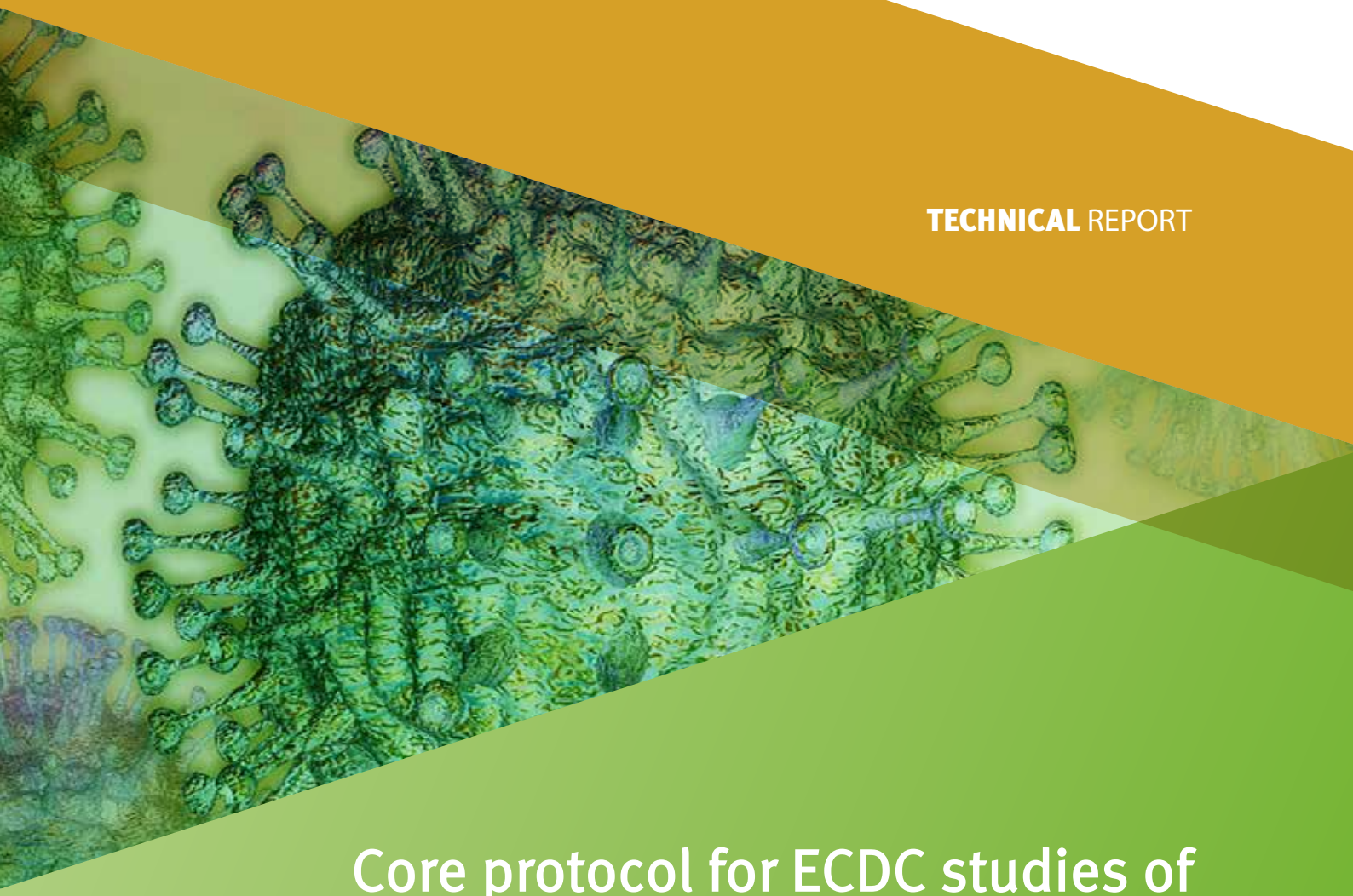

TECHNICAL REPORT

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 2.0

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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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Acknowledgements
The following names are of those currently participating in the hospital study (for experts who participated in the first ECDC expert meeting on COVID-19 VE studies on 29 January 2021, please see core protocol v01).

