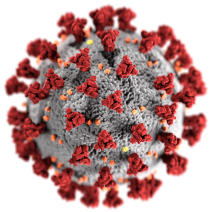
ACCESS

vACCine covid-19  monitoring readinESS

This protocol can be used by organizations for developing protocols to monitor COVID-19 vaccines post-introduction. Please reference as

Domingo-Diez J, Mira-Iglesias A, Carmona-Serrano T et al.

Core protocol for SARS-CoV-2 vaccine effectiveness studies (test-negative design studies) a protocol from the ACCESS project

DISCLAIMER

This template protocol has been accepted by EMA as a deliverable of the framework contract No EMA/2018/28/PE, taking into account the comments received in a large consultation of EMA's stakeholders. The protocol expresses the expertise of the authors and the ACCESS consortium as well as feedback received from EMA and stakeholders. It may not be understood or quoted as being made on behalf, or reflecting the position of the European Medicines Agency or one of its Committees or Working Parties

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Document History

Version	Date	Description
V1.1	03/07/2020	First draft
V1.2	15/07/2020	Update after comments from BL, MS, EP, HWK and LM
V1.3	15/07/2020	Update after comments from CW
V1.4	18/09/2020	Extension of "Sample size considerations" section
V1.5	23/09/2020	Update after comments from JF and CD
V1.6	10/12/2020	Update after Experts' comments

List of abbreviations

ACCESS	vACCine covid-19 monitoring readinESS
aOR	Adjusted Odds Ratio
CI	Confidence interval
CVE	Covid-19 vaccine effectiveness
DMP	Data management plan
DNA	Deoxyribonucleic acid
DRIVE	Development of Robust and Innovative Vaccine Effectiveness
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
FDA	Food and Drug Administration
GP	General Practitioner
IMI	Innovative Medicines Initiative
OR	Odds Ratio
RNA	Ribonucleic acid
RT-PCR	Reverse-transcription polymerase chain reaction
SAP	Statistical analysis plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
TND	Test-negative design
VE	Vaccine effectiveness
VLP	Virus-like particle

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Preface

The ACCESS project aims to set up a Europe-wide infrastructure to study the coverage, safety and effectiveness of the future COVID-19 vaccines as soon as they will be launched in the European market. In particular, one of the main objectives is to establish a platform able to collect data across different European countries, ensuring a wide geographical coverage and a large study sample size, to estimate the COVID-19 vaccine/s effectiveness (CVE) following the test-negative design.

In line with the protocols developed by DRIVE IMI project (https://www.drive-eu.org/) to monitor brand-specific influenza vaccine effectiveness at European level, ACCESS will generate a protocol to assess brand/type-specific CVE following a test-negative design (1, 2). The test-negative design is considered as the most efficient approach currently available for routine assessment of influenza VE (3).

The test-negative design is a variation of the classical case-control study. Patients fulfilling a previously established case definition are enrolled at hospitals (or Primary Care) and tested for the virus of interest. The VE is estimated comparing the odds of vaccination among patients testing positive (cases) vs. those testing and negative (controls), after adjusting for potential confounders (3). This design can avoid or minimize biases such as selection bias by healthcare-seeking behavior, as it is assumed that healthcare-seeking behaviour is similar between the cases and controls. Biases related to exposure misclassification can be also limited by ascertaining vaccination by consulting medical records, vaccination cards or other health registries and avoiding self-reporting.

As with any observational study, vaccine effectiveness estimates following a test-negative design can be biased due to misclassification of disease status. Although, part of this misclassification can be reduced by restricting the analysis to those patients attending hospital a short time after onset of symptoms as we propose in this protocol template, using diagnostic assays with imperfect sensitivity and specificity (RT-PCR for SARS-CoV-2 has proven to significantly vary in its sensitivity), appears to be particularly important with respect to COVID-19 (4).

It is suspected that low sensitivity and specificity are likely to introduce more bias in a test-negative design than in a traditional cohort or case-control study. In a traditional cohort or case-control study, imperfect assays only affect members of the source population that develop symptoms and are tested for illness; the majority of the source population is not tested, so only a small proportion of non-cases can be misclassified by imperfect diagnostic tests. In contrast, because a test-negative study solely focuses on the subset of the population that meet some testing criteria, all non-cases in a test-negative study could potentially be misclassified (4). However, several publications analyzed the impact of the sensitivity and specificity of the test on the influenza vaccine effectiveness estimates through different approaches (TND, cohort study and case control study) and they reported non-significant differences across study designs, concluding that it is the specificity of the test what really impacts the vaccine effectiveness estimates instead of the study design itself (5).

Similar findings would be expected when performing this analysis in relation to COVID-19 and, due to the features of the design, a test-negative study can be easily implemented in ongoing surveillance systems as no substantial additional funding is required (3). The harmonization of the analytic approaches in different sites following this common core protocol could lead ACCESS to obtain large sample sizes that allow obtaining robust CVE estimates in different populations of interest (e.g. individuals at risk of severe COVID-19, essential workers, vulnerable groups…) (6).

1.Background

The novel coronavirus SARS-CoV-2 was detected at the end of 2019 and has originated a pandemic that represents a challenging situation around the world (7). Due to the global public health emergency, the development of potential treatments and vaccines to inhibit the infection and its spread became a priority.

Vaccines against SARS-CoV-2 will play a key role to prevent individuals from COVID-19, but development of vaccines usually takes several years (only 18 months for COVID-19 vaccine is expected). However, regulatory entities as the EMA and the FDA announced the development of procedures to speed up the evaluation and authorization processes (8). There are more than 150 candidate vaccines under investigation and several in clinical evaluation and nearing end of Phase 3 clinical trials (9). Among all these vaccines there are RNA, DNA, inactivated, protein subunit, non-replicating viral vector, replicating viral vector, live attenuated virus and virus-like particle (VLP) vaccines (9).

