MASTER PROTOCOL

Brand-specific COVID-19 vaccine effectiveness against severe COVID-19 disease in Europe

A contribution of COVIDRIVE, a public-private partnership
to estimate brand-specific COVID-19 vaccine effectiveness in Europe.

COVIDRIVE

Version 4.0

10 Oct 2022

CONTRIBUTORS and VERSION CONTROL

Contributing organisations to this Master Protocol

Organisation
P95
FISABIO
THL
Astrazeneca
Bavarian Nordic
CureVac
GSK
Janssen
Moderna
Novavax
Sanofi
Valneva

Abbreviations: FISABIO, Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana; GSK, GlaxoSmithKline.

Version control table for this master protocol

Version	Version date	Reason for new version
1.0	February 9, 2021	First draft
1.1	February 15, 2011	Addressing comments from partners
2.0	February 25, 2021	Sample size section, questions on ADL, risk-taking behaviour. Information to collect on critical COVID-19 patients, master ICF
2.1	March 9, 2021	Addressing comments from partners
2.2	March 15, 2021	Addressing comments from partners and feedback from feasibility working group TC
3.0	April 23, 2021	Addressing comments from ISC, EMA, ECDC
3.1	June, 2021	Minor correction to exposure definitions; submitted to EU PAS on 02/08/2021 (EUPAS42328)
3.2	June, 2021	Removing 'other hospital controls'
3.3	December, 2021	Amendments: • use the ECDC possible case definition for SARI instead of the stricter WHO case definition • restructuring the order and organisation of the secondary and exploratory objectives without changing the content • adding variables: - use of anti-SARS-CoV-2 antibody products or similar for pre-exposure prophylaxis, post-exposure prophylaxis and post symptom-onset but prior hospitalisation - full COVID-19 vaccination history including additional doses - symptoms related to the SARI case definition • in addition to RT-PCR, also allowing confirmation of COVID-19 using RNA amplification systems with at least the same sensitivity as RT-PCR (e.g. TMA). • improving sample size section • improving Annex 1 (VAED)
3.9	January, 2022	Objective: • adding additional dose vaccination Statistical analysis: • allowing to use GEE models in case cell counts are too low Protocol sent to the technical working group for review
4.0	October, 2022	Addressing comments from partners and ISC Addition of exclusion criteria: • other than EMA-approved

	Addition of comparator groups to objectives Include clarification additional dose comparison to statistical analyses section Update Annex 6 Addition of contact persons list

Version approval status for Study Contributors

Study site (Study Contributor)	Date of initial EC submission	Master protocol version in initial EC submission	Date of initial EC approval	Date of submission of amendment master protocol v3.3 to the EC	Date of EC approval of amendment master protocol v3.3	Enrolment date of first prospective participant	Enrolment date of first retrospective participant
FISABIO, Spain	17 Mar 2021	V2.2	01 Apr 2021	09 Feb 2022	23 Feb 2022	15 Sep 2021	N/A
	TBC	V2.0	01 Jun 2021	18 Jan 2022	15 Feb 2022	20 Oct 2021	01 Jun 2021
HUVH, Spain	TBC	V2.0	01 Jun 2021	18 Jan 2022	15 Feb 2022	14 Feb 2022	30 Oct 2021
CIRI-IT, Italy	TBC	V3.1	03 May 2021	TBC	24 Jan 2022	16 Nov 2021	N/A
Klinik Favoriten, Austria	20 Oct 2021	V3.1	29 Nov 2021	TBC	19 Jan 2022	04 Apr 2022	01 Jun 2021
UZA, Belgium	02 Dec 2021	V3.1	08 Dec 2021	28 Dec 2021	10 Jan 2022	30 Dec 2021	01 Jun 2021
St Pierre, Belgium	25 Nov 2021	V3.1	07 Dec 2021	28 Dec 2021	10 Jan 2022	01 Jun 2022	01 Jun 2021
GH Charleroi, Belgium	13 Jul 2022	V3.3	TBC	NA	NA	TBC	01 Jun 2022

Abbreviations: CIRI-IT, Centro Interuniversitario per la Ricerca sull'Influenza e le altre Infezioni; FISABIO, Fundación para Fomento de Investigación Sanitaria y Biomédica la Comunidad Valenciana; GH Charleroi, Grand Hôpital de Charleroi; GTPUH, Germans Trias i Pujol University Hospital; HUHV, Hospital Universitari Vall d'Hebron; N/A, Not Applicable – no retrospective recruitment; TBC, to be confirmed; UZA, Universitair Ziekenhuis Antwerpen.

BACKGROUND OF THIS MASTER PROTOCOL

This master protocol describes a non-interventional study to estimate the effectiveness of COVID-19 vaccines against COVID-19 severe disease in Europe. The study is a multi-country, hospital-based, case-control study with test-negative controls (test-negative case-control design, TNCC). This master protocol will be used to create Study Requestor-specific protocols that meet the requirements of the Study Requestor and to create site-specific protocols that reflect the data collection and requirements at the specific Study Sites (Study Contributors). This Master protocol is set up to harmonise Study methods (e.g., study objectives, subject inclusion/exclusion criteria, case definitions, exposures, outcomes and data collection) and to mutualise healthcare providers/study site resources in primary data collection.

This master protocol has been developed by the COVIDRIVE public-private partnership. Current COVIDRIVE members are FISABIO (Spain), P95 (Belgium), THL (Finland), AstraZeneca (UK), CureVac (Germany), GSK (Belgium), Janssen (Belgium), Moderna (US), Novavax (US), Sanofi (France), Valneva (Austria) and Bavarian Nordic (Denmark). Bayer contributed to this protocol on behalf of the CureVac-Bayer COVID-19 vaccine collaboration. The outline of this master protocol was developed in parallel to the writing of similar protocols by other initiatives (ECDC/WHO-EU, ACCESS). The COVIDRIVE outline and master protocol were subsequently harmonised with the ECDC/WHO-EU protocol to facilitate the comparison of study results. Comments received by the COVIDRIVE Independent Scientific Committee (ISC), the EMA and ECDC are reflected in version 2.3 and all subsequent versions of this protocol. Additional comments received by the COVIDRIVE ISC are also reflected in version 4.0.