Cyril Barbezang,e Nathalie Bossuyt, Sarah Denayer, François Dufrasne, Sébastien Fierens, Melissa Vermeulen (Sciensano, Belgium); Thomas Demuyser, Xavier Holemans, Benedicte Lissoir, Lucie Seyler, Els Van Nedervelde (Universitair Ziekenhuis Brussel, Belgium), (Grand Hôpital de Charleroi, Belgium); Marieke Bleyen, Door Jouck, Koen Magerman, (Jessa Ziekenhuis, Belgium); Marc Bourgeois, Benedicte Delaere (Université catholique de Louvain, Belgium); Evelyn Petit, Marijke Reynders (Algemeen Ziekenhuis Sint-Jan Bugge-Oostende, Belgium); Nicolas Dauby, Marc Hainaut (CHU Saint-Pierre, Belgium); Maja Ilić, Pero Ivanko, Zvjezdana Lovrić Makarić, Iva Pem Novosel, Goranka Petrović, Petra Smoljo, Irena Tabain (Croatian Institute of Public Health, Croatia); Diana Nonković (Teaching Public Health Institute of Split-Dalmatia County, Croatia); Petr Husa, Lenka Součková (University Hospital Brno, Czechia); Hana Orliková (National Institute of Public Health, NIPH, Czechia); Anna Maisa, Isabelle Parent, Sibylle Bernard-Stoecklin (Santé Publique, France); Odile Launay, Zineb Lesieur, Liem Luong, Claire Rekacewicz, Yacine Saidi (REIVAC, France); Silke Buda, Ralf Dürrwald, Ute Preuß, Janine Reiche, Kristin Tolksdorf, Marianne Wedde (Robert Koch Institute, Germany); Annamaria Ferenczi, Krisztin J Horváth, Beatrix Oroszi (Semmelweis Univeristy, Hungary); Lisa Domegan, Róisín Duffy, Joan O'Donnell (Health Protection Surveillance Centre, Health Service Executive, Ireland); Giedre Gefenaite, Indrė Jonikaitė, Monika Kuliešė, Aukse Mickiene, Roberta Vaikutytė (Lithuanian University of Health Sciences); Françoise Berthet, Ala'a Al Kerwi (National Health Directorate, Luxembourg); Myriam Alexandre, Nassera Aouali, Guy Fagherazzi (Luxembourg Institute of Health); Marc Simon (Centre Hospitalier Luxembourg); Maria-Louise Borg, John Paul Cauchi, Ausra Dziugyte, Tanya Melillo (Ministry of Health, Malta); Verónica Gómez, Raquel Guiomar, Irina Kislaya, Ausenda Machado, Ana Paula Ambrósio Rodrigues (Instituto Nacional de Saúde Doutor, Portugal); Mihaela Lazar, Odette Popovici ('Cantacuzino' National Military-Medical Institute for Research and Development, Romania); Isabela Ioana Loghin (Clinical Hospital of Infectious Diseases and University of Medicine and Pharmacy 'Gr. T. Popa', Iasi, Romania); Corneliu Petru Popescu (Dr Victor Babes Clinical Hospital of Infectious and Tropical Diseases, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania); Grupo SiVIRA de vigilancia y efectividad vacunal (Acute Respiratory Infections Surveillance System, Spain); Iván Martínez-Baz, Cristina Burgui, Itziar Casado Buesa, Jesús Castilla (Instituto de Salud Pública y Laboral de Navarra – IdiSNA – CIBERESP, Spain).

The following ECDC staff provided substantial input during the production/revision of the document (alphabetical order): Karam Adel Ali, Sabrina Bacci, Piotr Kramarz and Nathalie Nicolay.

This core protocol is based on 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 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).

Suggested citation: European Centre for Disease Prevention and Control. Core protocol for ECDC studies of vaccine effectiveness against hospitalisation with Severe Acute Respiratory Infection laboratory-confirmed with SARS-CoV-2 or seasonal influenza - Version 2.0. Stockholm: ECDC; 2023.

Stockholm, January 2023

ISBN: 978-92-9498-615-3
doi: 10.2900/69245
Catalogue number TQ-07-23-040-EN-N

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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 week 39, 2022, over 168 million cases and more than 1.1 million deaths had been reported in the European Union/European Economic Area (EU/EEA) [1]. As of December 2022, seven vaccines had been authorised by the European Commission based on the scientific opinion of the European Medicines Agency (EMA) for use in the European Union (Comirnaty, COVID-19 Vaccine Valneva, Nuvaxovid [previously Novavax], Spikevax [previously COVID-19 vaccine Moderna], Vaxzevria [previously AstraZeneca], and Jcovden [previously Covid-19 Vaccine Janssen] and VidPrevtyn Beta (indicated as a booster)) and three adapted vaccines had been authorised as boosters (Comirnaty Original/Omicron BA.1, Comirnaty Original/Omicron BA.4-5, Spikevax bivalent Original/Omicron BA.1). Many other vaccines 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 European Medicines Agency (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), 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 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.

ECDC already began building infrastructure to perform COVID-19 vaccine effectiveness (CVE) studies in 2020, using the lessons learned from other vaccine effectiveness studies. 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 vaccine effectiveness against hospitalisation with Severe Acute Respiratory Infection laboratory-confirmed with SARS-CoV-2 or with influenza, version 2.0, represents an update to the main elements for a multi-country hospital-based study of COVID-19 vaccine effectiveness in patients hospitalised with Severe Acute Respiratory Infection (SARI), already published as version 1.0 [8]. This version includes a section on influenza vaccine effectiveness, outlining the agreed methods for collecting data related to SARS-CoV-2 and influenza infections at country level, and including a plan for 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. The study period runs during the influenza circulation season for influenza vaccine effectiveness study. It would be beneficial if those countries only measuring vaccine effectiveness (VE) for COVID-19 also test for influenza during the influenza season, as well as 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 the conduct of vaccine effectiveness studies, using this protocol as a basis, 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.

