hospitals with electronic patient records and/or diagnosis codes commonly displayed, SARI-related ICD codes (or other codes used for SARI surveillance) may be used. Patients admitted with any of the ICD codes listed in Table 3 will be approached; those meeting the SARI case definition and the inclusion criteria will be invited to be part of the study and give consent, if required by the country's legislation (Figure 1).

Figure 1. Proposed inclusion algorithm for hospitals/services relying on common use of ICD codes, hospital-based COVID-19/influenza vaccine effectiveness study



For hospitals where ICD codes on admission are not systematically collected or accessible, all patients will be systematically screened. This should be done by sensitising the medical staff at the beginning of the study (Figure 2) and following up with regular study coordinator reviews.

Figure 2. Proposed inclusion algorithm for hospitals/services systematic screening of all admitted patients, hospital-based COVID-19/influenza vaccine effectiveness study



Retrospective recruitment (or 'catching-up' on already diagnosed patients) is not recommended for the CVE study, as not all COVID-19 patients exhibit SARI symptoms and it will be difficult to determine the reasons for testing retrospectively.

- Each study site/country to describe procedures used to identify study participants.

In the event of test scarcity, extreme workload, or budget limiting inclusion to a threshold of patients, the study sites/countries may need to switch from exhaustive to systematic sampling (e.g. inclusion of patients every second day, or only on certain days in the week). Forward planning should be undertaken by the study sites for systematic sampling procedures. During the period of systematic selection, the study sites should make sure that they document the sampling fraction.

- Where a study site/country is not testing all SARI cases to describe the systematic sampling procedure, if systematic sampling is not being carried out, the criteria for testing should be explained.
- Each study site/country using ICD-10 codes for case identification should list the codes used.

Table 2. Diagnosis codes for which patients could be screened for onset of SARI symptoms, COVID-19/influenza in hospital-based VE studies

Category	Morbidity	ICD-9	ICD-10
Influenza-like illness	Cough	786.2	R05
	Difficulty breathing	786.05	R06
	Sore throat	784.1	R07.0
	Dysphagia	787.20	R13
	Fever	780.6	R50.9
	Headache	784.0	R51
	Myalgia	729.1	M79.1
	Fatigue/malaise	780.79	R53.1, R53.81, R53.83
Cardiovascular diagnosis	Acute myocardial infarction/acute coronary syndrome	410-411, 413-414	I20-23, I24-25
	Heart failure	428 to 429.0	I50, I51
Respiratory diagnosis	Emphysema	492	J43.9
	Chronic obstructive pulmonary disease	496	J44.9
	Asthma	493	J45
	Myalgia	729.1	M79.1
	Dyspnoea/respiratory abnormality	786.0	R06.0
	Respiratory abnormality	786.00	R06.9
	Shortness of breath	786.05	R06.02
	Tachypnoea	786.06	R06.82
	Other respiratory abnormalities	786.09	R06.00, R06.09, R06.3, R06.89
Infections	Pneumonia and influenza	480-488.1	J09-J18
	Other acute lower respiratory infections	466, 519.8	J20-J22
	Viral infection, unspecified	790.8	B34.9
	Bacterial infection, unspecified	041.9	A49.9
	Myocarditis	429.0	I40.9
	Bronchitis	490, 491	J40, 41
Inflammation	SIRS* non-infectious without acute organ dysfunction	995.93	R65.10
	SIRS* non-infectious with acute organ dysfunction	995.94	R65.11
Abdominal symptoms	Vomiting	787.0	R11
	Diarrhoea	009.3, 787.91	A07.9, K52.9
	Abdominal pain	789.0	R10
Diagnoses related to deterioration of general condition or functional status	General physical deterioration, lethargy, tiredness	780.79	R53.1, R53.81, R53.83
	Anorexia	783.0	R63.0
	Feeding difficulties	783.3	R63.3
	Abnormal weight loss	783.21	R63.4
	Other symptoms/signs concerning food and fluid intake	783.9	R63.8
	Disorientation/altered mental status	780.97	R41.0
	Dizziness and giddiness	780.4	R42
	Infective delirium	293.0, 293.1	F05
	Coma	780.01	R40.2
	Transient alteration of awareness	780.02	R40.4
	Other alteration of consciousness (somnolence, stupor)	780.09	R40.0, R40.1
	Febrile convulsions (simple), unspecified	780.31	R56.00
	Complex febrile convulsions	780.32	R56.01
Other	Anosmia, ageusia, myalgia	781.1, 729.1	R43.0, R43.2, M79.1

** SIRS: Systemic inflammatory response syndrome*

3.7 Laboratory methods

Study nurses or physicians will collect respiratory specimens (see Section 4.4) from all eligible patients, respecting safety standards for COVID-19 and influenza, and following WHO biosafety guidelines.[7]

- Each study site/country to describe the type (nasopharyngeal/oropharyngeal or both) and number of swabs taken for each patient.

Influenza laboratory confirmation will be done using RT-PCR or multiplex RT-PCR. Specimens will undergo molecular analysis for currently circulating influenza viruses.

PCR should be run with the inclusion of an internal/external quality control. It is recommended that the quality of the samples be monitored using an internal control to check for the presence of human cells in respiratory specimens.

[7] Any non-propagative diagnostics (e.g. sequencing, RT-PCR) should be conducted at a facility using procedures equivalent to biosafety level 2 (BSL-2), while propagative work (e.g. virus culture, isolation or neutralisation assays) should be conducted at a containment laboratory with inward directional airflow (BSL-3). Patient specimens from suspected or confirmed cases should be transported as UN3373, 'biological substance category B'. Viral cultures or isolates should be transported as category A, UN2814, 'infectious substance, affecting humans'[32].

ECDC's recommendation for SARS-CoV-2 laboratory confirmation is by viral RNA detection with nucleic acid amplification tests, such as RT-PCR. Specimens will undergo molecular analysis for currently circulating SARS-CoV-2 virus. During the influenza season, influenza virus tests will also be performed (and this is also recommended for countries not performing IVE), provided that there is circulation of influenza viruses in the community [30,31]. This is especially important to identify any potential association between influenza and SARS-CoV-2.

Following the procedures outlined by each study, all or a systematic sample of the detected viruses will undergo gene sequencing. The sampling procedure can include sequencing all viruses, or a systematic sample. The systematic sample should be representative of cases and be large enough to provide reasonable precision when calculating proportions of virus change over time. Guidance on random sampling for selection of samples for sequencing is provided in Annex 3.

If sequencing is performed, gene sequences should also be uploaded to GISAID's open access EpiCoV or EpiFlu platform (https://gisaid.org/ and raw WGS data should be uploaded to the EU portal (ENA) database). Gene sequence information can be provided directly to the coordinating central hub for the study, or the GISAID EpiCoV/EpiFlu accession number can be provided alongside the study's unique identifier to link these data (see Annex 3, after the section on random sampling). Processed genetic information (e.g. name of genetic clade) can also be included within the epidemiological database. The proportion of specific COVID-19 subvariants may be used to define a subvariant dominating period (e.g. >= 90% of isolates of a specific subtype during a defined period) [21-24].

- Each study site/country to describe the laboratory procedures (samples taken, storage, transport).
- Each study country to describe the tests and kits used (and their sensitivity, specificity and positive predictive value for COVID-19 and influenza, and if necessary, for the detection of other respiratory viruses).
- Each study site/country to describe if the laboratory participates in QA/QC (Quality Assurance/Quality Control) schemes.
- Each study site/country to describe the selection of specimens (including Ct value threshold) and the procedures for genetic and antigenic characterisation, where appropriate.
- Each study site/country to describe sequencing methods and the process for selection of samples for further characterisation.
- Each study site/country to describe whether specimens are tested for other respiratory viruses (e.g. whether influenza continues to be tested systematically during the season and stops once the influenza season is over, or is only tested if the COVID-19 result is negative, etc.)

3.8 Exposure (vaccination)

3.8.1 Definition of vaccination status

General relevant vaccination definitions

An individual will be considered as unvaccinated or completely vaccinated ± booster dose(s) against COVID-19 with a product-specific vaccine under the following categories (and only if information on all doses to date is provided):

- Patients will be considered as unvaccinated if they never received COVID-19 vaccine or if they were vaccinated on the day of, or any time after onset of symptoms;
- Completely vaccinated with primary series (single-dose vaccine) if they have received one dose 1–13 days* before symptom onset;
- Completely vaccinated with primary series (two-dose vaccine) if they have received both doses 1–13 days* before symptom onset;
- Completely vaccinated with primary series plus at least one booster dose if they received complete primary series vaccination (see above) plus one or more booster doses of COVID-19 vaccine;
- Completely vaccinated with at least primary series if they received complete primary series vaccination (see above), regardless of whether any booster dose of COVID-19 vaccine was also received;
- Completely vaccinated with primary series plus N boosters if they have received complete primary series vaccination (see above) plus N booster doses 1–13 days* before symptom onset.

Specific vaccination definitions

COVID-19 vaccination rollout schedules are evolving, and this section will need to be updated on an ongoing basis to reflect any new vaccination schedules.

Current season (or season of interest) COVID-19 vaccine

An individual will be considered as unvaccinated or vaccinated against COVID-19 with a product-specific vaccine under the following categories:

- **Unvaccinated** if they **did not receive a dose** during the COVID-19 vaccination campaign of interest, regardless of how many previous doses of COVID-19 vaccine they had received in past COVID-19 vaccination campaigns.
- **Vaccinated with** any **dose** as part of the COVID-19 vaccination campaign of interest:
  - if **they received a dose** during the campaign and at least 14 days* before symptom onset, regardless of how many previous doses of COVID-19 vaccine they had received in other COVID-19 vaccination campaigns.

** The exact number of days will depend on the vaccine; this number may change and the protocol will be updated when more information is available.*

It is crucial that the vaccination status and date of vaccination variables are collected with the utmost care to ensure data completeness and quality. The definition of vaccination status will be updated considering evolving decisions related to vaccination programmes, such as the use of different products for subsequent doses as well as additional doses. It is highly recommended that sites collect the **brands of each COVID-19 vaccine received**, most importantly the brand of the first and last dose (to differentiate between primary series with single- vs two-dose vaccines).

It is also highly recommended that if a site cannot collect information on every prior dose, information should ideally be collected on:

- The first dose
- The penultimate dose
- The last dose.

➢ Each study site/country to describe the country COVID-19 vaccination recommendations and schedule, including specific recommendations by age/at-risk groups, and policy regarding timings between doses of primary course and booster doses, as well as the timing of vaccine rollout.

➢ Each study site to describe the COVID-19 vaccination variables they are collecting.

Exposure comparison groups

The above vaccination definitions can be used to estimate CVE in general. The table below focuses on exposed and reference groups to estimate CVE for the seasonal COVID-19 vaccination campaign of interest. The choice of comparison groups will depend on the analysis objectives and public health message of interest.

Table 3. Suggested comparison groups for CVE analysis

Exposed	Reference group	Analysis objective and restrictions
Vaccinated with any dose of COVID-19 vaccine as part of the COVID-19 vaccination campaign of interest	**Unvaccinated** in the COVID-19 vaccination campaign of interest	To estimate **overall** CVE of the current COVID-19 vaccination campaign in the general population, regardless of vaccination history. **Both groups are restricted** to those not vaccinated six months prior to the start of the vaccination campaign[a]
Vaccinated with any dose of COVID-19 vaccine as part of the COVID-19 vaccination campaign of interest	**Unvaccinated** in the COVID-19 vaccination campaign of interest, but vaccinated ≥6 months prior to the vaccination campaign	To estimate **relative** CVE of the current COVID-19 vaccination campaign; to understand the additional effect of the current COVID-19 vaccination campaign to prior vaccination ≥6 months earlier **The exposed group is restricted** to those not vaccinated six months before the start of the vaccination campaign[a]
Vaccinated with any dose of COVID-19 vaccine as part of the COVID-19 vaccination campaign of interest	**Never vaccinated** with COVID-19 vaccine	To estimate **absolute** CVE of the current COVID-19 vaccination campaign **Neither group is restricted** by time since previous vaccination
Completely **vaccinated with primary series plus at least one booster dose** received as part of the COVID-19 vaccination campaign of interest	Completely **vaccinated with at least primary series but with no doses received** in the COVID-19 vaccination campaign of interest	To **estimate relative (incremental)** CVE of the current COVID-19 vaccination; to understand the additional effect of the current COVID-19 vaccination campaign Both groups are restricted to those not vaccinated in the six months prior to the start of the vaccination campaign[a]

[a] The six months can be varied (e.g. three or five months) in sensitivity analyses. In a sensitivity analysis, vaccination six months prior to the start of the vaccination campaign can be substituted with six months prior to swab/onset.

Many other analyses may be of interest, including comparing CVE of specific number of doses (e.g. two booster doses) compared with those who were eligible for the specific number of doses, but did not receive it (e.g. the comparison of those receiving two booster doses to those receiving one booster dose, among those eligible for two booster doses).

➢ Each study site to describe the exposure and reference groups of interest for comparison.

Current seasonal influenza vaccine

- A SARI patient will be considered as **vaccinated** against influenza with any vaccine as part of the current influenza vaccination campaign if he/she has received one dose of the influenza vaccine ≥14 days before SARI symptom onset.
- A SARI patient will be considered as **unvaccinated** if he/she did not receive influenza vaccine as part of the current influenza vaccination campaign or if he/she was vaccinated after onset of symptoms. (Anyone vaccinated <14 days before SARI symptom onset will be excluded from the primary analysis).