« This protocol is based on COVIDRIVE's Master Protocol. Several partners are using this study to collect brand-specific vaccine effectiveness data. The main data collection is common across partners. »

STUDY-SPECIFIC PROTOCOL

Brand-specific COVID-19 vaccine effectiveness against severe COVID-19 disease in Europe

Version [X.X]

[MM/DD/YYYY]

1 TITLE PAGE

« Text between square brackets [ ] are placeholders to be completed. Text between double angle quotation marks « » are instructions to be deleted afterwards. »

Abbreviated study title	[internal abbreviated study title]
Full study title	[internal full study title]
Study ID	[internal study ID]
EU PAS registry number	[number]
Master Protocol version	[number]
Protocol version	[number]
Date of protocol version	[date]
Active substance(s)	[name]
Medicinal product(s)	
Product reference	
Procedure number	
Indication(s)	
Marketing authorisation holder(s)	
Study Requestor(s)	[company or institution name(s)]
Study status	Non-interventional
Research question and objectives	***« Objectives to be selected/modified »*** Co-primary objectives: 1. To estimate brand-specific COVID-19 vaccine effectiveness (CVE) against hospitalisation due to laboratory-confirmed SARS-CoV-2 in severe acute respiratory infection (SARI) patients who have been vaccinated with **at least 1 COVID-19 vaccine dose,** compared to unvaccinated patients. 2. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who have **completed a primary series vaccination,** compared to unvaccinated patients. *3.* To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who previously completed a primary series with any COVID-19

	vaccine and have received **at least one additional COVID-19 vaccine dose [(1)],** compared to, ▪ unvaccinated patients ▪ patients who previously completed at least a primary series with any COVID-19 vaccine but who did not receive the last additional dose of interest [(2)]. 4. [Only to support the interpretation of objective 3] [(3)]: To estimate CVE across brands against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who **previously completed at least a primary series with any COVID-19 vaccine but who did not receive the last additional dose of interest [(2)]**, compared to unvaccinated patients Secondary objectives: See Section 1414.2. Exploratory objectives: See Section 1414.3.
Country(ies) of study	[name 1, name 2, …]
Protocol main author(s)	[name 1, name 2, …]

(1) Throughout the protocol, additional dose refers to booster doses (1st, 2nd, 3rd,…). COVID-19 vaccine dose will be classified as primary (P) or additional dose (N) by expert consensus

(2) Patients who did not receive the last additional dose of interest received one dose less (P+N-1) compared to the patients who received one additional dose of the vaccine of interest (P+N), further explanation can be found in section 15.14.4.

(3) The SARI patients used for the supporting objective are exactly the same patients as the ones used for the comparator groups of the supported objective.

This protocol contains confidential information that should only be disclosed to those persons responsible for execution and organisation of the study and on condition that all such persons agree not to further disseminate it.

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6 ABBREVIATIONS

ADE	Antibody-dependent enhancement
CCA	Complete case analysis
CIOMS	Council for International Organisations of Medical Sciences
COVID-19	Coronavirus disease 2019
CRS	COVIDRIVE Research Server
CVE	COVID-19 vaccine effectiveness
DMP	Data management plan
DPO	Data protection officer
ED	Emergency Department
EDC	Electronic Data Capture
ECDC	European Center for Disease Prevention and Control
EDTA	Electronic data transfer application
EMA	European Medicines Agency
EU	European Union
EU/EEA	European Union/European Economic Area
GDPR	General Data Protection Regulation
GEE	Generalised Estimating Equations
GEP	Good Epidemiological Practice
ICF	Informed consent form
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive care unit
IHME	Institute for Health Metrics and Evaluation
LAR	Legally Acceptable Representative(s)
MAH	Marketing authorisation holder
NIP	National immunisation programmes
NPI	Non-pharmaceutical interventions
PAES	Post-authorisation efficacy study
QAAC	Quality Assurance and Audit Committee
RE-MA	Random-effects meta-analysis
RDP	Remote desktop protocol
RMP	Risk management plan
RT-PCR	Reverse transcription polymerase chain reaction
rVE	relative Vaccine Effectiveness
SARI	Severe acute respiratory infection
SARS-CoV-2	Severe acute respiratory syndrome Coronavirus 2
SAP	Statistical analysis plan
SFTP	Secure file transfer protocol
TFL	Tables, figures, and listings
TMA	Transcription mediated amplification
TNCC	Test-negative case-control design
SEIR	Susceptible – exposed – infectious – recovered
SOP	Standard operating procedure
VAED	Vaccine-associated enhanced disease
VAERD	Vaccine-associated enhanced respiratory disease
WHO	World Health Organisation

7 RESPONSIBLE PARTIES

« Complete for study-specific protocols. »

7.1 Principal investigator

Name:
Organisation:
Address:
E-mail:

7.2 Study Requestor(s)

Name:
Organisation:
Address:
E-mail:

Name:
Organisation:
Address:
E-mail:

7.3 Study sponsor

Name:
Organisation
Address
E-mail:

7.4 Study team

Name, role:
Organisation:
Contribution:
E-mail:

Name, role:
Organisation:
Contribution:
E-mail:

Name, role:
Organisation:
Contribution:
E-mail:

7.5 Study contributors (sites)

Organisation:
Address:
Name investigator:
E-mail:

Organisation:
Address:
Name investigator:
E-mail:

7.6 External partner(s)/committee(s)

Name, role:
Organisation:
Contribution:
E-mail:

Name, role:
Organisation:
Contribution:
E-mail:

Name, role:
Organisation:
Contribution:
E-mail:

8 ABSTRACT

Background

- Since its emergence in 2019, SARS-CoV-2 has become a great challenge to public health with the COVID-19 waves having devastating societal impacts.
- COVIDRIVE is a public-private partnership built upon the IMI-DRIVE project and adapting its tools and structure to the specificities of COVID-19 vaccine effectiveness (CVE). COVIDRIVE was launched in June 2021 to address the joint need to monitor COVID-19 vaccination programs for public health institutues and assess brand-specific COVID-19 vaccine effectiveness for vaccine companies as part of their regulatory obligations. COVIDRIVE started its study's patient recruitment in September 2021.
- The 'Consideration on core requirements for Risk Management Plans (RMPs) of COVID-19 vaccines' by the European Medicines Agency (EMA) states that "Vaccine effectiveness studies should be included and that it is recommended for the Marketing Authorisation Holder (MAH) to make use of existing EU efforts that could provide brand-specific data reliably and timely" [1]. The COVIDRIVE project fits this recommendation and aims to build a European platform for continuous monitoring of COVID-19 vaccines' effectiveness informing regulatory and public health authorities.
- The first COVID-19 vaccines have received marketing authorisation and there are more COVID-19 vaccines to come.
- COVIDRIVE developed the initial version of the study outline of this protocol in parallel to the development of similar protocols by other initiatives [2,3]. The current protocol and its amendments have been harmonised with the other protocols to facilitate results' comparison, potential future data sharing or collaboration in Europe.