This document represents version 2.0 of the core protocol, and succeeds version 1.0, which has already been adapted and implemented at country level. Results from the implementation of the VEBIS multi-country study from version 1 are available publicly on ECDC's website[1]. This document and its country-level adaptations will continue to be updated and revised on a regular basis.

[1] https://www.ecdc.europa.eu/en/covid-19/prevention-and-control/vaccines

1 Background

1.1 Context: COVID-19

The end of 2019 saw the emergence of a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19) with substantial disease burden [1].

As of December 2022, seven of the originally authorised COVID-19 vaccines and three adapted vaccines for use as boosters had received conditional marketing authorisation from the European Commission (EC) based on the scientific opinion of the European Medicine Agency (EMA) (Table 1) [2,9].

Table 1. COVID-19 vaccines authorised and used in the EU/EEA, as of December 2022

Vaccine	Age of recommendation	Primary dose regimen	Booster dose
Vaxzevria (AZD1222)	18+ years	Two doses given between four and 12 weeks after the first dose.	A booster dose may be given at least three months after the second dose.
Comirnaty (BNT162b2) 30 micrograms per dose (12+ years), 10 micrograms per dose (5-11 years), 3 micrograms per dose (six months – four years).	Six months and above	Two doses three weeks apart in individuals aged five years and above. Three doses. In children from six months to four years, the first two doses are given three weeks apart, followed by a third dose given at least eight weeks after the second dose.	May be given as a booster given at least three months after the second dose in individuals aged 12+ years. May be given as a booster at least six months after the second dose of primary vaccination in individuals aged 5-11 years.
Comirnaty Original/Omicron BA.1	12+ years	No	May be given as a booster at least three months after the second dose in individuals aged 12+ years. May be given as a booster at least six months after the second dose of primary vaccination in individuals aged 5-11 years May be given as a second booster to those aged 12+ years three months after first booster.
Comirnaty Original/Omicron BA.4-5	Five years and above	May be given for primary vaccination in non-immune individuals.	May be given at least three months after primary vaccination or a booster dose with a COVID-19 vaccine to those aged 12+ years. May be given as a booster dose three months after primary vaccination or first booster in those aged five years and over.
Jcovden (Ad26.COV 2.5)	18+ years	Single dose	May be used as booster dose given at least two months after the first dose of Jcovden.
Spikevax (mRNA-1273) 50 micrograms per dose (12+ years) 25 micrograms per dose (six months - five years)	Six months and above	Two injections 28 days apart.	May be given as a booster at least three months after the second dose in individuals aged 12+ years.
Spikevax bivalent Original/Omicron BA.1 50 micrograms per dose (12+ years) 25 micrograms per dose (six months - five years).	Six years and above	No	May be given to adults and children from six years, at least three months after primary vaccination or a booster dose with a COVID-19 vaccine.
Spikevax bivalent Original/Omicron BA.4-5,	12+ years	No	May be given to adults and children from six years, at least three months after primary vaccination or a booster dose with a COVID-19 vaccine.
Nuvaxovid (NVX-CoV2373)	12+ years	Two doses given three weeks apart.	May be used as a booster in adults who have had Nuvaxovid, an mRNA vaccine or an adenoviral vector vaccine as their primary vaccination.
VidPrevtyn Beta	18+ years	No.	May be used as a booster dose at least four months after a previous mRNA or adenoviral vector COVID-19 vaccine.
COVID-19 vaccine Valneva (inactivated, adjuvanted) (VLA2001).	18 to 50 years	Two doses given four weeks apart.	No.

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 [10]. 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 [11].

1.2 Context: 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 [12]. 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 [13,14].

Influenza viruses undergo frequent genetic and antigenic changes and vaccine-induced immunity usually does not last more than 6–12 months (sometimes less). As a consequence, 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.

Influenza VE is only partially correlated with the degree of virological match between the virus strains included in the vaccine and the circulating strains in an influenza season or a pandemic. Immunological correlates of protection are not well defined. As a consequence, EMA has stopped requiring annual immunogenicity studies from vaccine producers prior to marketing their products, and now requires brand-specific IVE data [3]. Although it recognises the challenges in collecting brand-specific data for every product and season, EMA expects that results of effectiveness studies by brand will contribute important information to the overall clinical evidence available for each influenza vaccine, especially new vaccines. Results of vaccine effectiveness studies may yield potential signals that require further investigation to determine the drivers of estimated effectiveness, facilitating the consideration of regulatory actions [3].

With the exception of some of the 2009 pandemic vaccines and of some new vaccine formulations (live attenuated influenza vaccine (LAIV)), seasonal trivalent and quadrivalent influenza vaccines may be authorised nationally. The available vaccine products, the target groups for vaccination and vaccination coverage all vary across countries. New vaccines are being developed for which limited or no effectiveness data are yet available in the EU. Several studies suggest that adjuvanted vaccines are more immunogenic against seasonal influenza than non-adjuvanted in the elderly population, but their protective effect against clinical disease is unclear. A comparison by vaccine type (adjuvanted vs non-adjuvanted, live attenuated vs inactivated, egg- vs cell-based), group (split virion, subunit, etc.) and product (vaccine brands) would provide essential information for vaccine recommendations and health economic assessments.