Product-specific seasonal influenza vaccine

- A SARI patient is considered as **vaccinated** against influenza with a product-specific vaccine during the current season if he/she has received a vaccination with an influenza vaccine of a named product ≥14 days before symptom onset.
- A SARI patient is considered as **unvaccinated** if he/she did not receive influenza vaccine with a named product in the current season of if he/she was vaccinated after onset of symptoms. (Anyone vaccinated <14 days before SARI symptom onset will be excluded from analysis.)

Each study site/country to document COVID-19 and seasonal influenza vaccine products used.

3.9 Data to be collected, including potential effect modifiers and confounding factors

3.9.1 Patient characteristics

The following patient characteristics need to be documented to describe the study population.

- Age in years;
- Sex;
- Pregnancy status (see Section 3.9.11);
- Smoking history (see Section 3.9.12);
- Healthcare worker status (see Section 3.9.13);
- Occupation (optional);
- Ethnic group (optional);
- SES/deprivation (optional).

➢ Each study site/country to describe community measures in place to limit exposures.

3.9.2 Clinical characteristics (symptoms and markers of severity)

Collection of good quality symptom information is crucial for VE studies to be able to validate the case definition used (see section 3.5). If only CVE is estimated, the following clinical characteristics and markers of disease severity should be collected:

- fever or feverishness;
- cough;
- shortness of breath.

In addition, study sites may collect the following **additional** symptoms for CVE, which are associated with COVID-19 illness and are part of ECDC's COVID-19 case definition:

- anosmia;
- ageusia;
- dysgeusia.

In addition, for study countries participating in IVE estimation, information on the following **additional** symptoms for IVE should also be collected:

- headache;
- sore throat;
- myalgia;
- malaise;
- deterioration of general condition (asthenia, weight loss, anorexia).

The following symptoms are **optional** for the hospital-based CVE study:

- coryza, rhinitis;
- sore throat;
- chest pain;
- chills;
- fatigue;
- nausea;
- vomiting;
- abdominal pain;
- diarrhoea;
- conjunctivitis;
- confusion;
- dizziness;
- tachypnoea or other signs of low oxygen saturation (restlessness);
- rash or other dermatological manifestation;
- palpitations/rapid heartbeat.

The following information can be used to indicate severity when measuring CVE to prevent severe disease:

- oxygen use;
- ICU admission;
- invasive ventilation;
- death.

Study sites should also collect information on:

- date of first key symptom onset.

3.9.3 Information on swab and test results

For each patient, sites will collect information on:

- date of admission (to allow estimation of and stratification by time from onset to hospitalisation, and to measure length of hospital stay);
- date of discharge/death (to allow the length of hospital stay to be measured);
- date of swab or date sample obtained (to allow estimation of and stratification by delay from swab to onset);
- information on COVID-19/influenza test(s) performed and laboratory results:
  - type of influenza and/or COVID-19 test (PCR, rapid test)
  - result of influenza and/or COVID-19 test
    - including information on antigenic and genetic analysis, if available

Some studies will be carrying out testing for other respiratory viruses. Study sites can collect:

- test results from any other respiratory viruses (e.g. rhinovirus, RSV, enterovirus, adenovirus, human metapneumovirus, seasonal coronaviruses, etc.)

3.9.4 Pre-existing chronic conditions

SARI patients (in particular, those who are ultimately included as controls) with underlying conditions may be included due to an exacerbation of these conditions, unrelated to SARI. These patients may be more likely to be infected with SARS-CoV-2/influenza, or to develop more severe disease than the source population. Furthermore, these patients may be more likely to be vaccinated against COVID-19/influenza than the source population and the CVE/IVE may therefore be underestimated. The presence of underlying conditions will be documented among all recruited SARI patients.

Underlying conditions which could be potential confounding factors/effect modifiers are shown in Table 4 (for their ICD codes, see Annex 4).

Table 4. Recommended and optional pre-existing conditions as potential effect modifiers or confounding factors

Recommended	Optional
Asthma	Anaemia/chronic haematologic disease
Immunodeficiency (including HIV infection) and organ transplant	Asplenia
Cancer (solid organ and haematological)	Chronic liver disease/cirrhosis
Diabetes mellitus	Dementia
Heart disease (excluding hypertension)	Neuromuscular disorders
Hypertension	Renal disease (exclude acute renal failure)
Lung disease (excluding asthma)	Rheumatologic diseases
Obesity ***or***	Stroke
• height and weight, ***or***	Tuberculosis
• BMI[8] (sites to include whichever is feasible/available)	

- Each study site/country to keep a list to include pre-existing conditions defining target groups for vaccination in their country.
- Each study site/country to define the list of chronic conditions to be included and state whether they are used to define target groups for vaccination, as well as any pre-existing medications being taken.

3.9.5 Severity of underlying condition/healthcare utilisation

The severity of an underlying condition could be an effect modifier or a confounding factor (i.e. not just presence of underlying condition). To document and control for healthcare-seeking behaviour in control groups and the severity of the underlying conditions, information will be collected on the number of hospital admissions due to underlying conditions in the 12 months prior to inclusion in the study.

3.9.5 Ethnicity

Documentation of the ethnicity remains optional. Some studies have shown that certain ethnic groups may be at higher risk, either of becoming infected with SARS-CoV-2, or of developing severe COVID-19. Uptake of, or access to vaccination may also be linked to ethnicity. Not all sites/countries collect, or are able to collect, this information. Even if all sites /countries were able to collect information on ethnic group, each group may be defined differently in different countries. The definitions for each ethnic group will need to be standardised across study sites before this information can be collected robustly and used to investigate CVE by ethnic group for pooled data. However, any site(s)/countries which can or do already collect this information may find it useful for examining their national CVE estimates by ethnic group.

- Each study site/country to indicate whether they can or do collect information on ethnic groups, and define their ethnic groups and (proposed) method of collecting the data (e.g. by self-reported ethnicity, from patient notes, or any other method).

3.9.6 Vaccination status – vaccines other than influenza/COVID-19

Study sites can collect (if desired) information on pneumococcal disease (pneumococcal polysaccharide vaccine (PPV) and pneumococcal conjugate vaccine (PCV)), respiratory syncytial virus (RSV; once available) and/or other relevant vaccinations. In particular, RSV vaccination may be of relevance for IVE/CVE studies if uptake is good and it has been recommended to similar target groups as the influenza/COVID-19 vaccine . Vaccination status variables could include the following for each disease (pneumococcal/RSV/other):

- vaccination status;
- type of vaccine;
- number of doses;
- either date or year of vaccination where available.

For study countries that are **not** participating in IVE, information on previous influenza vaccination (including date of vaccination) will also be collected.

- Each study site/country to document other vaccination status variables collected in their IVE and CVE studies.

3.9.7 Medication status for chronic condition(s)

The use of specific types of chronic medications prior to vaccination or illness may modify or confound the effect of the vaccine. For influenza, data on statin use should be collected otherwise the documentation of the medication status remains optional.

[8] Obesity defined as BMI>29.

Definition of medication status for pre-existing chronic condition(s):

- An individual is considered as 'on medication' if he/she has received the medication at least once during the six months before:
  - the first dose of pandemic COVID-19 vaccination (if date of medication use available: for the analysis measuring the effect of chronic medications on CVE);
  - onset of SARI symptoms (for unvaccinated individuals: for the analysis measuring the effect of chronic medications on COVID-19);
  - hospitalisation.
  - An individual is considered as 'not on chronic medication' if he/she did not receive medication before the periods specified in the protocol above to document such medication use.

3.9.8 Antiviral administration

The use of antivirals pre-hospitalisation should be documented: type, dosage (if possible) and date of administration (patients receiving antivirals two weeks prior to swabbing will be excluded from CVE/IVE analyses), as this may lead to misclassification biases.

- Each study country to list any antivirals administered prior to hospitalisation.

3.9.9 Previous SARS-CoV-2/influenza infection

Individuals who have been previously infected may have a greater response to the vaccine or be less likely to be reinfected, even if unvaccinated. Previous infection may impact the probability of receiving a COVID-19 vaccine (e.g. if the perception of risks associated with a new SARS-CoV-2 infection differs by previous infection status) and the risk of infection (due to immunity conferred by past exposure to SARS-CoV-2) [28]. Therefore, confounding of CVE by previous infection status may arise. Previous infection status may also be an effect modifier, as COVID-19 vaccination may provide greater absolute benefit to people without pre-existing immunity [29].

If possible, study sites will collect the following information:

- whether the patient had a previous positive SARS-CoV-2 test(s) (yes/no/unknown)
- optional:
  - type(s) of test: PCR, rapid test (in case of multiple positive test results, the most recent)
  - date(s) of test (in case of multiple positive test results, the most recent)
  - history of COVID-19, e.g., clinical confirmation.

If all study sites collect information on previous SARS-CoV-2 infection, the following analyses will be conducted with the pooled data. Otherwise, these analyses will be conducted in the subset of sites that collect this information. In the primary analysis, patients testing SARS-CoV-2 positive in the previous 60 days will be excluded from the analysis (this will avoid including cases who test positive due to prolonged shedding of a given illness episode and avoid including controls who are not at risk of being a case, according to the ECDC reinfection definition) [28]. Separate sensitivity analyses could be carried out including controls who recently tested SARS-CoV-2 positive, adjusting CVE estimates for previous SARS-CoV-2 infection, or stratifying CVE estimates by previous SARS-CoV-2 infection, if sample size allows. Additionally, if sample size allows and information is available, controls previously infected with SARS-CoV-2 will be included or excluded depending on number of days since last infection (to be explored in sensitivity analyses), or variant of infection.

- Each study site/country to collect and describe measure(s) used to capture prior SARS-CoV-2/influenza infection.

3.9.11 Pregnancy status

Pregnancy status will be collected and coded for women aged 15–55 years as follows: pregnant (yes/no/do not know), and if yes: trimester (1/2/3/do not know).

3.9.12 Smoking history

Smoking history will be collected and coded as follows: never-smoker, former smoker (stopped smoking at least one year before inclusion in the study), current smoker (smoking currently or stopped within a year of study recruitment).

3.9.13 Healthcare worker

The definition of a healthcare worker for the purposes of this study is anyone working (paid or on a regular voluntary basis) in healthcare who has contact with any type of patient during his/her work. This includes doctors, nurses, emergency medical personnel, medical and nursing students having contact with patients, and porters and cleaners. It also includes anybody working in a nursing/residential home for the elderly who has contact with residents. Study sites should collect information on healthcare worker status where possible. Patients with known healthcare worker status will be excluded from analyses for both CVE and IVE.

- Each study site/country to indicate whether they can collect information on healthcare worker status.

3.9.14 Other occupations

As some occupations predispose individuals to greater exposure, and may be a proxy for attitudes towards vaccination, where possible, countries may collect additional information on occupation for stratification in analysis by type of occupation. Documentation of this variable remains optional.

- Each study site/country to indicate whether they intend to/can also collect information on occupation in general (optional).

3.9.15 Presence of other respiratory virus infections

It is important to document the presence of influenza (for study countries not participating in IVE) and other respiratory viruses in cases and controls. Analysis will document the presence of other respiratory infections (e.g. RSV) among patients testing negative for SARS-CoV-2, and those who are positive.

- Each study site/country to list the other respiratory infection viruses that they test for (including influenza).

3.9.16 Healthcare utilisation in the previous 12 months

In order to document and control for healthcare-seeking behaviour and the severity of underlying conditions, study sites can collect:

- the number of hospital admissions due to underlying conditions in the 12 months prior to inclusion in the study.

3.12.1 Administrative information

Study identifiers

For each country/study sites, the following characteristics need to be documented:

- Country, site, priority vaccination target group(s) and their modifications;
- Hospital (unique number not including hospital name, to allow adjustment by hospital in analyses);
- Patient unique ID (note: this is not a patient identifiable ID such as date-of-birth or national ID number, but a unique identifier for a pooled database).

Hospital/ward information

The following dates and other hospital information need to be documented:

- Date of onset, admission, discharge, death;
- First ward of referral;
- Any hospital stay (for pre-existing chronic condition) in previous 12 months (optional);
- Date of swab/sample.

Data entry validation

For hospitals using electronic medical records, if paper questionnaires are used, a sample of them will be checked against the medical records and against the study database. For hospitals using electronic patient hospital records, a sample of records from the study database can be compared with the medical records. Concurrence between patient records/reports by study participants will be measured when/if records are available.

- Each study site/country to specify how data are validated;
- The specific validation procedures, including sample size calculation for questionnaire validation (if applicable) should be specified in the study annexes;
- Vaccination status, date, dose(s) if relevant and vaccine brand should be collected carefully and validated.

3.10 Sample size

Providing VE estimates for each separate study is one of the objectives of this project. Therefore, the minimum sample size should be estimated for each study to obtain precise CVE/IVE estimates. The pooled analyses should not prevent study teams at the country level from including a large enough sample size to obtain exact estimates for each country-specific study.

- Each study site/country to specify the minimum sample size calculation.