Research question

To continuously monitor CVE against COVID-19 hospitalisations at the brand level using a network of hospitals across Europe.

Objectives

« Objectives are to be selected, prioritised, and modified by the Study Team. The objectives 1 and 2 are to be interpreted as the evaluation of the effectiveness of primary vaccination with unvaccinated subjects as comparator group. Objective 3 is to be interpreted as the evaluation of the effectiveness of additional dose(s). Each unique combination of COVID-19 vaccine doses observed in the study will be classified as primary series or additional dose/booster by expert consensus (within and between study teams). The status of 'completed primary series' and number of additional doses received will be similarly established. Objectives can differ between the study-requestor-specific protocols.»

Co-primary:

1. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in severe acute respiratory infection (SARI) patients who have been vaccinated with **at least 1 COVID-19 vaccine dose,** compared to unvaccinated patients.
2. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who **completed a primary series vaccination,** compared to unvaccinated patients.
3. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who previously completed a primary series with any COVID-19 vaccine and have received **at least one additional COVID-19 vaccine dose** [(1)], compared to,
    - unvaccinated patients
    - patients who previously received a primary series vaccination with any COVID-19 vaccine but who did not receive the last additional dose of interest [(2)]
4. [Only to support the interpretation of objective 3 [(3)]]: To estimate CVE across brands against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who **previously completed at least a primary series with any COVID-19 vaccine but who did not receive the last additional dose of interest [(2)]**, compared to unvaccinated patients.

Secondary: All secondary objectives are stratifications to the co-primary objectives.

1. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who have been vaccinated with **at least 1 COVID-19 vaccine dose**, compared to unvaccinated patients,
    - by SARS-CoV-2 genetic variants.
    - within populations of special interest (e.g. specific age groups, specific immunocompromised or chronic conditions, pregnant women).
    - by time since last COVID-19 vaccine dose.
    - by time between COVID-19 vaccine doses.
2. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who have **completed a primary series vaccination,** compared to unvaccinated patients,
    - by SARS-CoV-2 genetic variants.
    - within populations of special interest (e.g. specific age groups, specific immunocompromised or chronic conditions, pregnant women).
    - by time since last COVID-19 vaccine dose.
    - by time between COVID-19 vaccine doses.
3. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who previously completed a primary series with any COVID-19 vaccine and have received **at least one additional COVID-19 vaccine dose [(1)],** compared to (1) unvaccinated patients

and to (2) patients who previously completed a primary series with any COVID-19 vaccine but who did not receive the last additional dose of interest [2],

- by SARS-CoV-2 genetic variants.
- within populations of special interest (e.g. specific age groups, specific immunocompromised or chronic conditions, pregnant women).
- by time since last COVID-19 vaccine dose.
- by time between last two COVID-19 vaccine doses.
- by number or type(s) [4] of the COVID-19 vaccine doses given prior to the last dose.

4. [Only to support the interpretation of secondary objective 3 [3]]: To estimate CVE across brands against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who **previously completed at least a primary series with any COVID-19 vaccine but who did not receive the last additional dose of interest** [2], compared to unvaccinated patients,

   - by SARS-CoV-2 genetic variants.
   - within populations of special interest (e.g. specific age groups, specific immunocompromised or chronic conditions, pregnant women).
   - by time since last COVID-19 vaccine dose.
   - by time between last two COVID-19 vaccine doses.
   - by number or type(s) [4] of the COVID-19 vaccine doses received.

Exploratory: Exploratory objectives 1 to 4 are stratifications to the co-primary objectives.

1. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in severe acute respiratory infection (SARI) patients who have been vaccinated with **at least 1 COVID-19 vaccine dose,** compared to unvaccinated patients,

   - by severity level [5].
   - by calendar time [6].

2. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who **completed a primary series vaccination**, compared to unvaccinated patients,

   - by severity level [5].
   - by calendar time [6].

3. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who previously completed a primary series with any COVID-19 vaccine and received **at least one additional COVID-19 vaccine dose** [1]**,** compared to (1) unvaccinated patients and to (2) patients who previously completed a primary series with any COVID-19 vaccine but who did not receive the last additional dose of interest [2],

- by severity level [5].
- by calendar time [6].

4. [Only to support the interpretation of exploratory objective 3 [3]]: To estimate CVE across brands against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who **previously completed at least a primary series with any COVID-19 vaccine but who did not receive the last additional dose of interest** [3], compared to unvaccinated patients,
    - by severity level [5].
    - by calendar time [6].
5. To estimate the brand-specific effect of COVID-19 vaccination in patients who have *[been vaccinated with at least 1 COVID-19 vaccine dose – received primary series – …]* [7] on **length of hospital stay** (in days) due to laboratory-confirmed SARS-CoV-2 admission compared with patients who *[are unvaccinated – have been vaccinated with at least 1 COVID-19 vaccine dose - …].*
6. To study the potential occurrence of **vaccine-associated enhanced disease (VAED)** by describing the **clinical and laboratory features of critical COVID-19 disease** [8] cases, by **COVID-19 vaccine exposure status and time since vaccination.** [9]

(1) Throughout the protocol, additional dose refers to booster doses (1st, 2nd, 3rd…). COVID-19 vaccine dose will be classified as primary (P) or additional dose (N) by expert consensus.

(2) Patients who did not receive the last additional dose received one dose less (P+N-1) compared to the patients who received one additional dose of the brand of interest (P+N), further explanation can be found in section 15.14.4.3.

(3) The SARI patients used for the supporting objective are exactly the same patients as the ones used for the comparator groups of the supported objective.

(4) Only estimated if the type includes at least two brands or only the brand of interest.

(5) Three mutually exclusive categories: (a) hospital admission without intensive care unit (ICU) admission and without in-hospital death, (b) ICU admission without in hospital death and (c) in-hospital death.

(6) Calendar time at date of hospital admission as a proxy for changing genetic variants of the SARS-CoV-2 virus.

(7) The text between square brackets needs to be selected to match the exposure definitions from the co-primary objectives.

(8) Critical COVID-19 disease is defined as being admitted to ICU due to laboratory-confirmed SARS-CoV-2.

(9) It is postulated that the potential VAED risk may change with waning vaccine-induced immunity, hence with time since vaccination as a proxy.

Study methods

Study design: A multi-country hospital-based case-control study with test-negative controls (test-negative case-control study).