Early-season IVE by product and influenza type/subtype is also critical for the WHO vaccine composition meeting discussions, in order to formulate vaccine selections for the subsequent season. A lack of early season IVE results could also result in a failure to use alternative measures (antivirals as a preventive measure if there are low IVE estimates), leading to increased disease burden and costs.

Two questions have recently been raised and the answers to these may modify our understanding of influenza immunology, the vaccines needed to prevent influenza and the recommended strategies required. The first question is to understand why the measured IVE decreases during some influenza seasons [15-18]. Potential explanations are the respective role of amino acid substitutions in widely circulating viruses during the season and the potential decreasing protection conferred by seasonal vaccines given from October each season. In addition, for influenza A(H3N2) there is an issue with egg- versus cell-based vaccines. It has been observed that mutations that emerge during cultivation of the virus for vaccine manufacturing may affect VE. The second question is to understand if, and how, former seasonal influenza vaccinations modify the effectiveness of current seasonal vaccines [19,20]. Long-term multi-centre studies are needed, allowing for the early and late season measurement of IVE, with a sufficient sample size to be able to answer these questions.

1.3 ECDC CVE and IVE 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 [4]. This 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 such 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 already began building infrastructure to perform COVID-19 vaccine effectiveness (CVE) studies in 2020, using the lessons learned from other vaccine effectiveness studies (Table 2). 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 the effectiveness studies is also one of the key features, with a progressive inclusion of further countries foreseen over time.

Table 2. Type of studies and settings within the VEBIS infrastructure, as of November 2022

Setting	Type of study	Main outcome	References
Hospitals	Test negative design	Severe disease; influenza and COVID-19	[8,21-24]
Healthcare workers cohort	Cohort study	Infection, COVID-19	[25,26]
Electronic healthcare databases	Cohort study	Hospitalisation, death, COVID-19	[27]
Primary care	Test negative design	Moderate disease (~ARI/ILI), influenza and COVID-19	[28]

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 update, including estimation of influenza vaccine effectiveness (IVE), is presented in this document as version 2.0.

1.4 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 2.0, 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 the aim of implementing 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[2]. Through the Member States hospitals have been recruited that are capable of applying the core protocol and therefore contributing to the EU-level monitoring of CVE and ultimately IVE. Each study site has been identified through a process involving ECDC's relevant National Coordinator[3].

This core protocol is therefore primarily intended to guide the implementation of ECDC-funded studies. However, ECDC encourages the conduct of VE studies, using this protocol as a basis, 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.

[2] 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).

[3] 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

This document presents version 2.0 of the core protocol. Version 1.0 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.

2 Objectives

2.1 Primary objective

The primary objective is to measure, within each European country/site participating in both CVE and IVE[4] and in a pooled, multi-country analysis, 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. 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.

- ➢ 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.

[4] Countries only participating in COVID-19 vaccine effectiveness studies can ignore references to measurement of influenza vaccine effectiveness throughout the document.

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, belonging to the target group for vaccination, 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 once COVID-19 vaccine is available for each target group and SARS-CoV-2 is circulating in the participating country. In order to determine SARS-Cov-2 variant dominance, ECDC surveillance data on variants of concern can be used.

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 and it finishes at the end of the influenza period. Cases and controls are included from the week of onset of the season's first influenza-positive case in each country-specific study. Each country/study site should clearly describe the criteria used to define the beginning and the end of the influenza circulating period.

Participating hospitals carry out the 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 and for the general population.

3.4 Outcomes

CVE 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).

IVE 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 as co-infected with SARS-CoV-2 (where possible).

3.5 Definitions

3.5.1 Hospitalised patient

A hospitalised patient is a SARI patient 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; **or**
- 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[5]. Compared with the World Health Organization (WHO) SARI case definition[6] (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 (confirmed cases: CVE)

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 (confirmed cases: IVE)

A confirmed influenza case will be defined as a hospitalised patient fulfilling the SARI case definition, with a respiratory sample PCR-positive for influenza[7].

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 (for CVE) by PCR on admission to hospital or a respiratory sample negative for influenza (for IVE) [27,28].

It is advised that all sites test for both SARS-CoV-2 and influenza during 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).

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

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

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

Controls that are negative by PCR but have Ct results suggestive of COVID-19[8], 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 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.

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).

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

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 or serology 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;
- 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).