Sample size estimation in VE estimation is different from sample size estimation in hypothesis testing. Rather than focusing on whether a VE estimation includes 0% or not, it is the precision of the estimate which is more important. For example, with a VE of 70%, a lower boundary confidence interval of 1% does not provide a very informative VE estimate, even if the confidence interval does not include 0%. It is more important to have a VE estimate that is precise around the point estimate of 70% (e.g. with a lower boundary of 50%). In fact, a low VE estimate, which can be the case in particular stratified analyses, needs a very large sample size to provide a VE estimate where the confidence interval does not include 0%. For example, if the true VE is 5–10%, then a study providing a lower boundary not including 0% would be unreasonably large.

The following sample size estimates focus on precision of the VE estimate (Table 5).

The odds ratio (OR) has confidence intervals that are symmetrical around the point estimate in the log scale. However, due to the properties of the OR, these are asymmetrical around the point estimate on the arithmetic scale. The length of the confidence interval of an odds ratio on the arithmetic scale will therefore always be shorter at the lower limit (which will never reach zero). When converted to VE (VE=1-OR), the length of the confidence interval will always be shorter at the upper limit. Hence, the focus is on the precision of the lower limit of the confidence interval, and for Table 6 below, a potential range of between 10 and 30% (or 0.1–0.3) has been selected for this limit. A case-to-control ratio of 1:1 is also assumed, including varying vaccine coverage among the source population between 30% and 90%, and varying VE (with the OR between 0.1 and 0.7).

Table 5. Sample size calculations

Lower CI boundary	Controls/ case	Detectable OR	Vaccine coverage in source population/controls	Number of cases	Number of controls	IVE/CVE	CI
0.3	1	0.1	0.3	60	60	90	60–98
0.3	1	0.2	0.3	85	85	80	51–92
0.3	1	0.3	0.3	118	118	70	40–85
0.3	1	0.4	0.3	157	157	60	30–77
0.3	1	0.5	0.3	203	203	50	20–69
0.3	1	0.6	0.3	255	255	40	10–60
0.3	1	0.7	0.3	314	314	30	0–51
0.2	1	0.1	0.3	96	96	90	70–97
0.2	1	0.2	0.3	148	148	80	60–90
0.2	1	0.3	0.3	216	216	70	50–82
0.2	1	0.4	0.3	299	299	60	40–73
0.2	1	0.5	0.3	395	395	50	30–64
0.2	1	0.6	0.3	507	507	40	20–55
0.2	1	0.7	0.3	633	633	30	10–46
0.1	1	0.1	0.3	241	241	90	80–95
0.1	1	0.2	0.3	433	433	80	70–87
0.1	1	0.3	0.3	681	681	70	60–77
0.1	1	0.4	0.3	985	985	60	50–68
0.1	1	0.5	0.3	1 346	1 346	50	40–58
0.1	1	0.6	0.3	1 764	1 764	40	30–49
0.1	1	0.7	0.3	2 240	2 240	30	20–39
0.3	1	0.1	0.4	42	42	90	60–98
0.3	1	0.2	0.4		63	80	49–92
0.3	1	0.3	0.4	91	91	70	40–85
0.3	1	0.4	0.4	125	125	60	30–77
0.3	1	0.5	0.4	165	165	50	20–69
0.3	1	0.6	0.4	212	212	40	10–60
0.3	1	0.7	0.4	265	265	30	0–51
0.2	1	0.1	0.4	68	68	90	70–97
0.2	1	0.2	0.4	111	111	80	60–90
0.2	1	0.3	0.4	168	168	70	50–82
0.2	1	0.4	0.4	238	238	60	40–73
0.2	1	0.5	0.4	323	323	50	30–64
0.2	1	0.6	0.4	421	421	40	20–55
0.2	1	0.7	0.4	534	534	30	10–46
0.1	1	0.1	0.4	170	170	90	80–95
0.1	1	0.2	0.4	323	323	80	70–87
0.1	1	0.3	0.4	528	528	70	60–77
0.1	1	0.4	0.4	786	786	60	50–68
0.1	1	0.5	0.4	1 098	1 098	50	40–58
0.1	1	0.6	0.4	1 466	1 466	40	30–49
0.1	1	0.7	0.4	1 891	1 891	30	20–39
0.3	1	0.1	0.5	32	32	90	60–98
0.3	1	0.2	0.5	51	51	80	51–92
0.3	1	0.3	0.5	77	77	70	40–85
0.3	1	0.4	0.5	109	109	60	30–77

Lower CI boundary	Controls/ case	Detectable OR	Vaccine coverage in source population/controls	Number of cases	Number of controls	IVE/CVE	CI
0.3	1	0.5	0.5	148	148	50	20–69
0.3	1	0.6	0.5	193	193	40	10–60
0.3	1	0.7	0.5	246	246	30	0–51
0.2	1	0.1	0.5	51	51	90	70–97
0.2	1	0.2	0.5	90	90	80	60–90
0.2	1	0.3	0.5	142	142	70	50–82
0.2	1	0.4	0.5	208	208	60	40–73
0.2	1	0.5	0.5	289	289	50	30–64
0.2	1	0.6	0.5	384	384	40	20–55
0.2	1	0.7	0.5	495	495	30	10–46
0.1	1	0.1	0.5	129	129	90	80–95
0.1	1	0.2	0.5	262	262	80	70–87
0.1	1	0.3	0.5	447	447	70	60–78
0.1	1	0.4	0.5	687	687	60	50–68
0.1	1	0.5	0.5	983	983	50	40–58
0.1	1	0.6	0.5	1 337	1 337	40	30–49
0.1	1	0.7	0.5	1 751	1 751	30	20–39
0.3	1	0.1	0.6	26	26	90	60-98
0.3	1	0.20	0.60	45	45	80	50-92
0.3	1	0.30	0.60	71	71	70	40-85
0.3	1	0.40	0.60	103	103	60	30-77
0.3	1	0.50	0.60	143	143	50	20-69
0.3	1	0.60	0.60	191	191	40	10-60
0.3	1	0.70	0.60	247	247	30	0-51
0.2	1	0.10	0.60	41	41	90	70-97
0.2	1	0.20	0.60	78	78	80	60-90
0.2	1	0.30	0.60	130	130	70	50-82
0.2	1	0.40	0.60	197	197	60	40-73
0.2	1	0.50	0.60	280	280	50	30-64
0.2	1	0.60	0.60	380	380	40	20-55
0.2	1	0.70	0.60	497	497	30	10-46
0.1	1	0.10	0.60	104	104	90	80-95
0.1	1	0.20	0.60	229	229	80	70-87
0.1	1	0.30	0.60	410	410	70	60-78
0.1	1	0.40	0.60	651	651	60	50-68
0.1	1	0.50	0.60	953	953	50	40-58
0.1	1	0.60	0.60	1 322	1 322	40	30-49
0.1	1	0.70	0.60	1 760	1 760	30	20-39
0.3	1	0.10	0.70	23	23	90	60-98
0.3	1	0.20	0.70	43	43	80	50-92
0.3	1	0.30	0.70	71	71	70	40-85
0.3	1	0.40	0.70	108	108	60	30-77
0.3	1	0.50	0.70	153	153	50	20-69
0.3	1	0.60	0.70	207	207	40	10-60
0.3	1	0.70	0.70	272	272	30	0-51
0.2	1	0.10	0.70	36	36	90	70-97
0.2	1	0.20	0.70	75	75	80	60-90
0.2	1	0.30	0.70	131	131	70	50-82
0.2	1	0.40	0.70	205	205	60	40-73
0.2	1	0.50	0.70	298	298	50	30-64
0.2	1	0.60	0.70	412	412	40	20-55
0.2	1	0.70	0.70	548	548	30	10-46
0.1	1	0.10	0.70	90	90	90	80-95
0.1	1	0.20	0.70	219	219	80	70-87
0.1	1	0.30	0.70	413	413	70	60-78
0.1	1	0.40	0.70	676	676	60	50-68
0.1	1	0.50	0.70	1 015	1 015	50	40-58
0.1	1	0.60	0.70	1 435	1 435	40	30-49
0.1	1	0.70	0.70	1 941	1 941	30	20-39
0.3	1	0.10	0.80	22	22	90	60-98
0.3	1	0.20	0.80	47	47	80	50-92
0.3	1	0.30	0.80	82	82	70	40-85
0.3	1	0.40	0.80	128	128	60	30-77
0.3	1	0.50	0.80	187	187	50	20-69
0.3	1	0.60	0.80	259	259	40	10-60
0.3	1	0.70	0.80	344	344	30	0-51
0.2	1	0.10	0.80	35	35	90	70-97
0.2	1	0.20	0.80	82	82	80	60-90
0.2	1	0.30	0.80	151	151	70	50-82

Lower CI boundary	Controls/ case	Detectable OR	Vaccine coverage in source population/controls	Number of cases	Number of controls	IVE/CVE	CI
0.2	1	0.40	0.80	245	245	60	40-73
0.2	1	0.50	0.80	365	365	50	30-64
0.2	1	0.60	0.80	514	514	40	20-55
0.2	1	0.70	0.80	694	694	30	10-46
0.1	1	0.10	0.80	89	89	90	80-95
0.1	1	0.20	0.80	241	241	80	70-87
0.1	1	0.30	0.80	477	477	70	60-78
0.1	1	0.40	0.80	808	808	60	50-68
0.1	1	0.50	0.80	1 242	1 242	50	40-58
0.1	1	0.60	0.80	1 789	1 789	40	30-49
0.1	1	0.70	0.80	2 458	2 458	30	20-39
0.3	1	0.10	0.90	30	30	90	60-98
0.3	1	0.20	0.90	71	71	80	50-92
0.3	1	0.30	0.90	129	129	70	40-85
0.3	1	0.40	0.90	208	208	60	30-77
0.3	1	0.50	0.90	310	310	50	20-69
0.3	1	0.60	0.90	437	437	40	10-60
0.3	1	0.70	0.90	591	591	30	0-51
0.2	1	0.10	0.90	48	48	90	70-97
0.2	1	0.20	0.90	124	124	0.8	60-90
0.2	1	0.30	0.90	238	238	0.7	50-82
0.2	1	0.40	0.90	397	397	0.6	40-73
0.2	1	0.50	0.90	605	605	0.5	30-64
0.2	1	0.60	0.90	868	868	0.4	20-55
0.2	1	0.70	0.90	1 190	1 190	0.3	10-46
0.1	1	0.10	0.90	121	121	0.9	80-95
0.1	1	0.20	0.90	361	361	0.8	70-87
0.1	1	0.30	0.90	751	751	0.7	60-78
0.1	1	0.40	0.90	1 311	1 311	0.6	50-68
0.1	1	0.50	0.90	2 061	2 061	0.5	40-58
0.1	1	0.60	0.90	3 022	3 022	0.4	30-49
0.1	1	0.70	0.90	4 216	4 216	0.3	20-39

The sample size estimates above are for the crude analysis and an adjusted analysis would require a higher sample size.

The sample size should also be respected for each population subgroup for which a sub (stratified) analysis (e.g. effect modification) is planned.

See also the Analysis section on sample size requirements for analyses.

3.11 Data

3.11.1 Datasets and coding

Some study sites may not be able to collect all information proposed above. Study sites should indicate which variables they can collect and which data source they will use in Annex 1: List of variables collected, definition and coding. Study sites can use the coding (variable names and values) as specified in Annex 1, or use their own coding. For the pooled analysis, if study site-specific coding is used, a database dictionary should be supplied alongside the data.

3.11.2 Data collection instrument and sources of information

Data are to be collected using a standardised questionnaire/data collection form. The source(s) of data may include:

- vaccination card/certificate;
- hospital medical records;
- interview with patient or his/her family;
- communication with the patient or his/her family via mobile phone;
- interview with patient's treating/admitting physician or GP;
- interview with patent's pharmacist;
- vaccination register;
- laboratory records.

➢ Each study site/country to define the sources of information used for each variable collected and the potential limitations.

➢ Each study site using study site-specific coding to provide a data dictionary for pooled analyses.

3.12. Data management

3.12.1 Data collection, entry and storage at study site level

Web-based data collection methods or paper-based methods can be used. Data entry procedures will include checks to minimise data entry errors.

Information on antigenic, when available, and genetic analyses, including GISAID accession number, can be included in the epidemiological database or stored separately on an Excel spreadsheet (see Annex 2).

All data should be stored and processed in a way compliant with EU general data protection regulations (GDPR) [29].

- Study sites to specify procedures of data collection and entry;
- Study sites to specify methods of data storage and their compliance with the EU GDPR requirements;
- Study sites to provide a codebook that includes the variable names, variable descriptions, and the coding of variable values (see also Annex 1).

3.12.2 Data checking and cleaning

Data checking will be carried out at the study site level. Summary and frequency tables as well as visual representations of appropriate variables are used to find illegal, implausible or missing values within the dataset. Checks for inconsistencies are carried out (e.g. date of swab before date of symptom onset). These values should be checked against the questionnaires or queried against the hospital record. Any missing data will be described.

Any changes or recoding to the data during the cleaning process (e.g. age to age groups) are documented and stored separately from the crude database. Guidance and/or example scripts for data cleaning can be provided if so desired.

Data checking is an iterative process (see Annex 3). After checking, data will be cleaned and stored separately from the source data. All changes to the data will be documented in scripts.