Data sources: A combination of primary and secondary data sources.

Study duration: Minimum 1 year with an expected study duration of 2 years.

Countries: The study will be conducted in multiple countries in Europe[(1)].

Study participants: Individuals presenting at the participating hospitals during the study period who 1) are hospitalised and meet the SARI case definition AND who 2) meet the following **inclusion criteria:**

- Ever eligible for COVID-19 vaccination following the regional/national immunisation recommendations prior to hospital admission
- Willing and able to provide informed consent, when applicable, obtained from the patient or from the patient's Legally Acceptable Representative(s) (LAR)

BUT who do NOT meet the following **exclusion criteria**:

- COVID-19 hospitalisation within 3 months prior to the current admission. Hospital transfers are not considered as a prior hospitalisation.
- Cannot be swabbed due to severe septum deviation, obstruction, or other conditions that contra-indicate swabbing.
- Received last vaccine dose with other than EMA-approved COVID-19 vaccine brand.

Hospitalised person: SARI patients will be identified among patients admitted to the hospital with at least one overnight stay.

SARI case definition (possible COVID-19 case): A possible COVID-19 case is defined as a hospitalised person with a suspicion of a respiratory infection with **at least one** of the following symptoms:

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

with symptom onset within the **last 14 days** prior to hospital admission as per ECDC definition [3].

Test-positive cases: study participants meeting the **SARI** case definition AND testing **positive** for at least one SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) or similar molecular assays (e.g. Transcription Mediated Amplification (TMA)) with specimens collected within 14 days prior and up to [72 hours][(2)] after hospital admission.

Test-negative controls: study participants meeting the **SARI** case definition AND testing **negative** for all SARS-CoV-2 RT-PCR or similar molecular assays (e.g. TMA) with specimens collected within 14 days prior and up to [72 hours][(2)]. after hospital admission. Test-negative controls must have a negative result for the RT-PCR or similar molecular assay within [72h][(2)] of at hospital admission.

Case-control ratio: When feasible and resource-saving, the number of controls sampled per calendar week will be restricted to maximum 3 times the number of cases sampled that same week.

[(1)] The list of countries will be extended as the network grows.[(2)] 72 hours after hospital admission is the maximum delay accepted for testing. The brand-specific protocol will specify whether the study uses a delay of 24 hours, 48 hours or 72 hours after admission.

Vaccine exposure

« Exposure outcomes to be aligned with study objectives. »

Vaccinated with at least one dose: vaccinated with **at least 1 dose** of the COVID-19 vaccine brand of interest [(1)] > 14 days prior to SARI symptom onset.

Completed primary series vaccination: **completed a primary series** with the COVID-19 vaccine brand of interest [(1)] > 14 days prior to SARI symptom onset.

At least one additional COVID-19 vaccine dose: **any COVID-19 vaccine dose** with the brand of interest [(1)] given **as last dose** > 14 days prior to SARI symptom onset to a subject who previously completed a primary series with any COVID-19 vaccine(s) [(2)] [(3)].

Previously vaccinated but did not receive the last additional dose of interest: previously completed at least a primary series with any COVID-19 vaccine prior to SARI symptom onset and was **eligible [(4)] to receive the last additional dose of interest but did not receive it.**

Recently vaccinated: vaccinated with any COVID-19 vaccine <= 14 days prior to SARI symptom onset [(5)].

Unvaccinated: did **not receive any COVID-19 vaccine dose.**

Other: additional vaccine exposure case definitions might be defined depending on the real-life use of the COVID-19 vaccines.

[(1)] The COVID-19 vaccine with brand of interest must be EMA approved.

[(2)] Throughout the protocol, additional dose refers to booster doses (1st, 2nd, 3rd…). COVID-19 vaccine dose will be classified as primary (P) or booster additional dose (N) by expert consensus.

[(3)] For the secondary objective, the study-requestor may define specific exposure based on the number of COVID-19 vaccine doses and type(s) of the COVID-19 vaccine doses given prior to the last dose.

[(4)] At least 3 months since last dose.

[(5)] Recently vaccinated patients will not be considered protected by the last vaccine dose. Their data use will be specified in the statistical analysis plan. This applies to both primary series and additional doses.

Covariates

Covariates: Variables that are potential confounders and/or effect modifiers and will be *collected at all study sites* include age, sex, history of medical diagnosis for selected morbidities of interest (asthma, lung disease, cardiovascular disease, hypertension, chronic kidney disease, type 2 diabetes, cancer, immunodeficiency), body mass index (BMI), vaccination against pathogens causing COVID-19 like symptoms (influenza, pneumococcus), and calendar time.

Variables that will be *potentially additionally collected at certain study sites* include previous SARS-CoV-2 infection, any use of monoclonal antibodies and other anti-SARS-CoV-2 antibody products as either treatment or pre- or post-exposure prophylaxis prior to hospitalisation. precautionary health behavior, employment as health care worker (HCW), long-term care facility residence and smoking history.

Sample size

Simulation-based sample size calculations were performed.

- For brand-specific primary series CVE estimates, having at least 2,210 SARI cases leads to an expected 95% confidence interval (CI) range ≤30%, assuming a study conducted in ten sites, an overall vaccination coverage of 50% to 90% in the study population, brand-specific vaccination proportions ranging from 10% to 50%, a case-control ratio of 1:1, and a CVE of 80% or 90%.

- For relative brand-specific CVE estimates of additional COVID-19 vaccine doses in subjects who were previously vaccinated, having at least 2,030 SARI cases leads to an expected 95% CI range ≤30%, assuming a study conducted in ten sites, an overall primary vaccination coverage of 80% in the study population with 90% receiving an additional COVID-19 vaccine dose, brand-specific vaccination proportions for the additional dose ranging from 10% to 50%, a case-control ratio of 1:1, an assumed CVE of comparator groups of 80% and a relative CVE of 70% to 80%.

An interim analysis is planned when data on a sufficient number of COVID-19 cases vaccinated with the brand-specific vaccine as primary series/additional last dose has been collected to provide expected 95% CIs range ≤15% or a power of 50% with the same assumptions as described above.

It is expected that at least ten study sites will be included in the study with a minimum of 400 SARI cases enrolled per 6 months per site. The sample size requirements strongly depend on the case-control ratio, overall vaccination coverage and share of the different vaccine brands. As such, the sample size requirements will be different for the different vaccine brands. In case the parameter settings used for these sample size calculations are very different from what is observed in the study, the sample size calculations will be updated accordingly.