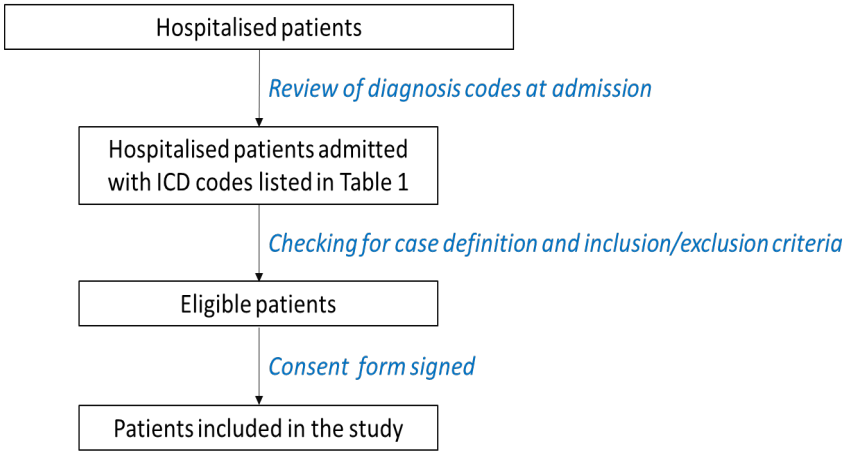
3.6 SARI patient identification – algorithm for patient inclusion

The 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

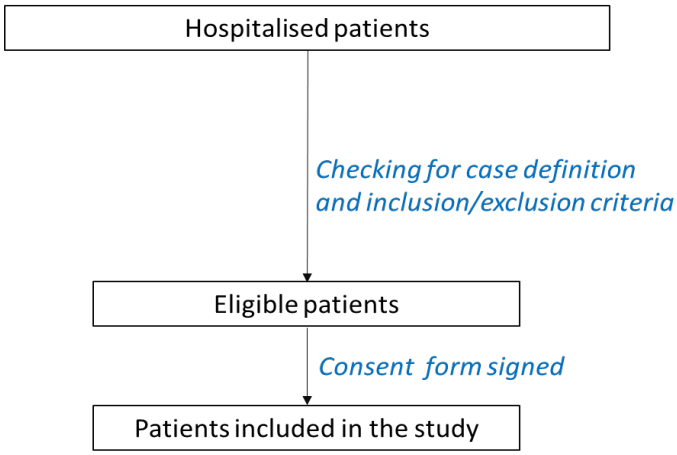
For hospitals with electronic patient records and/or diagnosis codes commonly displayed, SARI-related ICD codes (or other codes used for SARI surveillance) may be used. Patients admitted with any of the ICD codes listed in Table 3 will be approached; those meeting the SARI case definition and the inclusion 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 retrospectively the reasons for testing.

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

In the event of test scarcity, extreme workloads, 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 3. List of diagnosis codes for which patients could be screened for onset of SARI symptoms, COVID-19/influenza 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

Category	Morbidity	ICD-9	ICD-10
	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.[9]

- 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 presence of human cells in the respiratory specimens.

ECDC's recommendation ford 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.

[9] 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]

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

Current pandemic COVID-19 vaccine

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

- **Fully vaccinated with a primary course plus booster(s)** (two-dose vaccine): SARI patients will be considered fully vaccinated with booster(s) if they have **received both doses followed by booster dose(s)** at least 14 days[10] before SARI symptom onset.
- **Fully vaccinated with a primary course** (two-dose vaccine): SARI patients will be considered fully vaccinated if they have **received both doses** at least 14 days* before SARI symptom onset.
- **Fully vaccinated with a primary course** (single-dose vaccine): SARI patients will be considered fully vaccinated if they have **received one dose** at least 14 days* before SARI symptom onset.
- **Partially vaccinated** (two-dose vaccine only): SARI patients will be considered partially vaccinated if they have **received one of two doses** at least 14 days* before SARI symptom onset.
- SARI patients will be considered as **unvaccinated** if they **did not receive COVID-19 vaccine or** if they **were vaccinated after onset** of symptoms.

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 in light of evolving decisions related to vaccination programmes, such as the use of different products for subsequent doses as well as additional doses.

Current seasonal influenza vaccine

- A SARI patient will be considered as **vaccinated** against influenza with any vaccine during the current season if he/she has received at least 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 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 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.

[10] 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. If any patients were vaccinated earlier or later than recommended by manufacturers, sensitivity analyses will be performed for differing delays between first and second dose.

3.9 Potential confounding factors and effect modifiers

3.9.1 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. List of 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	Rheumatologic diseases
Obesity ***or***	Stroke
• height and weight, ***or***	Tuberculosis
• BMI[11] (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, and describe what the sources of information for these will be.

3.9.2 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.

3.9.3 Ethnicity (optional for CVE; not required for IVE)

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).

[11] Obesity defined as BMI>29.

3.9.4 Medication status for chronic condition(s) (optional for CVE; for IVE: statin use only)

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.

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); or
  - onset of SARI symptoms (for unvaccinated individuals: for the analysis measuring the effect of chronic medications on COVID-19); or
  - 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.

3.9.5 Chronic medication use status ascertainment (optional for CVE; not required for IVE)

The medication history includes the date the patient started the medication(s) where known; otherwise just the year, if the patient was known to have been on medication before vaccination or symptom onset, or if the precise date is unknown. If both of these are unknown, then a simple yes/no response will be used as to whether the patient was on the chronic medication before hospitalisation. In addition, medication history will include medication brand name, dose, and number/ frequency of doses.