3.13 Analysis

3.13.1 Individual (country/study site level) analysis

The timing to conduct each interim analysis will depend on the time needed to achieve the appropriate sample size and regular updates are foreseen. This will depend mainly on the incidence of hospitalisation, COVID-19/influenza incidence, vaccination coverage, the recruitment strategy within hospital/s and the number of participating hospitals/services per hospital.

Cases and controls will be described by baseline characteristics. Patients will be described according to:

- sex;
- age group;
- time: month of symptom onset;
- COVID-19 (CVE)/influenza (IVE) vaccination status;
- absence/presence of at least one, presence of more than one high-risk condition;
- specific chronic conditions (e.g. diabetes, respiratory, cardiovascular diseases, immunodeficiency);
- pregnancy;
- vaccination status of other vaccines;
- respiratory co-infections (where available);
- severity (ICU, oxygen use, invasive ventilation, death);
- SARS-CoV-2 variant/influenza (sub)type and clade (where possible) for cases;
- vaccine product (for vaccinated cases).

A sample layout of this descriptive analysis is provided in Table 6 below.

Table 6. Example of descriptive table for cases and controls; COVID-19/influenza hospital-based vaccine effectiveness study, ECDC multi-centre study, 2023

Variables	Number of laboratory-confirmed COVID-19 (or influenza) cases/total n (%)	Number of test-negative controls/total n (%)
Median age (IQR)	X	X
Missing	X	X
Age groups (years)		
20–59	x/x (x)	x/x (x)
60–79	x/x (x)	x/x (x)
≥ 80	x/x (x)	x/x (x)
Missing	X	X
Sex		
Female	x/x (x)	x/x (x)
Missing	X	X
Days between onset of symptoms and swabbing		
0	x/x (x)	x/x (x)
1	x/x (x)	x/x (x)
2	x/x (x)	x/x (x)
3	x/x (x)	x/x (x)
4–7	x/x (x)	x/x (x)
COVID-19/influenza vaccination	x/x (x)	x/x (x)
Missing	x	X
etc.		

This study is a case–-control study (test-negative design). The measure of association is the odds ratio (OR). This can be estimated by logistic regression. An OR = 1 indicates no association between an exposure and the outcome. An OR>1 indicates a potential risk factor, an OR < 1 indicates a potential protective factor, noting that the confidence interval around the OR helps with its interpretation.

For vaccination as a preventive factor, the CVE/IVE can be computed as CVE/IVE = (1 – OR)*100. A 95% confidence interval is computed around the point estimate.

Univariable analysis will be carried out to measure the CVE/IVE against being a laboratory-confirmed COVID-19/influenza SARI case. Stratified analyses (e.g. by sex and age group) can follow to better understand potential effect modifiers and confounders.

Prior to multivariable analysis, a model development strategy will be determined and included in the plan of analysis. In the final step, multivariable analysis will be carried out to take confounding factors and potential effect modifiers into account. This will provide adjusted ORs from which the CVE/IVE can be estimated using the formula above.

Output tables presenting CVE/IVE estimates

To present the results in the most transparent manner and to enable the reader to best understand the data, tables similar to the one illustrated below in Table 7 can be used (variables presented just to illustrate the output format). Useful information includes numbers of cases and controls (overall and vaccinated) and presentation of results for different models.

Table 7. Example of table displaying vaccine effectiveness against COVID-19/influenza adjusted for various co-variables overall and by age group, hospital-based COVID-19/influenza vaccine effectiveness ECDC multi-centre study, 2023

Clade/variant	Population included	Analysis scenarios/adjustments made	CVE (or IVE) (%)	(95% CI)
COVID-19	All ages	N (cases/ vaccinated; controls/ vaccinated)		
(or influenza)		Crude		
		Adjusted for onset date (cubic spline)		
		Adjusted for sex		
		Adjusted for chronic condition		
		Adjusted for age (cubic spline)		
		Adjusted for onset date, age (cubic spline)		
		Adjusted for onset date, chronic condition		
		Adjusted for onset date, age (cubic spline), chronic conditions, sex		
	20–59 years	N (cases/ vaccinated; controls/ vaccinated)		
		Crude		
		Adjusted for onset month, age (cubic spline)		
	60 years and over	N (cases/ vaccinated; controls/ vaccinated)		
		Crude		
		Adjusted for onset date, age (cubic spline), chronic condition, sex		

3.13.2 Sensitivity analyses

As sensitivity analyses, study sites can measure CVE/IVE:

- with different cut-offs of numbers of days between onset and swab;
- with different cut-offs of numbers of days between vaccination and symptom onset;
- with varying the post-vaccination periods (e.g. 7 days, 14 days, etc.) to be considered 'completely vaccinated' or 'partially vaccinated' (see Section 3.8.1);
- including, excluding, stratifying or adjusting by previous positive test status, and also by different delays between prior test and inclusion in the study;
- excluding patients testing positive prior to hospitalisation but negative in hospital;
- using only controls positive to other respiratory viruses;
- excluding controls testing SARS-CoV-2 positive (IVE) or influenza positive (CVE), or adjusting by COVID-19 vaccination (see also Section 5.1.7);
- using different reference groups for VE estimation (e.g. for CVE: unvaccinated people, people vaccinated with a smaller number of doses, people vaccinated in the previous season).
- 3.13.3 Pooled analysis.

The higher sample size for the pooled analysis will provide more precision around the VE estimates. Data can be coded as outlined in Annex 1, or a codebook can be provided by the study teams that includes the variable names, descriptions and coding. The central hub will perform data cleaning and document and share any further data cleaning and analysis with all study coordinators to ensure it can be reproduced.

See Annex 2 for details of the pooled analysis plan. For the pooled data, interim analyses will be conducted during different periods, if appropriate, and according to the available sample size.

The timing to conduct each interim analysis will depend on the time needed to achieve the appropriate sample size. This will depend mainly on the incidence of hospitalisation, COVID-19/influenza incidence, vaccination coverage, the recruitment strategy within hospitals and the number of participating hospitals/services per hospital.

The pooled analysis will be carried out in a similar way to the site-specific analysis. Country or study site will potentially be included as a fixed effect, or as a random effect in a multi-level model. Statistical heterogeneity between study sites will be determined in a two-stage analysis using the Q-test and the I^2 index [30].

3.14 Personal data protection

Each participating study site shall comply with the requirements of the data protection legislation (see Section 3.12.1), and with national ethics committee provisions. Informed consent will be required from all participants or their legal representatives. Where data protection legislation permits, the national ethics committees will specify whether oral or written consent is required. Specific consent procedures may be needed for unconscious patients and patients with deterioration of general condition or functional status, unable to sign the consent (e.g. oral witnessed consent, consent by next of kin, etc).

3.15 Training

Investigators and data collectors will be trained on the study protocol before the study begins. They will receive the protocol, questionnaires and laboratory respiratory specimen collection procedures.

➢ Each study site/country to describe the training to be organised.

4. Logistical aspects

4.1 Respiratory specimen collection

The default collection method for the respiratory specimen will be by means of nasal/nasopharyngeal swabbing or concurrent nasal and oral/oropharyngeal swabbing (or endotracheal aspirates in ICU). Personal protection equipment must be used in accordance with guidelines.

- Each study site/country to describe the specimen collection procedures.

4.2 Laboratory tests

High specificity is needed for COVID-19 confirmation. COVID-19 laboratory confirmation will be carried out using RT-PCR or multiplex RT-PCR. Influenza laboratory confirmation will be carried out using RT-PCR or by culture.

- Each study site/country to describe the tests and kits used for COVID-19 and influenza; and, if necessary, other respiratory virus detection.
- Each study site/country to specify sequencing methods.

PCR should include an internal/external quality control. It is advisable to monitor the quality of the respiratory samples by checking for presence of cells in the specimens. In addition, quality assurance of assay performance at sites should be evaluated by participating in External Quality Assessment Programmes (EQAS).

- Each study site/country to describe quality controls for specimens.
- Each study site/country to describe genetic and antigenic analyses.

5. Limitations

With any multi-centre study, there is always the potential for heterogeneity across study sites. In addition, during a pandemic with such high caseloads for hospitals, there may be difficulties in collecting all data, and not all cases included will have laboratory confirmation. There is also the possibility that very severely ill patients (e.g. those who are ≥80 years old, or who are extremely frail and/or in nursing homes) may not be admitted to hospital at all, and would be missed by the study. For both influenza and COVID-19, there is symptom variability across age groups (e.g. less fever seen in the elderly). Potential limitations to the CVE/IVE estimates are discussed below.

5.1 Potential biases

5.1.1 Bias from pooled estimates

With data from several hospitals in different countries being pooled, any bias in the individual studies will influence the pooled estimate. The power of the test for the presence of heterogeneity between individual studies is low if there are few sites/countries. In this case, the test may not be able to detect heterogeneity between them, despite this being present. It is important that heterogeneity is also assessed using qualitative knowledge about differences between studies. Depending on the nature of the bias, the inclusion of biased studies in the pooled estimate could lead to over- or underestimation of the true association between COVID-19/influenza vaccination and the outcome.

There are many conditions which could lead to bias at a single site or hospital. For CVE, with this new virus, there are new and evolving surveillance systems and strategies in each participating country. There are not only different tests being used, but a variation in the number of tests used to declare an individual negative. Another example is that, when under high pressure (e.g. high volume of patients to be admitted during a peak in the epidemic for any site), it is possible that some hospitals may switch to admitting only suspected COVID-19 patients, while others focus on non-COVID-19 patients. In the event of the former type of hospital participating, this could affect the recruitment of controls and result in cases being predominantly recruited from one hospital over another. If a participating site only has one hospital providing data, this could mean they are only able to provide information on cases. Conversely, if the single participating hospital was designated a non-COVID-19 admitting hospital, this site would only be able to provide information on controls.

To allow for complete assessment of heterogeneity, sites need to document all changes in their COVID-19 surveillance system and any in the influenza surveillance system during the study period.

- Each study site/country to document any changes in COVID-19/influenza surveillance during the study period, including allocation of participating hospitals to COVID-19 or non-COVID-19 admission status.

5.1.2 Negative confounding

Negative confounding refers to biases that reflect the fact that high-risk groups (people more likely to develop severe complications) will be more likely to be vaccinated and therefore reduce CVE/IVE. If negative confounding is present, the CVE/IVE will be underestimated. Adjustment for potential negative confounding factors documented in the study (e.g. age, presence of chronic diseases) will minimise negative confounding.

5.1.3 Positive confounding

Positive confounding refers to biases that reflect a 'healthy vaccinee effect'. People with a healthy lifestyle will be more likely to accept vaccination, thus leading to an increase in measured CVE/IVE. Similarly, people in a state of 'extreme frailty' will not be offered vaccination and, because they are frail, may be more likely to have severe disease. Individuals with risk-taking behaviour may also be averse to vaccination, which may also increase their exposure to disease. If positive confounding is present, CVE/IVE will be overestimated.

5.1.4 Unmeasured confounding

Positive and negative confounding will be minimised through stratification and multivariable analysis. It will not be possible to rule out the presence of characteristics in the study population for which no information is collected in the study questionnaire and this could lead to positive or negative confounding. Therefore, some residual unmeasured confounding may remain.

- Each study site/country to describe the potential limitations and representativeness of the subjects included.

5.1.5 Previous infection in cases or controls; inclusion of asymptomatic controls

Individuals who have previously been infected may have a different response to the vaccine or be less likely to be reinfected, even if unvaccinated. It is possible that some of the controls (those testing negative for influenza/SARS-CoV-2) may have themselves been positive for influenza/SARS-CoV-2 some time before. The proportion of these (potentially or partially immune individuals) in each country's dataset would depend on the circulation of the virus in the community during the months before the hospitalisation of the control. Knowledge of their prior infection could affect their likelihood to be vaccinated. For example, if someone knew that they had had COVID-19, despite having no symptoms (e.g. if they had had a screening test), they may be subsequently less likely to be vaccinated. This would lower vaccination coverage among controls and underestimate CVE. Similarly, if someone believed that they had had influenza but had not had a test, they may subsequently be less likely to be vaccinated. This would lower vaccination coverage among controls and underestimate IVE.

As time goes on, there will be more and more individuals in the population who have either had symptomatic or asymptomatic COVID-19. Many may not have been tested, especially if asymptomatic. Ascertainment of previous SARS-CoV-2/influenza infection in both cases and controls would therefore be very difficult and largely subjective. Results should be interpreted in light of this, and an estimate of a range of potential bias should be calculated around the CVE and IVE estimates. Where possible, sensitivity analyses should be conducted, excluding any SARI patient with previous SARS-CoV-2 or influenza infection confirmed by PCR.

As antibody tests become more widespread, then this may be included in the protocol.

5.1.6 Validation of exposure

The vaccination status is the exposure of interest and the validity of vaccination data should therefore be checked carefully. If the vaccination status is reported by the patient only, without further proof, information bias may occur. Vaccination status of cases and controls should be validated using an independent source (i.e. vaccination register, GPs).

- Each study site/country to describe the source of exposure validation and its potential limitations.