ACCESS will study the feasibility of establishing a hospital-based surveillance network able to rapidly assess the effectiveness of the different COVID-19 vaccines once they have been administered to the population. Therefore, this protocol template will serve as a guide for researchers to evaluate the COVID-19 vaccine/s effectiveness, following a test-negative design, through data prospectively collected in a previously established infrastructure. This protocol is based on DRIVE's experience with test-negative design studies for influenza vaccine effectiveness estimation (10).

Although there have been many published works on COVID-19, many aspects and characteristics of the disease remain unknown such as the seasonality of the virus or the target groups for vaccination. Accrual of knowledge in the coming months may help to better adapt this protocol. The current document represents a generic protocol for the study of the SARS-CoV-2 vaccine/s effectiveness in hospitalized patients presenting with symptoms matching the COVID-19 case definition (11).

ACCESS will consider different populations of interest (see Objectives) and patients with comorbidities, including chronic liver diseases, diabetes, cardiovascular diseases, cancer, immunodeficiencies, lung diseases, anemia, renal diseases, dementia, history of stroke, rheumatologic diseases (12). Serious complications that can derive in death were observed in older people and individuals with chronic underlying conditions such as cardiovascular or pulmonary diseases (13). Other risk condition, such as diabetes, hypertension or obesity will be also evaluated, as data supported that it increased COVID-19 susceptibility and severity and it was related to an overall worse prognosis (13, 14).

2. Objectives

The main objective of this protocol is to estimate COVID-19 vaccine effectiveness (CVE) against severe (hospitalized patients) COVID-19 disease, confirmed by RT-PCR.

Primary objective

1. Estimate CVE against severe COVID-19 disease confirmed by RT-PCR, **by vaccine brand,** overall and stratified by age group (<18, 18-60 and ≥60 years old), after adjusting for potential confounders.

Secondary objectives

2. Estimate CVE against severe COVID-19 disease confirmed by RT-PCR, **by vaccine brand**, **in specific populations of interest** (underlying chronic conditions, COVID-19 risk factors, immunocompromised…), after adjusting for potential confounders.

3. Estimate CVE against severe COVID-19 disease confirmed by RT-PCR, **by vaccine type**, overall and by age group (<18, 18-60 and ≥60 years old), after adjusting for potential confounders.

Exploratory objectives

4. Estimate CVE against severe COVID-19 disease confirmed by RT PCR, **by severity level** (requirement for ICU admission, mechanic ventilation, death), overall and by age group (<18, 18-64 and ≥65 years old) after adjusting for potential confounders, if sample size permitting.

5. Estimate CVE against severe COVID-19 disease confirmed by RT-PCR, by:

    a. Seasonal influenza vaccination status

    b. Pneumococcal vaccination status

    overall and by age group (<18, 18-60 and ≥60 years old) after adjusting for potential confounders.

6. Estimate CVE against COVID-19 disease confirmed by RT PCR, **by time since vaccination**, overall and by age group (<18, 18-64 and ≥65 years old), after adjusting for potential confounders.

All estimations will be conducted at site level and pooled later (see Statistical Analysis section). All analyses will be described, in detail, in a statistical analysis plan (SAP).

3. Methods

3.1 Study design and setting

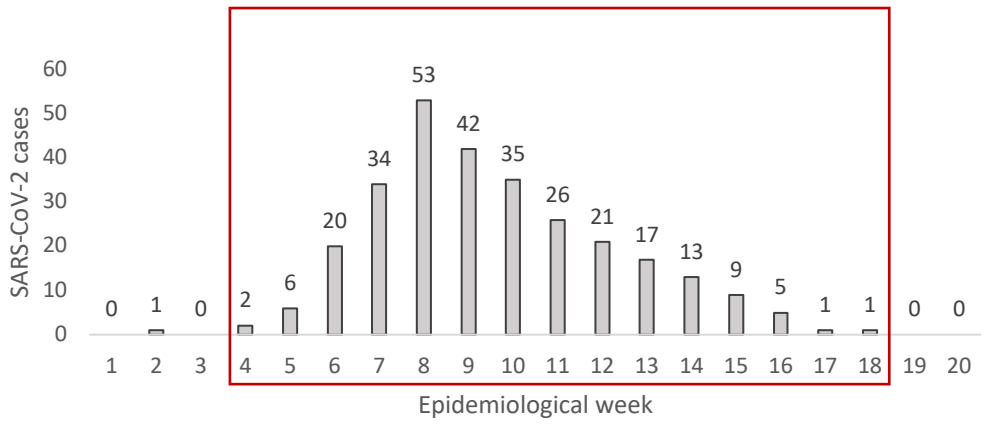
An observational prospective active-surveillance hospital-based study, following a test-negative design (TND), will be carried out in each participating site.

3.2 Study period

Based on current knowledge and epidemiological situation of the COVID-19 across Europe, a complete year since implementation of the protocol is proposed as an initial study period.

In subsequent years of the study, and if/when COVID-19 becomes seasonal, the COVID-19 study period could be restricted to some pre-specified months and it could be restricted for the analysis to the time encompassed between the first week after two consecutive weeks with at least two positive results for SARS-CoV-2 and the last week prior to the first of two consecutive weeks with no positive cases for SARS-CoV-2 detected, at the specific study site.

In the next figure, we illustrate the definition of outbreak (or COVID-19 circulation period) using fallacious data. In this case, the COVID-19 outbreak (or circulation period) would comprise the period between weeks 4 and 18 (both inclusive).



3.3 Study population

All-ages patients admitted to the hospital, through the Emergency Department or transferred from other hospitals or health facilities, fulfilling the ECDC case definition for COVID-19 disease.