Data collection and SARS-CoV-2 testing

Vaccination status, COVID-19 vaccine brand information and date of vaccination(s) will be ascertained by consulting vaccination registries, vaccination cards or medical records (depending on the country and region). Batch information will be additionally collected when available.

RT-PCR or another RNA amplification system with at least the same sensitivity as RT-PCR (e.g. TMA) will be required to confirm COVID-19 disease. Information on the SARS-CoV-2 genetic variants will be collected to the extent possible, preferably on all vaccine failures for brands of interest and on a sufficiently large proportion of the unvaccinated cases to meet the study objectives"

After study enrollment, data will be collected directly from the patient or by consulting medical records. Information to be collected at minimum includes date of SARI symptom onset, date of hospitalisation, and information on the potential confounders.

Context information on national/regional immunisation recommendations, SARS-CoV-2 genetic variant circulation and COVID-19 vaccine label information will be collected.

Statistical analysis

Descriptive analyses will be performed to describe the study population, the evolution of the SARS-CoV-2 dynamics and the COVID-19 vaccination coverage for the brands of interest.

Brand-specific CVE estimates pooled across study sites will be obtained through random-effects meta-analysis (RE-MA) on the log-transformed site-specific estimates, or alternatively, when cell counts are too low (i.e. resulting in non-robust RE-MA standard error estimates), Generalised Estimating Equations (GEE) will be used. Cell counts are expected to be low when the vaccine effectiveness is very high and/or the proportion of the vaccination coverage covered by the brand of interest is low.

- Pooled brand-specific CVE estimates will be obtained through RE-MA on the log-transformed site-specific estimates, where the latter are obtained using logistic regression, adjusting for the confounders. Restricted maximum likelihood will be used to obtain the pooled meta-analysis estimates and 95% CIs. The modified Hartung-Knapp correction will be used to estimate the variance of the mean effect. The estimates and 95% CIs will then be back-transformed to obtain the pooled CVE estimates and 95% CIs. Sensitivity analyses will be conducted when appropriate. Pooled brand-specific relative CVE estimates will be obtained using the same methods. One-stage pooling will be preferred when most, if not all, the sites have shared individual patient data; and additionally, when the number of clusters as well as the total sample size of the study are low, as this leads to more efficient estimates compared to two-stage methods. Two-stage pooling will be performed as a sensitivity analysis.
- For the GEE models, the approach for fitting logistic regression developed by Liang and Zeger [4] will be used, assuming an exchangeable correlation matrix to account for potential within-cluster homogeneity in outcomes. The robust sandwich estimator will be used to estimate the standard error of the marginal effect estimates. Clusters will be defined at hospital-level or hospital network-level, depending on the similarities of the hospitals belonging to the same network.

A full statistical analysis plan (SAP) will be developed prior to the conduct of the analysis.

Reporting

Progress reports will be prepared every two months. Interim analyses will be planned as appropriate. A final study report will be written for each of the individual COVID-19 vaccine brands of interest. In case the Study Requestor is an MAH, interim reports and final report will be submitted to EMA by the MAH to meet regulatory requirements.

Data management

Data collected at study sites will be checked for quality and transferred to a dedicated, secured central server hosted by P95. If patient-level data transfer is not possible, alternative solutions will be sought. A data management plan (DMP) is written prior to the start of the data collection. The DMP describes all functions, processes, responsibilities and specifications for data collection, cleaning, and validation.

The expert consensus group to classify each unique combination of COVID-19 vaccines doses as primary series or additional dose will consist of members of the Study Teams. In case of disagreement, COVIDRIVE's Independent Scientific Committee (ISC) will be consulted.

Ethical considerations

The site-specific protocols will be submitted to relevant ethics committee(s) (ECs) following local regulations. Informed consent will be obtained from all participants/guardians as specified by the national/regional EC.

Study limitations

- Low sensitivity and specificity of the RT-PCR test introduces stronger bias (towards underestimating the effectiveness) in the test-negative case-control design compared to the standard case-control design [5]. This bias with the test-negative design increases with increasing SARS-CoV-2 positivity rates within the SARI patients. This potential bias might be mitigated/explored by shortening the time lag between symptom onset and taking the respiratory sample as the sensitivity of the RT-PCR tests decreases with increasing time lag [6].
- The SARS-CoV-2 positivity rates within the SARI patients varies over time and might be very high during certain calendar months, potentially making it difficult to obtain a sufficient number of controls that allow adjustment for time-varying confounding.
- Subjects at highest risk for severe COVID-19 disease are targeted for vaccination first and might have a higher propensity to self-select for vaccination compared to subjects at lower risk. When not properly controlled for, this will lead to a substantial underestimation of the vaccine effectiveness.
- Most EU countries are implementing COVID-19 booster vaccination programmes, and increasingly heterogeneous vaccination policies are being adopted. Furthermore, additional COVID-19 vaccines are being marketed. The booster programmes and additional vaccine brands may result in complex and heterogenous combinations of COVID-19 vaccine doses. This heterogeneity potentially leads to paucity of study patients exposed to a specific combination of COVID-19 vaccine doses.
- The emergence of monoclonal antibodies and other anti-SARS-CoV-2 antibody products that impact the course of COVID-19 disease might affect the CVE estimates. Thus, confounders such as healthcare-seeking behaviour and chronic conditions might impact both the likelihood of vaccination and of treatment.
- Pre-existing immunity is a factor influencing vaccine effectiveness estimates. Prior natural infection is a typical reason for pre-existing immunity, however prior infections may be undocumented. A careful interpretation of all time-related effects will be warranted.

Dissemination

This generic protocol and its significant amendments will be posted on the European Union electronic Register of Post-Authorisation Studies (EU PAS) register. Study reports, each for a specific vaccine brand, will be posted on the EU PAS register and will be submitted to peer-reviewed open-source international journal(s).

Updates on study progress will be posted on the COVIDRIVE web site (www.covidrive.eu).

Funding

This generic Master protocol V4.0 has been developed by the COVIDRIVE partnership, which has received funds from AstraZeneca, Bavarian Nordic, CureVac, GSK, Janssen, Moderna, Novavax, Sanofi, and Valneva, leveraging public health capacity from FISABIO and THL and existing infrastructure at P95. Other partners (vaccine companies or other institutes) might join the COVIDRIVE project at later stages.
The execution of the study will be funded by companies, which may join progressively. This specific funding will be transparently acknowledged in all communications.