5.1.7 Inclusion of influenza-positive controls for CVE and SARS-CoV-2-positive controls for IVE

A key prerequisite of the test-negative design is that the vaccination of interest does not affect the control group. However, there may be a strong correlation between those receiving influenza and COVID-19 vaccines, which would introduce bias. For example, if inclusion of SARS-CoV-2-positive controls artificially lowers the vaccine coverage among influenza test-negative controls, there would be a bias towards a lower IVE. Similarly, inclusion of influenza-positive controls in CVE may artificially lower the vaccine coverage among SARS-CoV-2 test-negative controls, biasing towards a lower CVE. The test-negative design would no longer be valid.

To account for this, analyses should be carried out excluding SARS-CoV-2 controls (IVE) and influenza controls (CVE), if adequate information is available [31]. These estimates can be compared with the primary analysis including SARS-CoV-2/influenza controls.

Sensitivity analyses will be conducted, excluding controls who are positive for influenza from CVE estimation and controls who are positive for SARS-CoV-2 from IVE estimation.

5.1.8 Misclassification

The use of antivirals prior to swabbing in CVE/IVE studies may lead to misclassification biases. Sensitivity analyses will be run to exclude patients who were administered antivirals prior to swabbing. In addition, misclassification can occur due to test performance. In analysis, adjustment can be made for sensitivity and specificity of the tests. Sites may use different tests, so investigators should seek to use common international, national or research standards to address possible variation in test performance at sites. The UK National Institute of Biological Standards and Control currently offers international standards for molecular testing [32].

5.1.9 Other potential biases

Controls could come from different source populations with varying risk of infection with SARS-CoV-2/influenza, varying probability for acquiring COVID-19/influenza vaccination, etc. (e.g. depending on time of year). Time (onset date) will be used to adjust for seasonal differences. Analyses will also be stratified by time (e.g. onset quarter of the year). For COVID-19, as vaccination campaigns progress, the proportion of those unvaccinated will become very small. This population may be different from the general population. Analyses using relative VE (e.g. second compared to first booster vaccination) will be conducted.

- Each study site/country to describe timeline of vaccination for different target groups.

5.2 Representativeness of subjects included in the study

The study only includes cases that are hospitalised. Health-seeking behaviour may differ by country depending on the case management strategy (e.g. recommendation to stay at home with mild symptoms, and only see a GP if symptoms persist, followed by hospitalisation if severe). In some cases, the management strategy will have an impact on the delay between onset of symptoms and hospitalisation. This, in turn, may have an impact on the time lag between onset and respiratory specimen collection, and may affect positivity rates between study sites. In addition to the collection of dates of onset/admission/respiratory specimen collection, health-seeking behaviour and case-management strategies should be described for each study and it should be noted how these may affect the CVE/IVE estimates.

Some very severely ill patients will not be able to give informed consent and this group may therefore be under-represented among the subjects included.

It is important to consider the representativeness of the controls. For example, if controls were all to be influenza **and** COVID-19 negative, consideration should be given to whether they are representative of the source population in terms of vaccine coverage. After two years of vaccination, the COVID-19 vaccine coverage rates in most EU/EEA countries are quite high, particularly among older age groups. In 2023, most SARI patients may be vaccinated against COVID-19 and vaccine coverage among hospitalised controls could be 70% or higher. This may not be representative of the vaccine coverage in the general population. In this situation, analyses using relative VE (e.g. booster vaccination compared to primary course vaccination) could be considered (see Table 4 and Section 3.8 Exposure (vaccination)).

- Each study site/country to describe the potential limitations in terms of representativeness of the subjects included.
- Each study site/country to describe case-management strategy in their country.

This core protocol will continue to be updated in light of evolving scientific evidence and methodological considerations.

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Annex 1. List of variables, definitions and coding (hospital-based COVID-19 and influenza vaccine effectiveness studies minimum dataset)

Individual data:

- Each study site/country to list all the variables collected and their coding.
- Each study site/country to indicate all modifications in the variables collected compared to variables below.

Optional variables are moved to the end of the table and shaded in grey (for both new and old variables)

	Variable	Type	Values and coding	Definition
Section A Administrative information (study identifiers)	idcountry	Numeric (categorical)	Coded according to international country codes	Identifier uniquely identifying the country (for pooled datasets only)
	id	Numeric	Unique integer	Unique number for each patient
	hospitalcode	Numeric	Unique integer	Unique number for each hospital
Section B Patient information/ characteristics	consent	Numeric	0 = No	Agreement of patient to participate (where appropriate, i.e. for countries requiring consent)
			1 = Yes	
			2 = Not required	
			8 = Do not know	
	consent_sp	Text		Reason provided for non-participation
	age	Numeric (integer)		Age of patient
	sex	Numeric (categorical)	0 = female	Sex of patient
			1 = male	
			3 = other	
			8 = do not know	
	ltcf	Numeric (categorical)	0 = No	Patient residence at time of SARI onset. Whether patient was living in long-term care facility
			1 = Yes	
			8 = Do not know	
	hcw	Numeric (categorical)	0 = No	Whether the patient is a healthcare worker
			1 = Yes	
			8 = Do not know	
	smoking	Numeric (categorical)	0 = Never	Never, former (stopped smoking at least one year before inclusion in the study), current smoker (or stopped in the past year)
			1 = Former	
			2 = Current	
			8 = Do not know	
	pregnant	Numeric (categorical)	0 = No	Whether patient is pregnant (for women aged 15–55 years)
			1 = Yes	
			8 = Do not know	
Section C Hospital/ward, clinical course and outcomes	admitdate	Date	dd/mm/yyyy	Date of hospital admission
	outcome	Numeric (categorical)	1 = died	Indicate the outcome of the patient known at the time of data collection (note: this may be updated later) (updated to match TESSy)
			2 = discharged from hospital	
			3 = still on treatment	
			8 = unknown outcome	

	Variable	Type	Values and coding	Definition
	outcomedate	Date (dd/mm/yyyy)		Date of outcome
	icu	Numeric (categorical)	0 = No	Admission to intensive care unit (ICU) or high-dependency unit (HDU)
			1 = Yes	
			8 = Do not know	
	icuadmitdate	Date	dd/mm/yyyy	Date of ICU/HDU admission
	numberdaysicu	Numeric		Number of days in ICU/HDU
	resp_support	Numeric (categorical)	0 = None	Level of respiratory support
			1 = High-flow oxygen therapy (non-invasive ventilation)	
			2 = Invasive ventilation	
			3 = Extra corporeal membrane oxygenation (ECMO)	
			4 = Other	
			8 = Do not know	
	hospitalward	Numeric (categorical)	0 = Special COVID-19 ward	First ward of referral (NOTE: this may alternatively be sent as text, as for influenza)
			1 = Lung, pulm/respir.	
			2 = Internal medicine	
			3 = Infectious diseases	
			4 = Emergency or A&E	
			5 = Cardiology	
			6 = Geriatric	
			7 = ICU or HDU	
			9 = Other	
			10 = Obstetrics/gynaecology	
			11 = Surgery	
			12 = Paediatric	
			8 = Do not know	
	hospitalward_oth	Text		Specify other ward
Section D Pre-existing chronic conditions	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	
	heartdis	Numeric (categorical)	0 = No	Heart / cardiac disease (excluding hypertension)
			1 = Yes	
			8 = Do not know	
Section D *continued*	lungdis	Numeric (categorical)	0 = No	Chronic lung disease (excluding asthma)
			1 = Yes	
			8 = Do not know	
	diabetes	Numeric (categorical)	0 = No	Diabetes
			1 = Yes	
			8 = Do not know	
	hypert	Numeric (categorical)	0 = No	Hypertension

	Variable	Type	Values and coding	Definition
			1 = Yes	
			8 = Do not know	
	immuno	Numeric (categorical)	0 = No	HIV or other immunodeficiency disorders including organ transplantation
			1 = Yes	
			8 = Do not know	
	obese	Numeric (categorical)	0 = No	Obesity (only if height, weight and BMI not collected; can be calculated)
			1 = Yes	
			8 = Do not know	
	hosp_visit	Numeric (integer)		Number of times patient was admitted to hospital for an underlying chronic condition in the 12 months prior to current admission
Section E Medications for chronic medical conditions	statin_pre	Numeric (categorical)	0 = No	Patient was on statins since or from 01 Sept 2022
			1 = Yes	
			8 = Do not know	
	antivir_pre	Numeric (categorical)	0 = No	Antivirals given prior to swabbing
			1 = Yes	
			8 = Do not know	
Section F Vaccination status: COVID-19 vaccination	panvacc1dose	Numeric (categorical)	0 = No	Received pandemic COVID-19 vaccination, **first** dose
			1 = Yes	
			8 = Do not know	
	panvacc1date	Date	dd/mm/yyyy	Vaccination date, **first** dose
	panvacc1type	Text		Type of vaccine (product name)
	panvaccn-1dose	Numeric (categorical)	0 = No	Received pandemic COVID-19 vaccination, **penultimate** dose
			1 = Yes	
			8 = Do not know	
	Panvaccn-1date	Date	dd/mm/yyyy	Vaccination date **penultimate** dose
	Panvaccn-1type	Text		Type of vaccine (product name)
	panvaccndose	Numeric (categorical)	0 = No	Received pandemic COVID-19 vaccination, **last** dose
			1 = Yes	
			8 = Do not know	
	panvaccndate	Date	dd/mm/yyyy	Vaccination date **last** dose
	panvaccntype	Text		Type of vaccine (product name)
	panvaccdoses	Numeric		Total number of COVID-19 vaccine doses received
Section G Vaccination status: other vaccinations	flu_vacc	Numeric (categorical)	0 = No	Received current seasonal influenza vaccination
			1 = Yes	
			8 = Do not know	
	flu_vaccdate	Date	dd/mm/yyyy	Date of receiving the current season's influenza vaccination
	flu_vaccbrand	Text		Brand of the current season's influenza vaccination
	seasvacc_n1	Numeric (categorical)	0 = No	Received a seasonal influenza vaccination during the last season
			1 = Yes	
			8 = Do not know	
	seasvacc_n2	Numeric (categorical)	0 = No	Received a seasonal influenza

	Variable	Type	Values and coding	Definition
			1 = Yes	vaccination two seasons ago
			8 = Do not know	
	pneumo_vacc	Numeric (categorical)	0 = No	Pneumococcal vaccination received (any type, ever)
			1 = Yes	
			8 = Do not know	
	ppv_vaccdate	Integer	yyyy	Year of last PPV23 vaccination
	pcv_vaccdate	Integer	yyyy	Year of last PCV7/10 or 13 vaccination
Section H Symptoms at or prior to admission (for SARI case definition)	feverish	Numeric (categorical)	0 = No	Sub-febrility (37–38°C)
			1 = Yes	
			8 = Do not know	
	fever	Numeric (categorical)	0 = No	History of fever ≥ 38°C
			1 = Yes	
			8 = Do not know	
	cough	Numeric (categorical)	0 = No	Cough
			1 = Yes	
			8 = Do not know	
	sorethroat	Numeric (categorical)	0 = No	Sore throat
			1 = Yes	
			8 = Do not know	
	sob	Numeric (categorical)	0 = No	Shortness of breath
			1 = Yes	
			8 = Do not know	
	anosmia	Numeric (categorical)	0 = No	Loss of sense of smell
			1 = Yes	
			8 = Do not know	
	ageusia	Numeric (categorical)	0 = No	Loss of sense of taste
			1 = Yes	
			8 = Do not know	
	dysgeusia	Numeric (categorical)	0 = No	Alteration of sense of taste
			1 = Yes	
			8 = Do not know	
	headache	Numeric (categorical)	0 = No	Headache
Section H *Continued*			1 = Yes	
			8 = Do not know	
	myalgia	Numeric (categorical)	0 = No	Myalgia (muscle pains)
			1 = Yes	
			8 = Do not know	
	malaise	Numeric (categorical)	0 = No	Malaise
			1 = Yes	
			8 = Do not know	
	general_deter	Numeric (categorical)	0 = No	Deterioration of general condition (including asthenia, weight loss, anorexia, fatigue)
			1 = Yes	
			8 = Do not know	

	Variable	Type	Values and coding	Definition
	onsetdate	Date	dd/mm/yyyy	Date of onset of first symptom
Section I Laboratory tests and results (SARS-CoV-2): before hospitalisation	prev_labcovid	Numeric (categorical)	0 = No	Whether patient had a prior positive COVID-19 test
			1 = Yes	
			8 = Do not know	
	prev_labcovid_type	Numeric (categorical)	1 = RT-PCR	Type of prior COVID-19 test used (for positive result above)
			2 = Serology	
			3 = Rapid test	
			4 = Other	
			8 = Do not know	
	prev_labcovid_sp	Text		Specify other type of test used
	prev_labcovid_date	Date		Date of prior positive COVID-19 test
Section J Laboratory tests and results (SARS-CoV-2): during hospitalisation	lab_covtest	Numeric (categorical)	0 = No	Whether patient was tested for SARS-CoV-2 (during hospitalisation)
			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
	swabdate_cov	Date	dd/mm/yyyy	Respiratory specimen collection date for SARS-CoV-2 testing
	lab_covid	Numeric (categorical)	0 = Negative	Laboratory result: SARS-CoV-2
			1 = Positive	
			2 = inconclusive / undetermined	
			8 = Do not know	
	seq	Numeric (categorical)	0 = No	Whether patient sample was sequenced/sent for sequencing
			1 = Yes	
			8 = Do not know	
	genetic_group	Text		Laboratory result: genetic group
Section K Laboratory tests (other respiratory viruses)	swabdate_flu	Date	dd/mm/yyyy	Respiratory specimen collection date for influenza testing
	lab_fluany	Numeric (categorical)	0 = Negative	Laboratory result: any influenza virus type
			1 = Positive	
			2 = Not done	
			8 = Do not know	
	lab_flu_type	Numeric (categorical)	1 = influenza A(H1N1)	If positive for influenza, indicate which type and subtype, if known
			2 = influenza A(H3N2)	
			3 = influenza A (untyped)	
			4 = influenza B/Yamagata	
			5 = influenza B/Victoria	
			6 = influenza B (untyped)	
			8 = Do not know	
	lab_mers	Numeric (categorical)	0 = Negative	Laboratory result: MERS-CoV