Case definition for COVID-19 disease (ECDC, as of 29 May 2020)

The ECDC has established different criteria for COVID-19 disease identification (11):

- Clinical criteria
  Any person with at least one of the following symptoms:
  - Cough
  - Fever
  - Shortness of breath

    - Sudden onset of anosmia, ageusia or dysgeusia

  Additional less-specific symptoms may include headache, chills, muscle pain, fatigue, vomiting and/or diarrhoea.
- Diagnostic imaging criteria
  Radiological evidence showing lesions compatible with COVID-19.
- Epidemiological criteria
  At least one of the following two epidemiological links:
    - Close contact (see reference (15)) with a confirmed COVID-19 case in the 14 days prior to onset of symptoms.
    - Having been a resident or a staff member, in the 14 days prior to onset of symptoms, in a residential institution for vulnerable people where ongoing COVID-19 transmission has been confirmed.

According to these criteria, the ECDC has classified the cases as follows:

1. Possible case: Any person meeting the clinical criteria.
2. Probable case: Any person meeting the clinical criteria with an epidemiological link OR any person meeting the diagnostic imaging criteria.

ACCESS recommends to follow the **probable case** definition.

3.4 Outcomes

The outcome variable will be laboratory-confirmed SARS-CoV-2.

Case and control definitions

- Case: A patient from the study population fulfilling the probable case definition with a respiratory sample positive for SARS-CoV-2 (first sample taken in hospital or last sample taken before hospitalization).
- Control: A patient from the study population fulfilling the probable case definition with a respiratory sample negative for SARS-CoV-2 (first sample taken in hospital or last sample taken before hospitalization).

Exclusion criteria

The following exclusion criteria should be applied

1. Person 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)
2. Person has been hospitalized in the 30 days before the current hospitalization
3. Person has any contraindication for COVID-19 vaccine
4. Person has respiratory specimen taken 10 days or less after symptoms onset
5. Person was vaccinated against COVID-19 but not immunized at the symptoms' onset (after full vaccination if more than one dose is required)

3.5 Exposure

The exposure of interest is vaccine administration against SARS-CoV-2 infection in the period under study. Besides the vaccination status, the vaccination date, brand, and type of the vaccine will be required. Information regarding vaccination will be ascertained by consulting vaccination registries, vaccination cards or medical records.

➢ *Each study site to describe the precise way of vaccination status ascertainment (i.e. vaccinated yes/no), vaccine brand, vaccine type and vaccination date ascertainment.*

The CVE will be evaluated for the different vaccine brands. Moreover, the administered vaccines will be classified by the strategy used for antigen preparation, manufacturing process and other vaccine characteristics when estimating type-specific CVE.

Definition of vaccination status

For the period under study, an individual will be considered:

- vaccinated with the vaccine of interest if the patient has a record of SARS-CoV-2 vaccine administration and was immunized at symptoms onset (unknown, for influenza it is usually considered >14 days before symptoms onset).
- unvaccinated if the patient has no SARS-CoV-2 vaccine record.

An individual will be considered as vaccinated if vaccine administration is recorded in any registry, even if the patient does not recall it.

Patients vaccinated but not immunized at symptoms onset will be excluded from the analysis.

In case of multi-dose vaccines, the CVE will be estimated between unvaccinated and fully vaccinated individuals, excluding those partially vaccinated from the main analysis and evaluating them in a sensitivity analysis.

Time since vaccination

To evaluate the CVE according to the time between vaccine administration and symptoms onset, three (or more, if sample size permitting) groups will be defined by using tertiles or by previously establishing relevant categories (e.g. <2 months, 2-4 months, >4 months).

3.6 Covariates

For the pooled analysis, the following covariates will be mandatory:

- Age
- Sex
- Date of symptoms onset
- Date of hospitalization
- Presence of chronic underlying conditions (see Annex 1)

This minimum set of covariates is defined to allow sites with limited data on covariates to participate in the study, and to avoid reducing sample size by discarding data containing missing values for covariates.

However, if available and relevant, other variables may be used in individual study site analyses and, if possible, they will be harmonized between the study sites for pooled analysis according to the SAP. Variables to consider are the following:

- Number of primary care visits (or telephone assistance) 3 months prior to the study period describing a study subject's healthcare seeking behaviour

- Number of hospitalizations 12 months prior to the study period to be used as proxy for the severity of the chronic conditions
- Specific chronic underlying conditions (chronic pulmonary disease, cardiovascular disease, diabetes, liver disease, renal disease, neurologic/neuromuscular conditions, treatment-induced immunosuppression, disease-induced immunosuppression, or cancer (see Annex 1))
- Obesity
- Laboratory-confirmed influenza during the season under study
- Frailty status in older adults
- Requirement for ICU, assisted ventilation, death (to define distinct severity levels)
- Influenza vaccination status at symptoms onset
- Pneumococcal vaccination at symptoms onset

➢ *Each study site to describe the covariates included in the study and how these are identified.*

4. Data collection

Data collection and entry will be conducted at the site level. Data will be collected in a face-to-face/phone-based interview (directly with the patient or with a relative) using a standardised questionnaire/data collection form at the moment of swabbing and/or by consulting medical records. The questionnaire will be developed before the beginning of the study period according with the list of variables adopted at the study site level.

➢ *Each study site to describe the data collection tools used.*

➢ *Each study site to describe if and how informed consent is obtained.*

➢ *Each study site to document any protocol violations.*

Laboratory procedures

Respiratory specimens will be collected from those patients fulfilling the inclusion criteria (if they do not have a previous sample within 10 days of the symptoms' onset).

Laboratory confirmation should be done by reverse transcription-polymerase chain reaction (RT-PCR) – recommended nasopharyngeal or oropharyngeal swabs.