The sources of information for chronic medication status may include:

- consultation of the patient's hospital record;
- interview with the patient's GP;
- interview with the patient's pharmacist;
- data from the patient's insurance company showing evidence of pharmacy delivery or re-imbursement for chronic medication during the relevant period;
- interview with the patient and/or his/her relatives.

➢ Each study site/country will define chronic medication use based on the data collected.
➢ Each study site/country to describe how chronic medication status ascertainment will be performed.

3.9.6 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).

3.9.7 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).

3.9.8 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.

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

3.9.9 Other occupations (optional for CVE; not required for IVE)

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 (optional).

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

3.9.10 Other vaccinations

It is important to collect information on vaccinations received for pneumococcal disease (pneumococcal polysaccharide vaccine (PPV) and pneumococcal conjugate vaccine (PCV)), where available. For study countries that are not participating in IVE, information on previous influenza vaccination (including date of vaccination) will also be collected.

Previous pneumococcal vaccinations (and influenza vaccination, for study countries not participating in IVE)

Date of prior influenza vaccination and year of vaccination against pneumococcal disease are part of the data collection.

The sources of information for these vaccinations may include:

- vaccination registry;
- consultation of the patient's vaccination card/certificate;
- interview with the patient's GP;
- interview with the patient's pharmacist;
- data from the patient's insurance company showing evidence of pharmacy delivery or re-imbursement of the vaccine during the relevant period;
- interview of the patient and/or his/her relatives;
- self-reported vaccination status via photo on mobile phone.

➢ Each study site/country to indicate whether vaccination information (including date of vaccination) will be available for influenza and/or pneumococcal disease.
➢ Each study site/country to describe how previous influenza/pneumococcal vaccination status is documented.

3.9.11 Antiviral administration

The use of antivirals[12] prior to swabbing may lead to misclassification biases. Sensitivity analyses are planned to exclude patients who were administered antivirals prior to swabbing, and to document whether the patients received any antiviral treatment in the two weeks preceding symptom onset and the type (curative or preventive) of antivirals received.

➢ Each study site/country to list any antivirals administered.

3.9.12 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. Respiratory Syncytial Virus (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).

3.9.13 Setting (long-term care facilities versus community)

Older and vulnerable populations, already at greater risk of severe disease, are often situated in localised settings such as long-term care facilities (LTCF), where they are more at risk of localised outbreaks than residents in the general community (as was observed in the early phase of the pandemic, when there were many hospitalisations of people in long-term care). It is also possible, however, that an entire LTCF (residents and staff) is vaccinated, providing them with less chance of exposure than the general population. Stratifying by setting (LTCF versus community) will help to adjust for differences between SARI patients who are LTCF residents and those who are not.

➢ Each study site/country to ensure setting is captured, particularly for SARI patients aged over 64 years.

3.9.15 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. Study participants should be asked about prior test results and prior symptoms to determine possibility of prior infection. A sensitivity analysis will be conducted by excluding individuals with prior infection.

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

[12] Types of antivirals will be determined as more research becomes available.

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 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 focussing 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 5 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

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	0.6	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
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

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	0.70	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
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 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 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.

3.12 Collected information

Collected information falls under the following main categories:

- study identification
  - country, hospital;
  - vaccination target groups;
  - first ward of referral;
  - ICU/other ward of admission.
- Patient characteristics (ethnic group optional)
- SARI signs, symptoms
  - current;
  - previous clinical symptoms (if no prior tests done).
- Other symptoms (optional)
- Dates
  - vaccination (COVID-19, influenza, pneumococcal disease);
  - onset of SARI symptoms;
  - admission, discharge;
  - swabbing.
- Laboratory
  - type of swab/sample (nasopharyngeal/sputum, etc.) (optional);
  - type of test;
  - results (including information from antigenic and genetic analysis, where available);
  - previous positive PCR for SARS-CoV-2/influenza or antigen test for SARS-CoV-2, if feasible (for sensitivity analyses).
- Underlying chronic conditions, including obesity (see Sections 3.9.1–3.9.5)
  - use of medications for chronic conditions (optional);
  - number of hospitalisations for chronic conditions in the previous 12 months (optional);
  - number of GP consultations in the previous 12 months (optional).
- Presence of other respiratory viruses infection (see section 3.9.12).
- Vaccination and antivirals (see Sections 3.8 and 3.9.10–3.9.11)
  - COVID-19 vaccination including number of doses, date, product/brand;
  - influenza vaccination from the current and two previous seasons;
  - pneumococcal vaccination status, type of vaccine and either date or year of vaccination *(optional)*;
  - antiviral administration.
- Setting (e.g. LTCF)
- Socioeconomic status (SES)/deprivation (optional)
- Outcome.

COVID-19 vaccine data collected will be revised as more information on the vaccine(s) and target groups becomes available.