	Variable	Type	Values and coding	Definition
			1 = Positive	
			2 = Not done	
			8 = Do not know	
	lab_othcov	Numeric (categorical)	0 = Negative	Laboratory result: other coronavirus
			1 = Positive	
			2 = Not done	
			8 = Do not know	
	lab_rsv	Numeric (categorical)	0 = Negative	Laboratory result: RSV
			1 = Positive	
			2 = Not done	
			8 = Do not know	
	lab_metap	Numeric (categorical)	0 = Negative	Laboratory result: metapneumovirus
			1 = Positive	
			2 = Not done	
			8 = Do not know	
	lab_adeno	Numeric (categorical)	0 = Negative	Laboratory result: adenovirus
			1 = Positive	
			2 = Not done	
			8 = Do not know	
	resp_path	Numeric (categorical)	0 = Negative	Other respiratory pathogen patient tests positive for
			1 = Positive	
			2 = Not done	
			8 = Do not know	
	resp_path_oth	Text		Specify other respiratory pathogen
Section B Patient information/ characteristics *Optional variables*	dob	Date	dd/mm/yyyy	Date of birth (only if no age) *(optional)*
	ethnic	Numeric (categorical)		Patient's ethic group (note: codes will be country-specific) *(optional)*
	ethnic_sp	Text		Other ethnic group not specified in coding above *(optional)*
	essential_worker	Numeric (categorical)	0 = No	Whether the patient is any other type of essential worker with much human contact (e.g. teacher, police person, supermarket worker) *(optional)*
			1 = Yes	
			8 = Do not know	
	esswork_sp	Text		Specify which other type of essential worker *(optional)*
	occupation	Text		Patient's occupation, if not already captured (note: this may be collected another way, e.g. by national occupational code, depending on country) *(optional)*
	height	Numeric (integer)		Height of patient in metres *(optional)*
	weight	Numeric (integer)		Weight of patient in kg *(optional)*
	ses	Numeric (categorical)		Indicate results from socioeconomic or deprivation index used *(optional)*
Section B *Optional variables continued*	trimester	Numeric (categorical)	1 = first trimester	If patient is pregnant, indicate which trimester (if known) *(optional)*
			2 = second trimester	
			3 – third trimester	

	Variable	Type	Values and coding	Definition
			8 = Do not know	
Section C Hospital/ward, clinical course and outcomes *Optional variables*	deathcause	Numeric (categorical)	1 = died from COVID-19 2 = died from influenza 3 = died from other cause	Cause of death *(optional)*
Section D Pre-existing chronic conditions *Optional variables*	bmi	Numeric (1 d.p.)		BMI of patient (only if available in place of missing weight/height) *(optional)*
	anaemia	Numeric (categorical)	0 = No	Anaemia/chronic haematologic disease *(optional)*
			1 = Yes	
			8 = Do not know	
	asplenia	Numeric (categorical)	0 = No	Asplenia (absence of/damage to spleen) *(optional)*
			1 = Yes	
			8 = Do not know	
	liverdis	Numeric (categorical)	0 = No	Chronic liver disease (excluding cancer) *(optional)*
			1 = Yes	
			8 = Do not know	
	rendis	Numeric (categorical)	0 = No	Renal disease (excluding cancer and acute renal failure) *(optional)*
			1 = Yes	
			8 = Do not know	
	dement	Numeric (categorical)	0 = No	Dementia *(optional)*
			1 = Yes	
			8 = Do not know	
Section D *Optional variables continued*	neuromusc	Numeric (categorical)	0 = No	Neuromuscular disorder *(optional)*
			1 = Yes	
			8 = Do not know	
	rheumat	Numeric (categorical)	0 = No	Rheumatologic disease *(optional)*
			1 = Yes	
			8 = Do not know	
	stroke	Numeric (categorical)	0 = No	Stroke *(optional)*
			1 = Yes	
			8 = Do not know	
	tuberc	Numeric (categorical)	0 = No	Tuberculosis *(optional)*
			1 = Yes	
			8 = Do not know	
	chronic_other_targetcovid	Numeric (categorical)	0 = No	Whether the patient has another chronic condition which the country target for COVID-19 vaccination
			1 = Yes	
			8 = Do not know	
	chronic_other_target_flu	Numeric (categorical)	0 = No	Whether the patient has another chronic condition which the country target for seasonal influenza vaccination
			1 = Yes	
			8 = Do not know	
	chronic_other_target_sp	Text		Specify other chronic condition and whether they are targeted for COVID-19 or seasonal influenza vaccination
Section E	metform_pre	Numeric (categorical)	0 = No	Metformin *(optional)*

	Variable	Type	Values and coding	Definition
Medications for chronic medical conditions *Optional variables*			1 = Yes	
			8 = Do not know	
	steroids_pre	Numeric (categorical)	0 = No	Steroids *(optional)*
			1 = Yes	
			8 = Do not know	
	corticost_pre	Numeric (categorical)	0 = No	Corticosteroids *(optional)*
			1 = Yes	
			8 = Do not know	
	nsaid_pre	Numeric (categorical)	0 = No	NSAID (non-steroidal anti-inflammatory drugs) *(optional)*
			1 = Yes	
			8 = Do not know	
	ace_pre	Numeric (categorical)	0 = No	ACE inhibitor (angiotensin converting enzyme inhibitors) *(optional)*
			1 = Yes	
			8 = Do not know	
	arb_pre	Numeric (categorical)	0 = No	ARB (angiotensin II receptor blockers) *(optional)*
			1 = Yes	
			8 = Do not know	
	dmards_pre	Numeric (categorical)	0 = No	Biological disease-modifying anti-rheumatic drugs (DMARDs) e.g. rituximab, tocilizumab, etc. *(optional)*
			1 = Yes	
			8 = Do not know	
Section E *Optional variables continued*	chemo_pre	Numeric (categorical)	0 = No	Chemotherapy (within 6 months or currently) for cancer *(optional)*
			1 = Yes	
			8 = Do not know	
	gliclaz_pre	Numeric (categorical)	0 = No	Gliclazides (for diabetes or heart failure) *(optional)*
			1 = Yes	
			8 = Do not know	
	psychotrop_pre	Numeric (categorical)	0 = No	Psychotropic drugs (including benzodiazepine, etc.) *(optional)*
			1 = Yes	
			8 = Do not know	
	chloroq_pre	Numeric (categorical)	0 = No	Chloroquine *(optional)*
			1 = Yes	
			8 = Do not know	
	hydroxychloroq_pre	Numeric (categorical)	0 = No	Hydroxychloroquine *(optional)*
			1 = Yes	
			8 = Do not know	
	other1_pre_sp	Text		Other pre-symptomatic medication #1 *(optional)*
	other2_pre_sp	Text		Other pre-symptomatic medication #2 *(optional)*
	other3_pre_sp	Text		Other pre-symptomatic medication #3 *(optional)*
Section H Symptoms at or prior to admission (for SARI case	chills	Numeric (categorical)	0 = No	"Chills", or shivering *(optional)*
			1 = Yes	
			8 = Do not know	

	Variable	Type	Values and coding	Definition
definition) *Optional variables*	coryza	Numeric (categorical)	0 = No	Coryza *(optional)*
			1 = Yes	
			8 = Do not know	
	vomit	Numeric (categorical)	0 = No	Vomiting *(optional)*
			1 = Yes	
			8 = Do not know	
	nausea	Numeric (categorical)	0 = No	Nausea *(optional)*
			1 = Yes	
			8 = Do not know	
	tach	Numeric (categorical)	0 = No	Tachypnoea or signs of low oxygen saturation *(optional)*
			1 = Yes	
			8 = Do not know	
	abdopain	Numeric (categorical)	0 = No	Abdominal pain *(optional)*
			1 = Yes	
			8 = Do not know	
	diarr	Numeric (categorical)	0 = No	Diarrhoea *(optional)*
			1 = Yes	
			8 = Do not know	
	palp	Numeric (categorical)	0 = No	Heart palpitations *(optional)*
Section H *Optional variables continued*			1 = Yes	
			8 = Do not know	
	chest	Numeric (categorical)	0 = No	Chest pain *(optional)*
			1 = Yes	
			8 = Do not know	
	dizzy	Numeric (categorical)	0 = No	Dizziness *(optional)*
			1 = Yes	
			8 = Do not know	
	dermato	Numeric (categorical)	0 = No	Rash or other dermatological manifestation of COVID-19 *(optional)*
			1 = Yes	
			8 = Do not know	
	confusion	Numeric (categorical)	0 = No	Confusion *(optional)*
			1 = Yes	
			8 = Do not know	
Section J Laboratory tests and results (SARS-CoV-2): during hospitalisation *Optional variables*	pcr2	Numeric (categorical)	0 = No	Whether a second PCR was done (if first PCR was negative) *(optional)*
			1 = Yes	
			8 = Do not know	
	lab_covidpcr2	Numeric (categorical)	0 = Negative	Second PCR result for virus type SARS-COV-2 *(optional)*
			1 = Positive	
			8 = Do not know	

Annex 2. Detailed pooled analysis plan

Pooled analysis outline

A pooled analysis is part of the primary objectives of the ECDC study. Country will be included potentially as a fixed effect or as a random effect in a multi-level model. Statistical heterogeneity between study sites will be determined, using the Q-test and the I^2 index [30].

Cases and controls will be described by baseline characteristics, and uni- and multivariable analyses performed as described in Section 3.13.1 for individual country level analysis.

Pooled analysis plan

Descriptive analysis

The proportion of eligible hospitalised cases and controls who agreed to participate in the study will be calculated. The proportion of patients not consenting will be documented. Patients excluded will be described in a study flowchart.

Patient inclusion depends on the SARI case definition(s) used for CVE and IVE estimates. Sensitivity analyses comparing CVE and IVE estimates based on alternative SARI case definitions are planned. In the primary analysis, CVE is estimated among SARI patients as defined in Section 3.5.2, while IVE is estimated among SARI patient defined as a hospitalised person with:

- at least one systemic symptom or sign: fever or feverishness, malaise, headache or myalgia or deterioration of general condition (asthenia or loss of weight or anorexia or confusion or dizziness);

AND

- at least one respiratory symptom or sign (cough, sore throat or shortness of breath)

on admission or within 48 hours after admission. The symptoms should not have started (or clearly worsened, if chronic) more than seven days before swabbing.

Cases and controls will be described by baseline characteristics.

The main characteristics of each study will be summarised individually, and will include:

- Number of hospitals participating and catchment population;
- Beginning of vaccination campaigns for COVID-19 and for influenza vaccines;
  - Beginning of the study;
  - End of the study;
  - Vaccine product(s) used;
  - Estimated vaccine coverage in the country/region by vaccine brand, by target vaccine group;
- Number of patients screened;
- Number of patients excluded per reasons for exclusion.

Measure of effect

This study is a case–control study (test-negative design). The measure of association is an odds ratio (OR). This can be measured by logistic regression. An OR = 1 indicates no association between an exposure and the outcome. An OR>1 indicates a potential risk factor, an OR < 1 indicates a potential protective factor, noting that the confidence interval around the OR helps with its interpretation.

For vaccination as preventive factor, the VE can be computed as VE = (1 – OR)*100. A 95% confidence interval is computed around the point estimate.

Pooled univariable analyses (VE estimates from crude OR)

Baseline characteristics of cases and controls will be compared using the chi-square test, Fisher's exact test, t-test or the Mann-Whitney test (depending on the nature of the variable and the sample size). The association (OR) between vaccination status and baseline characteristics will be measured for both case and control groups.

Stratified analysis

Depending on sample size, the analysis by vaccine product will be further stratified according to:

- sex;
- age group, e.g. 0–14 years, 15–49 years, 50–64 years, 65–79 years, 80+ years;
- specific chronic conditions (e.g. respiratory disease, diabetes, immunodeficiency[9]);
- absence, presence of at least one, presence of more than one high-risk condition;
- time: this will depend on timing of the pandemic/influenza season at sites/in countries and may just include one period at the start of the study once vaccines are available, and a specified period later on;
- dose (for CVE): partial vaccination, full vaccination, full vaccination plus booster;
- swab delay (0–3 days, 4–7 days; 8+ days);
- vaccination delay (<8 days, 8–14 days, >14 days, etc.);
- hospital admission delay (0–4 days, 5–9 days, 10 days +, onset after hospitalisation);
- previous vaccination against influenza and pneumococcal disease;
- prior infection with influenza or SARS-CoV-2 (prior to hospital admission for SARI);
- current co-infection with influenza (for CVE) or SARS-CoV-2 (for IVE) or other respiratory viruses (for both CVE and IVE);
- severity (ICU admission, ventilation/oxygen, death; for CVE);
- CVE/IVE at different time points in calendar time, e.g. by week or group of weeks (e.g. CVE for weeks 2–20, 21–42, etc.; IVE for interim season (to end January), and for the whole season);
- for the various groups of vaccines (if available/applicable), mode of injection (intradermal vs intramuscular);
- use of medications for chronic conditions (e.g. statins, for IVE);
- Other stratifications may be included.