- *Each study site to describe the specimen collection (i.e. to include a description of the criteria and procedure for swabbing at the site level).*
- *Each study site to describe the specimen storage and transport procedures.*
- *Each study site to describe the laboratory tests used (as well as their sensitivity and specificity) and the selection of specimens and the procedures for genetic and antigenic characterisation.*
- *Each study site to describe if the laboratory participates in QA/QC (Quality Assurance/Quality Control) schemes.*

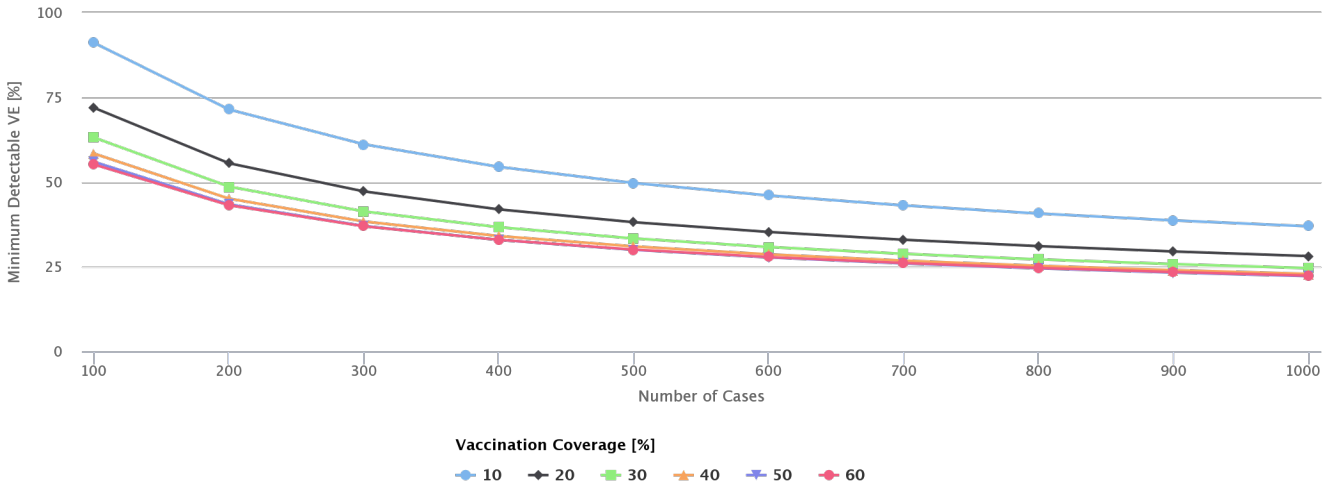
5. Sample size considerations

The minimum detectable CVE considering different sample sizes is provided in the table below. The calculations

are performed assuming 80% of power, two-sided 95% confidence levels and overall vaccination coverages of 10%, 20%, 30%, 40%, 50% and 60%. It is assumed to have a 1:1 control per case allocation ratio. ACCESS recommends a minimum of 100 SARS-CoV-2 positive cases per site (10 study sites x 100 cases = 1000 SARS-CoV-2 total cases).

Minimum detectable CVE*						
SARS-CoV-2 cases	Coverage					
	10%	20%	30%	40%	50%	60%
100	91.13	71.94	63.16	58.43	55.98	55.20
200	71.45	55.57	48.67	45.12	43.44	43.17
300	61.16	47.25	41.34	38.37	37.04	36.95
400	54.50	41.94	36.68	34.07	32.93	32.94
500	49.72	38.15	33.35	31.00	30.00	30.07
600	46.05	35.27	30.83	28.66	27.77	27.86
700	43.12	32.97	28.82	26.80	25.98	26.10
800	40.72	31.09	27.17	25.28	24.52	24.65
900	38.68	29.51	25.78	23.99	23.29	23.43
1000	36.94	28.15	24.59	22.89	22.23	22.38

*DRIVE web-application to perform sample size calculations for VE studies (http://apps.p-95.com/drivesamplesize/)

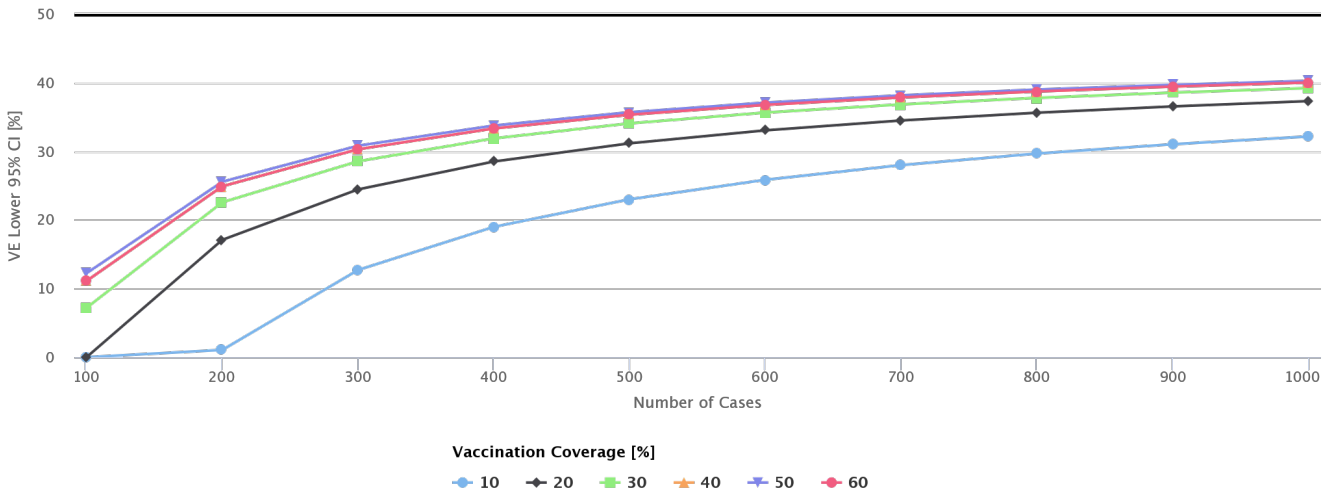


The precision of the estimates is provided in the table below expressed as the lower limit of the two-sided confidence interval of the anticipated true CVE (in %). The calculations are performed assuming 80% of power, two-sided 95% confidence levels and overall vaccination coverages of 10%, 20%, 30%, 40%, 50% and 60%. It is assumed to have a 1:1 control per case allocation ratio and an anticipated true CVE of 50%. ACCESS recommends a minimum of 100 SARS-CoV-2 positive cases per site.