COVIDRIVE partnership

COVIDRIVE is an open public-private partnership. Current members are FISABIO (Spain), P95 (Belgium), THL (Finland), AstraZeneca (UK), Bavarian Nordic (Denmark), CureVac (Germany), GSK (Belgium), Janssen (Belgium), Moderna (US), Novavax (US), Sanofi (France) and Valneva (Austria). The partnership aims to enable a continuous monitoring of brand- specific CVE in Europe.

Study status

Non-interventional

Study sponsor

P95

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9 AMENDMENTS AND UPDATES

Version	Version date	Reason for new version
V3.1	02 June, 2021	Submitted to EU PAS on 02/08/2021 (EUPAS42328)
V3.2	June, 2021	Removing 'other hospital controls'
V3.3	Dec, 2021	Amendments: • use the ECDC possible case definition for SARI instead of the stricter WHO case definition • restructuring the order and organisation of the secondary and exploratory objectives without changing the content • adding variables: - use of anti-SARS-CoV-2 antibody products or similar for pre-exposure prophylaxis, post-exposure prophylaxis and post symptom-onset but prior hospitalisation - full COVID-19 vaccination history including additional doses - symptoms related to the SARI case definition • in addition to RT-PCR, also allowing confirmation of COVID-19 using RNA amplification systems with at least the same sensitivity as RT-PCR (e.g. TMA). • Improving sample size section • Improving Annex 1 (VAED)
V4.0	Oct, 2022	Adding additional dose vaccine effectiveness to all relevant sections Adding exclusion criterium "received last vaccine dose with other than EMA-approved COVID-19 vaccine brand". Maximum delay for SARS-CoV-2 testing after hospital admission is extended from 24hours to 72 hours.

10 MILESTONES

« Modify milestones as appropriate »

Milestone	Planned date
<Registration of study protocol in the EU PAS register>	[Date]
Start of data collection	[Date]
End of data collection	[Date]
<Study progress report 1>	[Date]
<Study progress report x>	[Date]
<Study progress report x>	[Date]
<Interim report 1>	[Date]
<Interim report x>	[Date]
<Interim report x>	[Date]
Final report of study results	[Date]
<Registration of study results in the EU PAS register>	[Date]

11 INVESTIGATOR SIGNATURE PAGE

Study title: [title]

Protocol number: [number]

I have read and I understand the protocol and agree that it contains the ethical, legal, and scientific information necessary to participate in this study. My signature confirms the agreement of both parties that the study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to Good Epidemiological Practice (GEP), the ethical principles that have their origins in the Declaration of Helsinki and the General Data Protection Regulation (GDPR).

I will provide copies of this protocol as needed to all physicians, nurses, and other professional personnel responsible to me who will participate in the Study. I will discuss the protocol with them to assure myself that they are sufficiently informed regarding the conduct of the study. I am aware that this protocol will need to be approved by an appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC) prior to any patients being enrolled and that I am responsible for verifying whether that requirement is met. I agree to adhere to the attached protocol and if requested to provide copies of medical information for the purpose of verification of submitted information, I will comply.

Investigator:

_____
Print name

_____ _____
Signature Date

_____
Print name of institution or practice and location

12 SPONSOR SIGNATURE PAGE

Study title: [title]

Protocol number: [number]

Sponsor:

_____
Print name

_____ _____
Signature Date

_____
Print name of institution or practice and location

13 RATIONALE AND BACKGROUND

In December 2019, an outbreak of respiratory disease caused by a novel coronavirus strain was reported in Wuhan City, Hubei Province, China. The novel coronavirus was named 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2), while the disease associated with it is referred to as 'coronavirus disease 2019' (COVID-19). The virus spread to different parts of China and an increasing number of countries worldwide and on 12 March 2020 the World Health Organisation (WHO) announced that the outbreak was characterised as a pandemic. Following the identification of SARS-CoV-2 and its global spread, large epidemics of COVID-19 occurred in Europe. In response, European countries implemented large-scale unprecedented nonpharmaceutical interventions (NPIs) such as closure of schools and national lockdowns. Data collected by the European Centre for Disease Prevention and Control (ECDC) from 31 countries showed on [19 March 2021] a total of [24,175,984] COVID-19 cases and [577,310] related deaths in the European Union/European Economic Area (EU/EEA) since the start of the pandemic [1].

The development of safe and effective vaccines is key in containing the SARS-CoV-2 pandemic. As of [10 March 2021], the following COVID-19 vaccines have been granted conditional marketing authorisation in the European Union (EU) by the European Medicines Agency (EMA): Comirnaty® from BioNTech/Pfizer on 21 December 2020, COVID-19 Vaccine Moderna on 6 January 2021, COVID-19 Vaccine AstraZeneca on 29 January 2021 and COVID-19 Vaccine Janssen on 11 March 2021 [2].

Despite the thorough investigation of the efficacy of the COVID-19 vaccines during clinical trials, it is crucial to continue evaluating how well the vaccines prevent disease under real-world conditions once they are being used as part of the national immunisation programmes (NIPs). Booster vaccination has been shown to be effective [3, 4] and extensive COVID-19 booster vaccination programmes are being implemented in most European countries.

Questions that are typically unanswered by clinical trials and that remain to be evaluated by real-world effectiveness studies include amongst others the duration of vaccine protection and waning of immunity, effectiveness against disease by specific and newly emerging SARS-CoV-2 strains, effectiveness against severe COVID-19 disease, and effectiveness in special risk groups such as immunocompromised, frail or subjects with chronic conditions or existing comorbidities.

Many of the ongoing and planned real-world effectiveness evaluations make use of existing programmes for the evaluation of the effectiveness of influenza vaccines. In Europe, the I-MOVE (Influenza – Monitoring Vaccine effectiveness in Europe) network of public partners joined forces and created the I-MOVE COVID-19 consortium [5]. COVIDRIVE, a public-private partnership launched in June 2021, is leveraging DRIVE, an existing vaccine effectiveness platform that provides yearly brand-specific influenza vaccine effectiveness estimates to the EMA. COVIDRIVE was launched to address the joint need to monitor COVID-19 vaccination programmes for public health institutes and assess brand-specific COVID-19 vaccine effectiveness (CVE) for vaccine companies as part of their regulatory obligations. Current COVIDRIVE members are FISABIO (Spain), P95 (Belgium), THL (Finland), AstraZeneca (UK), Bavarian Nordic (Denmark), CureVac (Germany), GSK (Belgium), Janssen (Belgium), Moderna (US), Novavax (US), Sanofi (France) and Valneva (Austria).