Virus variant-specific outcomes will be used, if available and feasible at the time of analysis.

A sufficient sample size should be planned in order to ensure enough individuals in each stratum for a precise estimate. Effect modification will be assessed comparing the OR across the strata of the potential effect modifiers. Confounding will be assessed by comparing crude and adjusted OR for each potential confounder.

Multivariable analysis

A multivariable logistic regression analysis will be conducted to control for negative and positive confounding. Odds ratios and standard errors will be obtained. Variables will be tested for multicollinearity. Interactions will be tested using the likelihood ratio test or Wald's test and will be included in the model if significant at the 5% level. Factors other than statistical significance (prevalence of exposure, magnitude of OR) will also be used as criteria for inclusion of a variable or an interaction term. If possible, a variable for sex, age and onset time should always be included in the model.

Continuous variables

Continuous variables in the COVID-19/influenza datasets include age, time of onset of symptoms, and hospitalisations in the past 12 months. These variables can be coded as categories (e.g. age group, week of symptom onset, etc.) However, when coding continuous variables as categories, information may be lost, or introduce residual confounding and increase the standard error of the model. Tests will be carried out to see if these variables could be coded as a linear term, polynomial or a spline. In addition, a balance will be sought between simplicity of a model (so a non-expert can understand it), precision and a model that estimates the vaccine effect with the least bias.

Identifying heterogeneity, testing for heterogeneity

Country-specific crude and adjusted ORs and their confidence intervals will be plotted in separate forest plots. Following the core protocol minimises heterogeneity between studies. However, adherence to the protocol and study design and study quality characteristics will also be checked. Other study site characteristics will be assessed where feasible, such as types of circulating virus, information on healthcare use and organisation of the vaccination campaign. A qualitative decision will then be taken if one or more studies are substantially different from the other and should be excluded from the pooled analysis.

[9] Note: Five common pre-existing conditions are currently used in pooled analyses: asthma, lung disease, heart disease, diabetes and immunodeficiency. This list may change over time, as it depends on which conditions all study sites are able to collect.

Statistical heterogeneity between studies will be tested using the Q-test and the I^2 index (see boxes for formulae below). The Q statistic follows a Chi^2 distribution (with k-1 degrees of freedom). The Q-test reports presence or absence of heterogeneity, while the I^2 index (based on the Q-statistic) quantifies the extent of the heterogeneity. According to the Higgins and Thompson classification, an I^2 index of around 25% indicates low, 50% indicates medium and 75% indicated high heterogeneity between studies.

$$Q = \sum w_i \ (\log(OR_i) - \log(OR_F))^2$$

Where:

$$w_i = 1/v_i$$

v_i is the inverse variance of the estimated log odds ratio of study i

$$\log(OR_F) = \frac{\sum w_i \times \log(OR_i)}{\sum w_i}$$

$$I^2 = \frac{Q-(k-1)}{Q} \times 100\% \quad \text{for } Q > (k-1)$$

$$I^2 = 0 \quad \text{for } Q \leq (k-1)$$

Formulae are given here for completeness, in practice these measures are automatically calculated by many statistical software packages as part of the meta-analysis commands.

One-stage pooled analysis approach

If sample sizes are too small to measure vaccine effectiveness controlling for all potential confounders for each individual study site, a one-stage pooled approach will be used for analysis.

Individual study data will be pooled into one dataset and analysed as a one-stage model with study site as a fixed effect. This could provide a large enough sample size to obtain (for example) an estimate of CVE/IVE early in the study/season with reasonable precision. However, the results of this analysis should be interpreted with caution as it assumes not only that the underlying true exposure effect is the same in all studies, but also that the association of all covariates with the outcome is the same in all studies.

Formal tests of interaction between study site and covariates will be carried out to determine if the effect of each covariate differs across studies, to test the assumptions of the one-stage pooled fixed effect analysis.

The significance of interaction terms are themselves influenced by sample size and should also be interpreted with caution. Particular care needs to be taken if heterogeneity is found between study sites when using a one-stage fixed effects approach (see above section). Reasons for heterogeneity need to be thoroughly investigated and the assumptions underlying the one-stage pooling approach need to be revisited.

Controlling for hospital effect

Primary analysis will be carried out using simple logistic regression to obtain the individual study estimates. However, there could be an effect of the hospital that is related both to the exposure (propensity to vaccinate) and the outcome (in terms of swabbing behaviour). To adjust for this cluster effect, a multi-level logistic regression with each hospital as a random effect will be carried out when using one-stage pooled analysis.

Multi-level logistic regression can also be carried out for each individual study with hospital as a random effect. The two-stage model as outlined above will then be used to obtain a summary CVE/IVE measure, using these estimates.

The same applies to stratified analyses. The point estimates and confidence intervals from the multi-level and simple logistic regression will be compared in a sensitivity analysis.

Two-stage pooled analysis approach

If adequate sample size by study is achieved to obtain an adjusted OR, then a two-stage approach to pooled analysis will be taken.

Country-specific adjusted ORs and standard errors for the effect of COVID-19/influenza vaccination obtained from the individual studies will be combined in a model that incorporates random effects of the studies, to account for unmeasured country- and hospital-specific factors that differ between countries.

The country-specific exposure-disease effects (ORs) are then weighted by the inverse of their marginal variances. The marginal variance is the sum of the individual study-specific variances and the variance of the random study effects (τ2). This will give the pooled odds ratio and standard error.

$$\log(OR_R) = \frac{\sum w_i * \times \log(ORi)}{\sum w_i *}$$

$$wi* = \frac{1}{vi + \tau^2}$$

The country-specific ORs and their confidence intervals, along with the pooled OR, will be presented graphically in a forest plot. This model will also be compared against a two-stage analysis with fixed study effects, to assess the effects of model assumptions.

If, despite the common protocol, covariates were not uniformly collected in the different studies, then an analysis will be carried out to exclude certain studies and a comparison made with the analysis, including all studies. In a different scenario, analyses can also be carried out excluding certain study participants for whom variables were collected differently.

Further analyses

Where sample size allows, further analyses will be carried out. These include:

- CVE/IVE by time since vaccination. Time since vaccination can be calculated by subtracting the date of vaccination from the date of onset. Time since vaccination can then be modelled as a continuous variable, including correction for either stable or increased rate of COVID-19/influenza over time; cumulative risk of COVID-19/influenza.
- CVE and IVE for patients with previous influenza vaccination (current influenza season) vs no previous influenza vaccination.
- IVE and CVE for patients with previous COVID-19 vaccination (within 6 months) versus no previous COVID-19 vaccination.
- If negative CVE is found in some target groups
  - assess possibility of vaccine-mediated enhanced disease (VMED), which could manifest as negative CVE, by comparing severity in vaccinated and unvaccinated patients. Results should show reduced severity among vaccinated patients; findings of increased severity in vaccinated patients could suggest VMED.
- As a sensitivity analysis, CVE/IVE will be calculated:
  - using WHO versus ECDC case definitions for SARI;
  - considering those vaccinated <X days before onset of symptoms as unvaccinated (in the main analysis these records will be excluded);
  - including SARI patients testing positive for influenza/SARS-CoV-2 in the control group;
  - including SARI patients testing positive for influenza/SARS-CoV-2 in the case group;
  - including SARI patients whose influenza/COVID-19 vaccine status is unknown in the control group;
  - using, as a control group, only SARI patients testing positive for at least one non-influenza respiratory virus/non-coronavirus;
  - considering different restrictions according to swabbing delay (e.g. <14 days, <10 days, etc.);
  - considering the sensitivity and specificity of PCR;
  - based on assumptions of previous infections;
  - excluding participants who received antivirals ≤14 days prior to swabbing;
  - excluding all participants with lab-confirmed influenza/SARS-CoV-2 at any time after symptom onset, to reduce bias.
- This can then be repeated using RSV as a sham outcome (if multiplex results are available for any sites). There should be no association between COVID-19/influenza vaccination and RSV-positivity in the absence of confounding.

Time can be input as a variable in the model to assess whether it can be an effect modifier.

Minimum sample size

Sample sizes may be very small for some sub-analyses. Different criteria can be used to determine whether the sample size is large enough to obtain a valid measure of VE;

- there are at least 10–15 cases (or controls, whichever is smaller) in the sub-analysis for crude analyses and more for adjusted analyses (e.g. at least 10 for each parameter in the model);
- there are ≥5 records in each cell of the two-by-two table of case and vaccination status;
- the precision of the estimate does not span both -200% and 90% (uninformative).

With low sample size, approaches include collapsing categories, or modelling continuous variables in a different way (if applicable). Sensitivity analyses can be carried out using penalised logistic regression.

Use of propensity scores

To limit the number of co-variables to include in the multivariable model, **if sample size allows,** estimates will be built and adjusted based on propensity scores. Propensity scores can be defined as the conditional probability of receiving the vaccine given a number of observed co-variables.

In propensity score matching, a propensity score for vaccination is calculated for cases and controls. Cases and controls are then matched by propensity score and all non-matched patients are discarded. Variables used to calculate the propensity score will include variables related to the vaccination and outcome. Care will be taken to avoid correlation and overmatching.

Annex 3. Genetic characterisation in vaccine effectiveness studies

Virus selection

Objectives

- To describe the viruses included in ECDC's COVID-19 and influenza vaccine effectiveness (CVE/IVE) studies (overall, by site and by time period), in order to identify key SARS-CoV-2/influenza virus genotypic evolution that could affect vaccine effectiveness.
- To measure genetic variant-specific CVE and (sub)type-specific IVE among study sites.

To meet these objectives, it is important that the viruses sequenced are representative of the influenza/SARS-CoV-2 viruses from cases belonging to the VE study population. To achieve this, either all or a random selection of viruses are sequenced (among those that are technically feasible to sequence). In this way the selection will be independent of vaccination or clinical outcomes.

Study sites/country will select viruses from SARI patients included in the CVE/IVE studies testing positive for SARS-CoV-2/influenza. If feasible, before virus selection, study sites/countries should verify if the influenza/SARS-CoV-2 positive cases meet the criteria used to include cases in the CVE/IVE pooled analysis (e.g. target group for vaccination, vaccination status and date documented, delay symptom onset swabbing no more than 10 days, etc.).

Proportion of SARS-CoV-2/influenza viruses to characterise sampling fraction

Each study country has different resources, different incidence and a different proportion of genetic variants circulating.

Ideally, a study site will sequence all viruses for which sequencing is technically feasible. If this is not feasible, then the proportion sequenced (the sampling fraction) will be based on the study site resources and the epidemiological/virological situation. As a minimum, we suggest study sites/countries sequence 50% of viruses for which sequencing is technically feasible, to be reviewed during the course of the pandemic.

If study sites are sequencing a proportion of viruses (as opposed to all viruses), the sampling fraction can change over time, depending on resources. For example, during peak incidence only 50% of viruses could be sequenced and during periods of low incidence all viruses could be sequenced. When sequencing a proportion of viruses it is then important to adhere to the random selection process.

The proportions sampled over time should be documented in the 'Example of sampling fraction definition' Excel spreadsheet. An example appears in Figure A1.

Figure A1. Example of how to define sampling fractions over time using the Excel spreadsheet 'Example of sampling fraction definition.xlsx'

Time period	First date of time period	Last date of time period	Sampling fraction used	Date used for definition of time unit (onset date, swab date, other)	Comments
1	01/01/2021	31/01/2021	1	Date of swab	All specimens were characterised among those technically feasible
2	01/02/2021	30/04/2021	0.5	Date of swab	50% of specimens were characterised among those technically feasible

Each study country to

- define the sampling fraction used for each time interval (if all viruses characterised, then indicate 100%);
- document the sampling fraction for each time interval in the 'Example of sampling fraction definition.xlsx' document;
- take the sampling fraction into account when measuring site-specific genetic variant-specific VE (if applicable).

Procedures for random selection of specimens to be characterised

If a study country is not genetically characterising all viruses, then the random selection proposed should be used to select the viruses included in the multi-centre study. This should be done independent of any routine virological surveillance.

As it is difficult to prospectively randomise viruses to sequence, study sites can use a list of viruses by a predefined period (e.g. each week or month) to use for randomisation.

At the end of each period defined for the selection of strains, study sites will select viruses using random selection (e.g. the Bernoulli sampling method). This method ensures that each strain has the same probability of being selected.

- Each site to define who selects the strains to sequence (e.g. team of epidemiologists, team of virologists).

Steps to randomly select strains

Step 1: Sampling frame

- Create a list of all positive cases recruited for the period that study sites/country would like to sequence (week/month).
- Viruses already characterised by the National Reference Centre (or other laboratories) during that period will be part of the sampling frame to ensure representativity.
- Viruses with low viral load will be part of the sampling frame.
- If possible, sites/countries will exclude from the sampling frame the viruses from cases that could later be excluded from any pooled analysis (e.g. target group for vaccination, vaccination status and date documented, delay symptom onset swabbing no more than 10 days, etc.).