These are described in more detail below (see also Annex 1 for a complete variable list including coding).

3.12.1 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).

3.12.2 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.

3.12.3 Patient characteristics

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

- Age;
- Sex;
- Smoking history (see Section 3.9.5);
- Pregnancy status;
- Healthcare worker status;
- Occupation (optional);
- Ethnic group (optional);
- SES/deprivation (optional).

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

3.12.4 Clinical characteristics (symptoms and markers of severity)

The following clinical characteristics and markers of disease severity should be documented:

The four following key symptoms which are part of the WHO and ECDC COVID-19/influenza case definitions:

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

The following three symptoms 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 four symptoms should also be collected:

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

The following 14 symptoms are **optional** for the hospital-based CVE study:

- coryza, rhinitis;
- 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.

Date of first key symptom onset should be collected, as well as information on COVID-19/influenza test(s) and laboratory results, including information on antigenic and genetic analysis, if available. It is vital that this information is collected, as well as **date of vaccination**, **date of swab or date sample obtained** (to allow estimation of and stratification by delay from swab to onset), **date of admission** (to allow estimation of and stratification by time from onset to hospitalisation, and to measure length of hospital stay), and **date of discharge/death** (to allow the length of hospital stay to be measured.)

3.12.5 Case definition

Collection of good-quality symptom information is crucial for the CVE/IVE studies to be able to validate the case definition used. As a minimum, there is a need to collect data on the symptoms required for the SARI case definition. The following variables are imperative for application of the SARI case definition:

- fever or feverishness
  - if fever: measured fever (with temperature), or feverishness (to allow sensitivity analyses with other SARI case definitions);
- cough;
- shortness of breath;
- sudden onset of anosmia;
- sudden onset of ageusia;
- sudden onset of dysgeusia;
- onset date;
- admission date.

3.12.6 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. 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.

3.13 Data analysis

3.13.1 Individual (country /site level) analysis

Cases and controls will first be described by baseline characteristics. The timing to conduct each interim analysis will depend on the time needed to achieve the appropriate sample size; 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.

Patients will be described according to:

- sex;
- age group;
- healthcare worker status;
- time: month of symptom onset;
- COVID-19/influenza vaccination status;
- symptoms;
- absence/presence of at least one, presence of more than one high-risk condition;
- specific chronic conditions (e.g. respiratory, cardiovascular diseases);
- pregnancy, smoking status;
- pneumococcal vaccination status;
- 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;
- vaccination status, with vaccinated patients described by vaccine product.

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

This study is a case–control study (test-negative design). The measure of association is an 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 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 in Table 7 can be used (variables presented just as example of the output format). Useful information includes numbers of cases and controls (overall and vaccinated) and presentation of results for different models.

Table 6. Example of descriptive table for cases and controls; COVID-19/influenza hospital-based vaccine effectiveness study, ECDC multi-centre study, 2021

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
Healthcare worker	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.		

Table 7. Sample table - vaccine effectiveness against COVID-19/influenza adjusted for various co-variables by age group, hospital-based COVID-19/influenza vaccine effectiveness ECDC multi-centre study, 2022

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 Pooled analysis

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 using the Q-test and the I^2 index [33].

3.14 Personal data protection

Each country conducting the study shall comply with requirements stemming from data protection legislation and 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 stronger 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 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 be 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 prior 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 either by PCR or by serological tests.

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

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

It is possible that SARI patients who are also influenza-positive will be unsuitable controls for CVE, and those who are also SARS-CoV-2-positive will be unsuitable controls for IVE. There is limited information on co-infection with influenza and COVID-19 from the first wave of the pandemic in Europe, partly due to the timing of the pandemic being towards or after the end of the 2019–20 influenza season in many countries. The low number of co-infections described in the literature [34,35] could be due to lack of opportunity (there being little influenza circulating at that time) or a negative correlation between the two infections, with those positive for COVID-19 being unlikely to also be positive for influenza. In addition, those receiving COVID-19 vaccination are highly likely to have also received influenza vaccine. There is therefore the potential for a relationship between being positive for influenza and receiving COVID-19 vaccination, which introduces bias.

A similar situation could be observed for the reverse (i.e. inclusion of SARS-CoV-2-positive controls for IVE).

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.

5.1.7 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.

5.1.8 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 and serological testing [36].

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).

- 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 to be all 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. In 2022, 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.