Lower limit of the CVE 95% CI*						
SARS-CoV-2 cases	Coverage					
	10%	20%	30%	40%	50%	60%
100	0.00	0.00	7.19	11.11	12.23	11.11
200	1.06	17.10	22.57	24.90	25.57	24.90
300	12.71	24.45	28.54	30.30	30.81	30.30
400	18.99	28.51	31.88	33.33	33.75	33.33
500	23.01	31.16	34.07	35.33	35.69	35.33

600	25.85	33.05	35.64	36.76	37.09	36.76
700	27.99	34.49	36.83	37.85	38.15	37.85
800	29.67	35.62	37.78	38.72	38.99	38.72
900	31.03	36.54	38.55	39.43	39.68	39.43
1000	32.16	37.31	39.20	40.02	40.26	40.02

*DRIVE web-application to perform sample size calculations for VE studies (http://apps.p-95.com/drivesamplesize/)



As the optimal sample size strongly depends on the local vaccination coverage and vaccine type distribution, site-specific sample size recommendations will be formulated as part of the network expansion and site selection. Sample sizes smaller than recommended are allowed as the objective is not to have robust CVE at site level but ensure a sufficient sample size which allow to increase the power of the pooled analysis.

6. Data management

Each study site is responsible for the data collection, validation, and management of their individual study. A Data Management Plan (DMP) will be developed and the necessary infrastructure for data collection and analysis of the pooled data will be created.

- *Each study site to specify how data are collected (e.g. web-based, paper forms) and validated.*
- *Each study site to specify procedures of data management.*
- *Each study site to provide a codebook that includes the variable names, variable descriptions, and the coding of variable values, if not following the ACCESS procedures/codebooks/tools.*
- *Each study site to provide any checks in place in the data entry system to avoid mistakes in data entry, and whether source data verification was conducted and how.*
- *Each study site to specify the data checking and cleaning process.*

7. Statistical analysis

MAIN ANALYSIS

This section describes the main principles for the study site level analysis/ The details of adjustment for confounders and effect modifiers interaction or stratification are attempted to be harmonized between the study sites. The variables to adjust for and the heterogeneity/homogeneity between the study sites will be optimized according to availability of data.

PRIMARY OBJECTIVES

Demographics and baseline characteristics

The demographic and clinical characteristics of the study participants will be described (as well as missing information) for cases and controls and, analogously, for vaccinated and unvaccinated individuals (by vaccine type/brand and overall) and will be compared using the appropriated test according to the nature of the variables and the applicability assumptions.

CVE estimation

The adjusted CVE will be estimated as CVE = (1 – aOR) x 100%, where aOR denotes the adjusted odds ratio, comparing the odds of vaccination among SARS-CoV-2-positive study participants by the odds of vaccination among SARS-CoV-2-negative study participants. The 95% confidence intervals (CI) will be obtained as well. CVE estimates will be adjusted by including potential confounders in multivariable logistic regression models. Different CVE estimates will be provided stratifying by age groups.

The minimum set of potential confounders will include age, sex, calendar time (hospitalization date) and presence of chronic conditions. An extended set of confounders will also include number of General Practitioner (GP) visits/hospitalizations, specific chronic conditions, obesity, influenza vaccination status, pneumococcal vaccination status and anti-COVID-19 treatment use.

Missing data

The analysis will be a complete case analysis, dropping records with missing information for the outcome, exposure of interest or any of the mandatory covariates (see Annex 1).

SECONDARY OBJECTIVES

CVE estimates will be provided by vaccine type, and by vaccine brand for specific chronic conditions of interest, overall and by age group, following the previously described analysis.

EXPLORATORY OBJECTIVES

CVE will be estimated according to the time elapsed between vaccine administration and symptoms onset dates. A categorical variable will be defined according to number of days/months between vaccine administration and symptoms onset, taking as reference category not vaccinated patients. CVE estimates will be provided by influenza vaccination status, pneumococcal vaccination status and severity level overall and by age group, sample size permitting, following the previously described analysis.

POOLED ANALYSIS

A two-stage pooling of data from the different study sites will be carried out. For each CVE estimation, a random-effects meta-analysis will be performed pooling site-specific estimates (16). For this analysis, CVE

estimates which were minimally adjusted for (mandatory covariates) will be considered. A measure of the heterogeneity between study sites will be provided through the I^2 statistic, calculated according to Higgins et al (17).

SENSITIVITY ANALYSIS

Sensitivity analysis may be conducted, if appropriate, to explore time between onset of symptoms to swab or considering partially vaccinated individuals (in case of multi-dose vaccines), for instance. Other sensitivity analysis will be carried out by comparing pooled estimates obtained from the site-specific estimates using the minimum set of confounders and using the extended set of confounders (according to sites' data availability).

In case that more than one epidemic wave occurs within the study period, the effectiveness will be evaluated in each of the waves due to the different epidemiological and virological characteristics that may occur between them.

8. Limitations

Many existing influenza surveillance systems are expanding horizons and, therefore, taking advantage of the well-established infrastructures to analyze the new SARS-CoV-2. Some of these surveillance networks might be interested in joining the project, however, it can be difficult to homogenize all aspects treated in the ACCESS generic TND protocol across all sites.