Step 2: Randomisation

- List order all positive cases (viruses) by swab date.
- Assign a random number to each virus: the Excel function =RAND() can be used (this may be different if using a different language version of Excel).
- Copy the random number column and paste as values (this is important, otherwise they will keep changing) and then sort the list of cases (viruses) by random number in the pasted column (e.g. in order of high to low).

The STATA syntax below can be used. The example is a selection of 50% of 88 cases (44 strains to characterise).

```
sort swabdate
set seed 500
gen naleat=runiform(),
sort naleat
gen select=0
replace select=1 if _n<=44
list IDnumber strain select if select==1, noobs separator (44)
```

where 500 is the number used to set the seed. You can select another number but it is recommended that the 'set seed' be used to be able to replicate the selection.

Step 3: Selection

Based on the proportion of viruses sites/countries would like to sequence for this period (e.g. 50% or 75%), select the number of cases/viruses needed: start from the first case in the list and continue selecting the following cases until reaching the desired number (e.g. if 88 cases have been recruited in the study and the sampling fraction is 0.5, the first 44 cases in the list will be selected).

Step 4: Replacement of viruses randomly selected, but not characterised

Viruses that cannot be sequenced should be replaced using the same variant (or subtype/lineage) sampling frame. The strains will be replaced by the next ones in the list. So, for example, if 44 viruses would have been chosen from the randomised list and two are not feasible to sequence, then the viruses in the 45th and 46th line can be selected to sequence. The reasons for not sequencing selected specimens should be documented (e.g. low viral loads) and all study sites should document their Ct threshold for sequencing (if applicable).

Step 5: Increase in proportion sequenced if needed

If during the pandemic, the study site decides to increase the proportion sequenced for a given time period, it should go back to the sampling frame for that time period and continue selecting the subsequent strains from the ordered original list.

Data collected

For the viruses characterised, study sites/countries should fill in an Excel spreadsheet as shown below, with at least the following information available (see Figure A2 for an example):

- Country;
- Patient's study ID number;
- GISAID sequence database accession number;
- Selected for characterisation? (Y/N);
- Reasons for not characterising;
- If possible: Ct value;
- If possible: Type of sample (primary specimen or isolate).

Figure A2. Example of information collected on viruses using an Excel spreadsheet

Country	ID number	Reasons for no characterisation (for those selected not characterised)	Ct value clinical specimen	GISAID Accesion ID
Spain	2016128	Sequenced	20.48	EPI_ISL_691732
Spain	2016451	No product due to low viral load	31.52	N/A

Screenshot of Excel spreadsheet to collect information on proportions sequenced over time (sampling fraction):

Time period	First date of time period	Last date of time period	Sampling fraction used	Date used for definition of time unit (onset date, swab d	Comments
1					
2					
3					
4					
5					
6					
7					
8					
Example1	*01/01/2021*	*31/01/2021*	*1*	*Date of swab*	*(this is only an example;*
Example2	*01/02/2021*	*30/04/2021*	*0.2*	*Date of swab*	*(this is only an example;*

Figure A3. Example of sampling fraction definition

Screenshot of Excel spreadsheet to collect information on proportions sequenced over time (sampling fraction):

Country	ID number	Reasons for no characterisation (for those selected not characterised)	Ct value clinical specimen	GISAID Accesion ID
Spain	2016128	Sequenced	20.48	EPI_ISL_691732
Spain	2016451	No product due to low viral load	31.52	N/A

Example of genetic and antigenic analysis data

The minimum amount of data needed to obtain genetic data from GISAID (sequences of all viruses should be sent to GISAID's open access EpiCoV platform) is country, ECDC SARI VE study patient ID number and GISAID accession number. Additional information on Ct value and selection for characterisation and reasons for not characterising can also be collected (see Table A1 below).

Table A1. Example of a data collection form for genetic data

	Country	Study ID number	GISAID accession ID number	Selected for characterisation?	Reasons for not characterising?	Ct value	Type of sample (primary specimen or isolate)
Strain 1							
Strain 2							

Where only a random selection of viruses were sequenced, additional information on sampling fraction should be provided, to better understand how viruses were selected for sequencing over time. An example can be seen in Table A2 below.

Table A2. Example of document outlining how viruses were selected for sequencing over time

Period	First date of period	Last date of period	Sampling fraction	Date used for definition of time unit (onset date, swab date, other)	Comments
1					
2					
Example1	01/10/2020	31/12/2020	1	Date of onset	For example: all specimens were characterised
Example2	01/01/2021	15/02/2021	0.2	Date of onset	For example: 20% of all specimens were characterised

Annex 4. List of ICD-9 and ICD-10 codes for pre-existing chronic conditions

Category	ICD-9	ICD-10	Underlying conditions included
Anaemia	280–285	D50-64	Nutritional anaemias, Haemolytic anaemias, Aplastic and other anaemias and other bone marrow failure syndromes
Asplenia	746.87, 759.0	Q89.01, Q20.6, Z90.81	Malposition of heart, Anomalies of spleen, Isomerism of atrial appendages, Acquired and Congenital absence of spleen
Asthma	493.0, 493.1, 493.9	J45	Extrinsic asthma, Intrinsic asthma, Predominantly allergic asthma, Non-allergic asthma, Mixed asthma, Asthma unspecified
Chronic liver disease	571	K70, K72-74, K754, K769	Alcoholic liver disease, Hepatic failure, Chronic hepatitis, Fibrosis and cirrhosis of liver, Other inflammatory liver diseases
Cardiovascular diseases	093, 112.81, 130.3, 391, 393–398, 402, 404, 410–429, 745, 746, 747.1, 747.49, 759.82, 785.2-3	A52.01, B37.6, B58.81, I05-9, I11, I13, I20-25, I26.09, I26.9, I27, I30-51, I97.0-1, R00.1, T81.718A, T81.72XA, T82.817A, T82.818A, Q20-24, Q25.1-2, Q26.0-1, Q26.8, Q87.4, R01.1-2	Syphilitic aneurysm of aorta, Candidal endocarditis, Toxoplasma myocarditis, Chronic rheumatic heart diseases, Ischemic heart diseases, Hypertensive heart and chronic kidney disease, pulmonary embolism with acute cor pulmonale, pulmonary heart diseases, diseases of pulmonary vessels, Other forms of heart disease (including Nonrheumatic valve disorders, pericarditis, endocarditis, myocarditis, cardiomyophathy, heart failure, block, cardiac arrhythmias, heart failure), Complication of other artery / vein following a procedure, Embolism of cardiac/vascular prosthetic devices, implants and grafts, congenital malformations of cardiac chambers and connections or heart, Coarctation or atresia of aorta, Congenital malformations of great veins, Marfan's syndrome, Cardiac murmur
Diabetes	250	E10-11	Type 1 and Type 2 diabetes mellitus
Hypertension	401, 401.0, 401.9, 405, 405.91, 405.99,	I10, I15.8, I15, I15.1, I15.2, I97.3, I27.0	Hypertension (essential and secondary), Secondary to other [renal or endocrine] disorders, Malignant hypertension
Obesity	27800, 278.01, 278.03	E66.01, E66.2, E66.9	Obesity
Immunodeficiency* or organ transplant	042, 279, V08, V42	B20, D80-84, D89.8-9, Z21, Z94	HIV, immune deficiency, organ or tissue replaced by transplant
Neuromuscular disorders	358.00-358.1, 358.8, 358.9, 378.73, 775.2	G70-G70.01, G70.2, G70.80, G70.81, G70.9, G70.89, G73.7,	Myasthenia gravis, Myoneural disorders NEC/NOS, Neuromuscular disease strabism, Congenital and developmental myasthenia, Lambert-Eaton syndrome, Myoneural disorder NOS
Renal disease	274.1, 408, 580–591, 593.71–593.73, 593.9	M10.30, N00-19, N20.0, N28.9	Gout due to renal impairment, Glomerular diseases, Renal tubulo-interstitial diseases, Acute kidney failure and chronic kidney disease, Calculus of kidney, Disorder of kidney and ureter, unspecified
Dementia	290, 294, 331	F01, F03, F05, G30, G31, G91, G94	Vascular dementia, other dementia, Delirium due to known physiological condition, Alzheimer's disease, Other degenerative diseases of nervous system
Stroke	348, 438	G93, I67.83, I69	Brain disorders, Posterior reversible encephalopathy syndrome, Sequelae of cerebrovascular disease
Rheumatologic diseases	446, 710, 714	M30-34, M35.0, M35.5, M35.8-9, M05-06, M08, M12.00	Polyarteritis nodosa and related conditions, Other necrotising vasculopathies, Systemic lupus erythematosus (SLE), Dermatopolymyositis, Systemic sclerosis, Sicca syndrome, Multifocal fibrosclerosis, other systemic involvement of connective tissue, Rheumatoid arthritis with rheumatoid factor, Other rheumatoid arthritis, Juvenile arthritis, Chronic post-rheumatic arthropathy
Cancer	140–208	C00-96	Malignant neoplasms and neuroendocrine tumours

Category	ICD-9	ICD-10	Underlying conditions included
Lung disease	011, 490–511, 512.8, 513–517, 518.3, 518.8, 519.9, 714.81	A15, J40–47, J60–94, J96, J99, J182, **M34.81, M05.10**	Respiratory tuberculosis, Bronchitis, not specified as acute or chronic, Chronic bronchitis, Emphysema, Other chronic obstructive pulmonary disease, Asthma, Bronchiectasis, Hypersensitivity pneumonitis due to organic dust, Pneumoconiosis, Airway disease due to specific organic dust, Hypersensitivity pneumonitis due to organic dust, Respiratory conditions due to inhalation of chemicals, gases, fumes and vapor, Pneumonitis due to solids and liquids, Respiratory conditions due to other external agents, Acute respiratory distress syndrome, Pulmonary oedema, Pulmonary eosinophilia, not elsewhere classified, Other interstitial pulmonary diseases, Abscess of lung and mediastinum, Pyothorax, Pleural effusion, Pneumothorax and air leak, Other pleural conditions, Intraoperative and postprocedural complications and disorders of respiratory system, not elsewhere classified, Other diseases of the respiratory system, Hypostatic pneumonia, unspecified organism, **Systemic sclerosis with lung involvement, Rheumatoid lung disease with rheumatoid arthritis**
Tuberculosis		A15–A19	Primary respiratory tuberculosis, Respiratory tuberculosis unspecified, Tuberculosis of nervous system, Tuberculosis of other organs, Miliary tuberculosis

**Note: patients who are only treated with glucocorticoids and have no other immune deficiency, are considered immune suppressed when treated with high-dose corticosteroids (≥ 20 mg/day of prednisone or equivalent for ≥2 weeks) in the last three months.*

Annex 5. Study-specific annexes

The study specifications for each study site are summarised in the annexes. Each study site annex should include:

- the setting of the influenza and COVID-19 surveillance for IVE and CVE studies (number of hospitals included, catchment population if possible);
- description of target group(s) for vaccination and order/timeline of vaccination by group (when known), for the vaccine products used, including recommendations for delay between booster doses (if applicable);
- description of the epidemiological situation (incidence, number of influenza or COVID-19 cases)
- definition of the beginning of the study period for the IVE/CVE study (date/month/year), if applicable/possible;
- case definitions used for the IVE and CVE studies and procedures to select SARI patients;
- country procedures for oral or written informed consent;
- study sites measuring CVE to indicate which testing strategy they will use (testing all samples for both SARS-CoV-2 and influenza, or only testing for influenza in those negative for SARS-CoV-2);
- whether testing for other respiratory viruses will be carried out, or only SARS-CoV-2 and influenza (or only SARS-CoV-2);
- description of the laboratory procedures (samples taken, storage, transport), tests and the kits used (and their sensitivity, specificity, PPV) for influenza virus and SARS-CoV-2 and, if needed, other respiratory virus detection:
  - each study site to describe if the laboratory participates in QA/QC (Quality Assurance/Quality Control) schemes;
  - each study site to describe the selection of specimens and the methods for genetic and antigenic characterisation (when it becomes available).
- description of the safety measures carried out, related to swab procedures, handling of biological specimens, transport of samples, authorisation levels of biologists, biosafety levels of laboratories, etc.
- description of the vaccination variables being collected;
- each study site to document:
  - the vaccine products used;
  - if no precise dates of vaccination collected, the variable allowing a patient to be defined as vaccinated or unvaccinated.
- definitions of variables collected and the sources of information used for each variable collected:
  - study sites to provide a codebook that includes the variable names, variable descriptions, and the coding of variable values (see also Annex 1).
- description of procedures of data collection and entry, specification of methods of data storage and their compliance with the GDPR requirements. Study sites to describe how and who performs the database pseudonymisation/anonymisation prior to local data analysis. Each study site to describe the procedures to comply with the national ethics committee requirements and the type of informed consent needed as well as whether consent can be obtained for a legal tutor. Each study site to send a copy of the ethical approval to the coordinating centre.
- description of the provision of training of hospital study teams;
- documentation of any changes in influenza/ COVID-19 surveillance during the study period;
- description of the potential limitations and representativeness of the subjects included;
- description of the recommendations of rapid antigen test use over time and by age group (if relevant)
  - study sites to describe the availability of rapid tests and any recommendations around PCR confirmation of tests.

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