- 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 be updated in the 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 (Note coding change to match with ECDC coding)
			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 (Note coding change from 'residence' to match with TESSy coding of ltcf)
			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	
Section B *continued*	pregnant	Numeric (categorical)	0 = No	Whether patient is pregnant (for women aged 15–55 years)
			1 = Yes	
			8 = Do not know	
Section C	admitdate	Date	dd/mm/yyyy	Date of hospital admission

	Variable	Type	Values and coding	Definition
Hospital/ward, clinical course and outcomes	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	
	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 (updated to match TESSy)
	resp_support	Numeric (categorical)	0 = None	Level of respiratory support (updated to match TESSy)
			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	
Section D *continued*	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	
	lungdis	Numeric	0 = No	Chronic lung disease (excluding

	Variable	Type	Values and coding	Definition
		(categorical)	1 = Yes	asthma)
			8 = Do not know	
	diabetes	Numeric (categorical)	0 = No	Diabetes
			1 = Yes	
			8 = Do not know	
	hypert	Numeric (categorical)	0 = No	Hypertension
			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: pandemic 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)
	panvacc2dose	Numeric	0 = No	Received pandemic COVID-19 vaccination, second dose
			1 = Yes	
			2 = second dose NA	
			8 = Do not know	
Section F *continued*	panvacc2date	Date	dd/mm/yyyy	Vaccination date second dose
	panvacc2type	Text		Type of vaccine (product name)
	panvacc3dose	Numeric (categorical)	0 = No	Received pandemic COVID-19 vaccination, third dose
			1 = Yes	
			8 = Do not know	
	panvacc3date	Date	dd/mm/yyyy	Vaccination date third dose
	panvacc3type	Text		Type of vaccine (product name)
	panvacc4dose	Numeric (categorical)	0 = No	Received pandemic COVID-19 vaccination, fourth dose
			1 = Yes	

	Variable	Type	Values and coding	Definition
			8 = Do not know	
	panvacc4date	Date	dd/mm/yyyy	Vaccination date fourth dose
	panvacc4type	Text		Type of vaccine (product name)
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 vaccination two seasons ago
			1 = Yes	
			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	
Section H *Continued*	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	

	Variable	Type	Values and coding	Definition
	dysgeusia	Numeric (categorical)	0 = No	Alteration of sense of taste
			1 = Yes	
			8 = Do not know	
	headache	Numeric (categorical)	0 = No	Headache
			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	
	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	

	Variable	Type	Values and coding	Definition
	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
	swabdate_flu	Date	dd/mm/yyyy	Respiratory specimen collection date for influenza testing
Section K Laboratory tests (other respiratory viruses)	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
			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

	Variable	Type	Values and coding	Definition
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 1 = Yes 8 = Do not know	Whether the patient is any other type of essential worker with much human contact (e.g. teacher, police person, supermarket worker) *(optional)*
	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 2 = second trimester 3 – third trimester 8 = Do not know	If patient is pregnant, indicate which trimester (if known) *(optional)*
Section C Hospital/ward, clinical course and outcomes *Optional variables*	deathcause	Numeric (categorical)	1 = died from COVID-19	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 1 = Yes 8 = Do not know	Anaemia/chronic haematologic disease *(optional)*
	asplenia	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Asplenia (absence of/damage to spleen) *(optional)*
	liverdis	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Chronic liver disease (excluding cancer) *(optional)*
	rendis	Numeric (categorical)	0 = No 1 = Yes	

	Variable	Type	Values and coding	Definition
			8 = Do not know	Renal disease (excluding cancer and acute renal failure) *(optional)*
	dement	Numeric (categorical)	0 = No	Dementia *(optional)*
			1 = Yes	
			8 = Do not know	
	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	
Section D *Optional variables continued*	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 Medications for chronic medical conditions *Optional variables*	metform_pre	Numeric (categorical)	0 = No	Metformin *(optional)*
			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	
Section E	arb_pre		0 = No	

	Variable	Type	Values and coding	Definition
Optional variables continued		Numeric (categorical)	1 = Yes 8 = Do not know	ARB (angiotensin II receptor blockers) *(optional)*
	dmards_pre	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Biological disease-modifying anti-rheumatic drugs (DMARDs) e.g. rituximab, tocilizumab, etc. *(optional)*
	chemo_pre	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Chemotherapy (within 6 months or currently) for cancer *(optional)*
	gliclaz_pre	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Gliclazides (for diabetes or heart failure) *(optional)*
	psychotrop_pre	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Psychotropic drugs (including benzodiazepine, etc.) *(optional)*
	chloroq_pre	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Chloroquine *(optional)*
	hydroxychloroq_pre	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Hydroxychloroquine *(optional)*
	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 definition) *Optional variables*	chills	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	"Chills", or shivering *(optional)*
Section H *Optional variables continued*	coryza	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Coryza *(optional)*
	vomit	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Vomiting *(optional)*
	nausea	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Nausea *(optional)*
	tach	Numeric (categorical)	0 = No 1 = Yes	Tachypnoea or signs of low oxygen saturation *(optional)*

	Variable	Type	Values and coding	Definition
			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)*
			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	
Section H *Optional variables continued*	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 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. [8]

Cases and controls will be described by baseline characteristics, and uni- and multivariable analyses performed as described in Section 3.14.1 for individual analysis.

Pooled analysis plan

Descriptive pooled 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, along with reasons for not participating. 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

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, diabetes, obesity);
- 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.

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 six 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 that 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. We suggest that study sites/countries sequence as a minimum 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 the 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

Genetic and antigenic analysis data (example)

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 not all viruses were sequenced, but only a random selection of them, 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.*

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of the European Union

PDF ISBN 978-92-9498-615-3