Although participating sites will closely follow the generic protocol, several differences could arise regarding the data collection or the sampling strategy. Mandatory covariates have been reduced to the minimum in order to encourage a large number of sites participating in the study. Then, important information on other confounders to achieve better adjustments is limited. The study of the impact of the influenza vaccination on COVID-19 outcomes, as well as its interaction with the vaccine against SARS-CoV-2 would be intriguing. Nonetheless, this data could be difficult to come by.

Regarding the sampling methods, same samples could be used to test both influenza and SARS-CoV-2, but strategies could be different: systematic or random selection, routine care, all patients fulfilling COVID-19 probable case definition, at physician's discretion, etc. Moreover, as described at the beginning of this protocol template, the sensitivity and specificity of the diagnostic test could impact on the CVE, specially the specificity (5). We will collect this information from all participating sites, and it would be a good opportunity to develop further analysis on this topic of high interest.

Although a case-control study design is recommended in addition to the TND (4), the latter has been demonstrated as a valid approach to estimate vaccine effectiveness (5). A TND can be easily implemented in existing surveillance systems, facilitating logistics and saving time and resources as controls are automatically identified when identifying cases. Contrary, a case-control design requires extra efforts to select an appropriate control group, probably unaffordable efforts given the current situation in health settings.

It would be remarkably interesting to know about the target populations for vaccination against COVID-19 disease, as well as the recommendations of each vaccine type/brand. Nevertheless, some risk groups such as

healthcare workers or pregnant women cannot be particularly studied in the first stages of the study. All efforts will be combined to achieve the main objectives of this protocol. Although specific risk groups can be studied later, in principle we will focus on more general groups for which we can achieve an adequate sample size that allows us to obtain reliable estimates and conclusions.

Given the uncertainty around the SARS-CoV-2 pandemic development it is probable that other limitations will be identified during the implementation of this protocol. Thus, it will be key to constantly evaluate the potential limitations and risks derived of the changing nature of the pandemic and act accordingly by updating the present protocol if necessary.

9. Ethical evaluation and other relevant approvals

Each study site will comply with the relevant international, national and regional legal and ethics requirements and the declaration of Helsinki and ensures that the ethics committee of the institution has approved the study. Copies of the appropriate approvals from each site will be collected at the study site level and archived according with the local low law, but at least for 5 years.
Informed consent will be required from all participants or legal tutors/proxies; the national ethics committees will specify whether oral or written consent will be required. The following information should be specified: who is responsible for the study, aim of the study, nature of processed data, purposes of processing, purpose of the use of the data, recipients of possible data transfers, rights of data subject and consequences of not accepting the informed consent.

The only exception is where the study is part of an ongoing routine program evaluation required by ministry of health or a requisite part of the public health institution's work and would therefore fall outside the mandate for ethics committees. In these cases, a statement that no formal approval from ethics committee is required, is sufficient.

- *Each study site to describe the procedures to comply to the national ethics committee requirements and the type of informed consent needed as well as whether consent can be obtained for a legal tutor.*
- *Each study site to provide a copy of the ethical approval, Independent Review Board or equivalent, or a statement on why this is not needed.*

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Annex 1: Data description

Information collected by study sites will remain their choice. However, in order to harmonize data across them, each participating site will have to adapt their variables according to the ones listed in the following table. Although some variables are redundant, they are kept just in case that some study sites could access only to part of the information.

Variable number	Variable name	Character	Description	Additional info	Variable format	Values/coding	Example
PATIENT IDENTIFICATION							
1	country	Mandatory	Country code defined in ISO 3166-1 alpha-2		2 letters text		ES
2	site	Mandatory	Name of the participating site or entity		Text		FISABIO
3	region	Optional	Region name		Text		Valencia Region
4	idsetting	Mandatory for studies with more than 1 hospital	Hospital identifier		Text		02
5	idpatient	Mandatory	Patient identifier		Text		101
6	sex	Mandatory	Sex		Numeric (categorical)	1=Male 2=Female	2
7	ageyears	Mandatory	Age in years at admission		Numeric		63
8	agemonths	Mandatory for children <1 year old	Age in months at admission	Introduce 9999 for patients ≥1 year old	Numeric		6
ADMISSION DATA							
9	suddenonset	Optional	Sudden onset of symptoms	Within 7 days before admission	Numeric (categorical)	0=No 1=Yes 9999=No information	1
10	onsetdate	Mandatory	Date of symptoms		DD/MM/YYYY	Date within the	28/12/2021

			onset			study period	
11	admissiondate	Mandatory	Date of hospitalization	First point of contact (arrival at Emergency Department)	DD/MM/YYYY	Date within the study period	29/12/2021
12	fever	Optional	Fever or feverishness	A measured fever of ≥38°C or temperature 37-38°C with patient-reported feverishness	Numeric (categorical)	0=No 1=Yes 9999=No information	0
13	cough	Optional	Cough		Numeric (categorical)	0=No 1=Yes 9999=No information	1
14	breath	Optional	Shortness of breath	Subjective evaluation of breathing difficulty by patient or caregiver, or any of the following: respiratory rate ≥25/min (adults) or SpO2 <90% (unless chronic) or PaO2 <8 kPa or respiratory acidosis	Numeric (categorical)	0=No 1=Yes 9999=No information	0
15	anosmia	Optional	Loss of the sense of smell		Numeric (categorical)	0=No 1=Yes 9999=No information	0
16	ageusia	Optional	Loss of the sense of taste		Numeric (categorical)	0=No 1=Yes 9999=No information	1
17	dysgeusia	Optional	Perceptual change in the taste of food and drinks		Numeric (categorical)	0=No 1=Yes 9999=No information	0
18	headache	Optional	Headache		Numeric (categorical)	0=No 1=Yes 9999=No information	0
19	chills	Optional	Chills		Numeric (categorical)	0=No 1=Yes 9999=No information	1
20	muscle	Optional	Muscle pain		Numeric (categorical)	0=No 1=Yes 9999=No information	1

21	fatigue	Optional	Fatigue		Numeric (categorical)	0=No 1=Yes 9999=No information	0
22	vomiting	Optional	Vomits		Numeric (categorical)	0=No 1=Yes 9999=No information	0
23	diarrhoea	Optional	Diarrhoea		Numeric (categorical)	0=No 1=Yes 9999=No information	0
24	close_contact	Optional	Close contact	Close contact with a confirmed COVID-19 case in the 14 days prior to onset of symptoms	Numeric (categorical)	0=No 1=Yes 9999=No information	0
25	staff	Optional	Staff member	Having been a resident or a staff member, in the 14 days prior to onset of symptoms, in a residential institution for vulnerable people where ongoing COVID-19 transmission has been confirmed.	Numeric (categorical)	0=No 1=Yes 9999=No information	0
26	rx_evidence	Optional	Radiological evidence	Radiological evidence showing lesions compatible with COVID-19	Numeric (categorical)	0=No 1=Yes 9999=No information	1
27	probable_case	Mandatory	Probable case of COVID-19 disease		Numeric (categorical)	0=No 1=Yes 9999=No information	1
INCLUSION CRITERIA							
28	comm	Mandatory	Communication with patient/tutor		Numeric (categorical)	0=No 1=Yes 9999=No information	1
29	inst	Mandatory	Institutionalized	Living in a residential institution (e. g., long-term care facility, prison, militia or army)	Numeric (categorical)	0=No 1=Yes 9999=No information	0
30	prevhosp	Mandatory	Was the patient hospitalized in the 30 days prior to the		Numeric (categorical)	0=No 1=Yes	0

			current hospitalization?				
31	prevcov	Mandatory	Did the patient have a previous lab-confirmed SARS-CoV-2 in this season?		Numeric (categorical)	0=No 1=Yes 9999=No information	0
32	contra	Mandatory	Any contraindication for SARS-CoV-2 vaccination	Based on locally used criteria.	Numeric (categorical)	0=No 1=Yes 9999=No information	0
33	consent	Mandatory	Consent given		Numeric (categorical)	0=No 1=Yes 9999=Not applicable	1
34	consentwho	Mandatory	If consent is given, who gives the consent?		Numeric (categorical)	0=Patient 1=Parents/tutor 9999=Not applicable	0
COMORBIDITIES/RISK FACTORS							
35	chronic	Mandatory	Does the patient have at least one chronic disease?	Including obesity (BMI ≥30). Not including smoking or pregnancy.	Numeric (categorical)	0=No 1=Yes 9999=No information	1
36	liverdis	Optional	Chronic liver disease	Any of the following dg codes (ICD-10): B18, K70-74, K75.0-75.1, K75.3-75.9, K76-77 INCLUDING: Alcoholic liver disease, Toxic liver disease, Hepatic failure, Chronic hepatitis (viral & other), Fibrosis and cirrhosis of liver, Other inflammatory liver diseases, Other diseases of liver EXCLUDING: Clinically insignificant liver cysts	Numeric (categorical)	0=No 1=Yes 9999=No information	0
37	diabetes	Optional	Diabetes	Any of the following dg codes (ICD-10): E10-E14, O24 INCLUDING: Any form of diabetes, including sequelae & DM in pregnancy	Numeric (categorical)	0=No 1=Yes 9999=No information	0
38	cardiovasc	Optional	Cardiovascular diseases	Any of the following dg codes (ICD- 10): A52.0, B37.6, I01-02, I05-09, I11.0, I13.0, I13.2, I20-25, I26-28, I30-43, I44- 46, I48, I49.0, I49.5, I50-52, I70-71, Q20-Q28 INCLUDING: all conditions of heart & large vessels	Numeric (categorical)	0=No 1=Yes 9999=No information	1

				that are chronic or likely to have chronic sequelae. Cardiovascular syphilis, endo-, myo- and pericarditis, rheumatic fever, chronic rheumatic heart diseases, congenital malformations, hypertensive (renal) diseases with heart failure, ischaemic heart diseases, diseases of pulmonary circulation, atherosclerosis, cardiomyopathies, most conduction disorders, heart failure, aortic aneurysms & dissecation, other heart diseases and their complications. EXCLUDING: uncomplicated hypertension, previous uncomplicated pulmonary embolism (with no lasting cardiac insufficiency), paroxysmal tachycardias, most cases of premature depolarization.			
39	cancer	Optional	Cancer	Any of the following dg codes (ICD- 10): C00-97, D37-48, Z85, Z92.3, Z92.6. INCLUDING: All malignant neoplasms (both solid and haematologic) with potential to metastasize, either in treatment, active followup, or <5 years post curative treatment. EXCLUDING: Benign & in situ neoplasms. Basal cell carcinomas. Any cancer previously treated with curative intent & in complete remission for ≥5 years.	Numeric (categorical)	0=No 1=Yes 9999=No information	0
40	immuno	Optional	Immunodeficiency or organ transplant	Any of the following dg codes (ICD-10): B20-B24, D80–84, D89, Z94 INCLUDING: HIV infections, immunodeficiencies & organ transplants. or iatrogenic: ≥2 week systemic treatment, in the 3 months preceding symptom onset, with any of the following: corticosteroid (≥20 mg prednisolone daily or equivalent), ciclosporin, tacrolimus, mycophenolate, methotrexate, azathioprine, TNF-α blockers and other biological or cytostatic drugs with immunosuppressive effect EXCLUDING: Disorders of the immune system which do not lead to immunosuppression (e.g. some autoimmune conditions).	Numeric (categorical)	0=No 1=Yes 9999=No information	0
41	lungdis	Optional	Lung disease	Any of the following dg codes (ICD-10): A15-16,	Numeric (categorical)		1

				A19, A31.0, B33.4, E84.0, J40- 47, J60-70, J80-84, J85-86, J90-91, J92.9, J93-94, J95-99 INCLUDING: TB (pulmonary, miliary but not that of other systems), atypical mycobacteria, cystic fibrosis, asthma, COPD, bronchiectasis and other chronic sequelae of infections, chronic lung diseases due to external agents, interstitial lung diseases, pleural diseases, respiratory failure. EXCLUDING: acute respiratory infections, lung cancer, diseases of pulmonary circulation, pleural plaques without asbestos, previous uncomplicated pneumothorax.		0=No 1=Yes 9999=No information	
42	anemia	Optional	Anemia	Any of the following dg codes (ICD- 10): D50-D64 diagnosed before the onset of symptoms. EXCLUDING: coagulopathies, uncomplicated hypersplenism, hepato/splenomegaly (D65-69, D70-77, D80-84, D86, D89)	Numeric (categorical)	0=No 1=Yes 9999=No information	0
43	rendisease	Optional	Renal disease	Any of the following dg codes: (ICD- 10): I12-13, M10.30, N00-19, N20.0, N25-27, N28.0, N28.9, Q63.9, Z90.5 EXCLUDING: Clinically nonsignificant kidney cysts	Numeric (categorical)	0=No 1=Yes 9999=No information	0
44	dement	Optional	Dementia	Any of the following dg codes (ICD- 10): F00-03, F05.1, G30-31 EXCLUDING delirium w/o underlying dementia, hydrocephalus.	Numeric (categorical)	0=No 1=Yes 9999=No information	0
45	stroke	Optional	History of stroke	Any of the following dg codes (ICD-10): I61-64, I67.8, I69, G93.1 INCLUDING: both ischaemic and haemorrhaegic strokes and anoxic brain damage. Also counting previous episodes and clear ischaemic findings seen in cranial imaging (even if fully recovered / no symptoms).	Numeric (categorical)	0=No 1=Yes 9999=No information	0
46	rheumat	Optional	Rheumatologic diseases	Any of the following dg codes: ICD-10: M05–09, M13, M30–36, M45 INCLUDING rheumatoid diseases with presumed autoimmune origin and primarily musculoskeletal presentation. EXCLUDING: arthrosis, gout, scoliosis, infectious conditions etc.	Numeric (categorical)	0=No 1=Yes 9999=No information	0
47	obesity	Optional	Obesity	BMI ≥30 or the dg codes (ICD-10): E66, E68 EXCLUDING: local adiposity and "other	Numeric (categorical)	0=No 1=Yes	0

				hyperalimentation" (=vitamin overdoses etc.)		9999=No information	
48	pregnancy	Optional	Pregnancy	Any trimester at symptom onset.	Numeric (categorical)	0=No 1=Yes 9999=No information	0
TREATMENTS							
49	anticov_treatm	Optional	Has the patient received any treatment for COVID disease within the 2 weeks before swabbing?	INCLUDING: dexamethasone, remdesivir, favipiravir, lopinavir/ritonavir and non-steroidal anti-inflammatory drugs	Numeric (categorical)	0=No 1=Yes 9999=No information	1
50	antiviral_flu	Optional	Has the patient received an antiviral treatment for influenza within the 2 weeks before swabbing?	INCLUDING: oseltamivir, zanamivir, favipiravir and peramivir.	Numeric (categorical)	0=No 1=Yes 9999=No information	1
LABORATORY							
51	swabdate	Mandatory	Date of swabbing		DD/MM/YYYY	Date within the study period	30/12/2021
52	virus1	Mandatory	Laboratory result: virus type		Numeric (categorical)	0=Negative 1=SARS-CoV-2 2=Influenza 3=Other virus 9999=No information	1
53	virus2	Mandatory	In case of coinfection, second virus involved		Numeric (categorical)	0=No coinfection 1=SARS-CoV-2 2=Influenza 3=Other virus 9999=No information	1
HEALTHCARE-SEEKING BEHAVIOUR							
54	nhosp	Optional	Number of hospitalizations in the last year	Any overnight stay in hospital. (One disease episode counts as one hospitalization even if a patient is moved from one unit to another)	Numeric	≥0 or 9999=No information	2
55	gpvisit	Optional	Number of GP consultations in	Any consultation to nurse/GP/specialist in a primary care setting. Not counting follow-up visits	Numeric	≥0 or 9999=No	5

			the last year	for the same cause.		information	
ROUTINE ASPECTS							
56	hcw	Optional	Is the patient a healthcare worker?		Numeric (categorical)	0=No 1=Yes 9999=No information	0
57	kids	Optional	Regular contact with kids		Numeric (categorical)	0=No 1=Yes 9999=No information	1
58	functstatus	Optional	Dependency / Patient has difficulty in at least 1 of these categories: bathing dressing eating going to the toilet stairs walk wheelchair user	Difficulty = needs help from others	Numeric (categorical)	0=No 1=Yes 9999=Not applicable	0
VACCINATION							
59	covvaccany	Mandatory	Received SARS-CoV-2 vaccination in current season		Numeric (categorical)	0=No 1=Yes 9999=No information	1
60	covvaccbrand	Mandatory	Vaccine brand		Text		
61	covvacctype	Mandatory	Vaccine type		Text		
62	covvaccdate	Mandatory	Date of SARS-CoV-2 vaccination in current season		DD/MM/YYYY		11/10/2021
63	fluvacc	Optional	Received influenza vaccination in current season		Numeric (categorical)	0=No 1=Yes 9999=No information	1
64	fluvaccdate	Optional	Date of influenza vaccination		DD/MM/YYYY		08/09/2021
65	pneumovacc	Optional	Received any pneumococcal	Any time	Numeric (categorical)	0=No 1=Yes	1

			vaccination			9999=No information	
66	pneumovaccdate	Optional	Date of pneumococcal vaccination	Latest dose	DD/MM/YYYY		11/01/2018