This protocol details a non-interventional study to estimate the effectiveness of COVID-19 vaccines against COVID-19 related hospitalisations through the COVIDRIVE partnership. Studying the effectiveness against COVID-19 hospitalisations is prioritised as COVID-19 hospitalisations are the main reason for national and regional governments to impose NPIs. Hence, having accurate and timely information on how well the different COVID-19 vaccines protect and remain protective over time against hospitalisations is essential to successfully manage the pandemic. Considering the rarity of COVID-19 hospitalisations, clinical trials are not well suited to study this outcome and complementary real-world studies are required. Therefore, this protocol describes a multi-centre, hospital-based, case-control study with test-negative controls (test-negative case-control design, TNCC). Data will be collected through a wide network of hospitals located in several European countries. A hospital-based case control study is an efficient design for studying rare outcomes, potentially allowing for detailed medical information and additional data collection directly from the patient or healthcare provider.

In addition, the potential for vaccine-associated enhanced disease (VAED) will be studied as part of this vaccine effectiveness study as VAED relates to the efficacy/effectiveness outcomes. VAEDs are atypical and severe presentations of clinical infections affecting individuals exposed to a wild-type pathogen after having received a prior vaccine against the same [6, 7]. VAED is a theoretical concern for COVID-19 vaccines, based on observations from other respiratory viruses and from animal models of highly pathogenic coronaviruses [6, 7]. Historically, VAED has been observed following administration of measles and RSV vaccines [8]. While the underlying potential mechanisms for VAED are unclear, VAED invariably involves a memory immune response primed by vaccination and appears to target the same organs as wild-type infections [6, 7]. Given the lack of clinical findings, immunological assays, or biomarkers of VAED that can differentiate severe breakthrough disease from VAED at this time, it is challenging if not impossible to assess VAED on an individual case basis. Instead, the assessment of this theoretical risk needs to be at a population level. As VAED is postulated to occur with low levels of neutralising antibodies while the presence of non-neutralising or poorly neutralising antibodies still facilitate viral uptake, an association between VAED risk and time since vaccination may be observed if antibodies wane as has been observed in Dengue-naïve individuals [9].

14 RESEARCH QUESTIONS AND OBJECTIVES

14.1 Co-primary objectives

1. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in severe acute respiratory infection (SARI) patients who have been vaccinated with **at least 1 COVID-19 vaccine dose**, compared to unvaccinated patients

2. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who **completed a primary series vaccination,** compared to unvaccinated patients

3. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who previously completed their primary series with any COVID-19 vaccine and have received **at least one additional COVID-19 vaccine dose** [(1)]**,** compared to,

   - unvaccinated patients
   - patients who previously completed a primary series vaccination with any COVID-19 vaccine but who did not receive the last additional dose of interest [(2)]

4. [Only to support the interpretation of objective 3 [(3)]]: To estimate CVE across COVID-19 vaccine brands against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who **previously completed a primary series of vaccination with any COVID-19 vaccine but who did not receive the last additional dose of interest** [(2)], compared to unvaccinated patients

« Objectives are to be selected, prioritised, and modified by the study team. The objectives 1 and 2 are to be interpreted as the evaluation of the effectiveness of primary vaccination with unvaccinated subjects as comparator group. Objective 3 and 4 is to be interpreted as the evaluation of the effectiveness of additional dose. Each unique combination of COVID-19 vaccine doses observed in the study will be classified as primary or additional dose/booster by expert consensus (within and between study teams). The status of 'completed primary series' and number of additional doses received will be similarly established. Objectives can differ between the study-requestor-specific protocols.»

14.2 Secondary objectives

« All secondary objectives are stratifications to the co-primary objectives.»

1. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who have been vaccinated with **at least 1 COVID-19 vaccine dose**, compared to unvaccinated patients,

   - by SARS-CoV-2 genetic variants.
   - within populations of special interest (e.g. specific age groups, specific immunocompromised or chronic conditions, pregnant women).

- by time since last COVID-19 vaccine dose.
- by time between COVID-19 vaccine doses.

2. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who **completed a primary series vaccination,** compared to unvaccinated patients,
    - by SARS-CoV-2 genetic variants.
    - within populations of special interest (e.g. specific age groups, specific immunocompromised or chronic conditions, pregnant women).
    - by time since last COVID-19 vaccine dose.
    - by time between COVID-19 vaccine doses.
3. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who previously completed a primary series with any COVID-19 vaccine and have received **at least one additional COVID-19 vaccine dose** [(1)]**,** compared to (1) unvaccinated patients and to (2) patients who previously completed a primary series with any COVID-19 vaccine but who did not receive the last additional dose of interest [(2)],
    - by SARS-CoV-2 genetic variants.
    - within populations of special interest (e.g. specific age groups, specific immunocompromised or chronic conditions, pregnant women).
    - by time since last COVID-19 vaccine dose.
    - by time between last two COVID-19 vaccine doses.
    - by number or type(s) [(4)] of the COVID-19 vaccine doses given prior to the last dose.
4. [Only to support the interpretation of secondary objective 3 [(3)]]: To estimate CVE across brands against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who **previously completed at least a primary series with any COVID-19 vaccine but who did not receive the last additional dose of interest** [(2)], compared to unvaccinated patients,
    - by SARS-CoV-2 genetic variants.
    - within populations of special interest (e.g. specific age groups, specific immunocompromised or chronic conditions, pregnant women).
    - by time since last COVID-19 vaccine dose.
    - by time between last two COVID-19 vaccine doses.
    - by number or type(s) [(4)] of the COVID-19 vaccine doses received

14.3 Exploratory objectives

« Exploratory objectives 1, 2, 3 and 4 are stratifications to the co-primary objectives.»

1. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in severe acute respiratory infection (SARI) patients who have been vaccinated with **at least 1 COVID-19 vaccine dose,** compared to unvaccinated patients,
    - by severity level [(5)].
    - by calendar time [(6)].
2. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who **completed a primary series vaccination,** compared to unvaccinated patients,
    - by severity level [(5)].
    - by calendar time [(6)].
3. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who previously completed a primary series with any COVID-19 vaccine and have received **at least one additional COVID-19 vaccine dose [(1)],** compared to (1) unvaccinated patients and to (2) patients who previously completed a primary series with any COVID-19 vaccine but who did not receive the last additional dose of interest [(2)],
    - by severity level [(5)].
    - by calendar time [(6)].
4. [Only to support the interpretation of exploratory objective 3 [(3)]]: To estimate CVE across brands against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who **previously completed at least a primary series with any COVID-19 vaccine but who did not receive the last additional dose** of interest [(3)], compared to unvaccinated patients,
    - by severity level [(5)].
    - by calendar time [(6)].
5. To estimate the brand-specific effect of COVID-19 vaccination in patients who have *[been vaccinated with at least 1 COVID-19 vaccine dose–- completed primary series vaccination]* [(7)] on **length of hospital stay** (in days) due to laboratory-confirmed SARS-CoV-2 admission compared with patients who *[are unvaccinated – have been vaccinated with at least 1 COVID-19 vaccine dose - …]*.
6. To study the potential occurrence of **VAED** by describing the **clinical and laboratory features of critical COVID-19 disease** [(8)] cases, by **COVID-19 vaccine exposure status and time since vaccination.** [(9)]

[(1)] Throughout the protocol, additional dose refers to booster doses (1st, 2nd, 3rd…). COVID-19 vaccine dose will be classified as primary (P) or additional dose (N) by expert consensus.

(2) Patients who did not receive the last additional dose received one dose less (P+N-1) compared to the patients who received one additional dose of the vaccine of interest (P+N), further explanation can be found in section 15.14.4.

(3) The SARI patients used for the supporting objective are exactly the same patients as the ones used for the comparator groups of the supported objective.

(4) Only estimated if the type includes at least two brands or only the brand of interest.

(5) Three mutually exclusive categories: (a) hospital admission without intensive care unit (ICU) admission and without in-hospital death, (b) ICU admission without in hospital death and (c) in-hospital death.

(6) Calendar time at date of hospital admission as a proxy for changing genetic variants of the SARS-CoV-2 virus.

(7) The text between square brackets needs to be selected to match the exposure definitions from the co-primary objectives.

(8) Critical COVID-19 disease is defined as being admitted to ICU due to laboratory-confirmed SARS-CoV-2.

(9) It is postulated that the potential VAED risk may change with waning vaccine-induced immunity, hence with time since vaccination as a proxy.

15 RESEARCH METHODS

15.1 Study design

This study is a multi-country, multi-centre, hospital-based case-control study with test-negative controls (TNCC design).

A combination of primary and secondary data collection will be used to obtain the relevant data.

15.2 Study contributors (sites)

This is a multi-country, multi-centre study, with hospital sites in Europe. The participating studies sites are described in Table 1.

The participating study sites are either individual hospitals or hospital networks. Depending on the hospital, the data collection will be a prospective primary data collection and in some study sites, data will additionally be retrospectively retrieved from the existing hospital databases and linked data.

For every participating study site, a site-specific protocol will be written, describing details on patient flow, data collection, laboratory tests and genomic sequencing.

Table 1. Participating study sites.

Country	Hospital name	Site (location)	Hospital population	No. of hospital beds/ICU beds
« complete »				

15.3 Study population

The study population consists of individuals (patients), presenting at the participating hospitals during the study period, who

- meet the inclusion criteria (see Section 15.3.1) but who do NOT meet the exclusion criteria (see Section 15.3.2).

AND

- are hospitalised and meet the SARI case definition (see Section 15.6.2)

15.3.1 Inclusion criteria

Individuals (patients) need to fulfil the following inclusion criteria:

- Ever eligible for COVID-19 vaccination following the national/regional immunisation recommendations prior to hospital admission

  AND

- Willing and able to provide informed consent, when applicable, obtained from the patient or from the patient's Legally Acceptable Representative(s) (LAR)

15.3.2 Exclusion criteria

- COVID-19 hospitalisation within 3 months prior to the current admission. Hospital transfers are not considered as a prior hospitalisation
- Cannot be swabbed due to severe septum deviation, obstruction, or other conditions that contra-indicate swabbing
- Received last vaccine dose with other than EMA-approved COVID-19 vaccine brand (EMA approval status at time of hospitalisation)

15.4 Study period

« Modify as appropriate »

From month 202[X], with a minimum duration of 12 months and an expected duration of two years

15.5 Study outcomes

« Study outcomes to be aligned with study objectives. »

The outcome of interest for the primary analysis will be SARS-CoV-2 detection in patients hospitalised with SARI symptoms. SARS-CoV-2 infection should be laboratory-confirmed by Reverse transcription polymerase chain reaction (RT-PCR) or another RNA amplification system with at least the same sensitivity as RT-PCR (e.g. Transciption mediated amplification (TMA)). As the SARS-CoV-2 testing practices might change over time, the test requirement for confirmation of COVID-19 disease might

be revisited. The impact of such revisions on the potential for disease misclassification will be considered.

The secondary outcomes include:

- Detection of SARS-CoV-2 genetic variants in patients hospitalised due to laboratory-confirmed SARS-CoV-2.

The exploratory outcomes include:

- Hospitalisation due to laboratory-confirmed SARS-CoV-2 by level of severity: (i) hospital admission without intensive care unit (ICU) admission and without in-hospital death, (ii) ICU admission without in-hospital death and (iii) in-hospital death.
- Clinical and laboratory features of critical COVID-19 disease cases in patients hospitalised due to laboratory-confirmed SARS-CoV-2. Critical COVID-19 disease is defined as being admitted to an ICU.

15.6 Definitions

15.6.1 Hospitalised patient

Persons admitted to the hospital with overnight stay. In case of referral to another hospital, the date of hospital admission is defined as the date of first admission.

15.6.2 SARI patient (possible COVID-19 cases)

A possible COVID-19 case is defined as a hospitalised person with a suspicion of a respiratory infection with **at least one** of the following symptoms:

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

with symptom onset within the **last 14 days** prior to hospital admission as per ECDC definition [10].

15.6.3 Test-positive case

A study participant who:

- meets the **SARI** case definition (see Section 15.6.2)

  AND

- tests **positive** in at least one SARS-CoV-2 RT-PCR or similar molecular assays with specimen(s) collected between 14 days prior to and up to [72 hours][1] after hospital admission[1].

  [1] 72 hours after hospital admission is the maximum delay accepted for testing. Each brand-specific protocol will specify whether the study uses a delay of 24 hours, 48 hours or 72 hours after admission.

15.6.4 Test-negative control

A study participant that:

- meets the **SARI** case definition (see 15.6.2)

  AND

- tests **negative** for all SARS-CoV-2 RT-PCR or similar molecular assays with specimen(s) collected between 14 days prior to and up to [72 hours] [1] after hospital admission.. Test-negative controls must have a negative result for the RT-PCR or similar molecular assay within [72h][1] of hospital admission.

  [1] 72 hours after hospital admission is the maximum delay accepted for testing. The brand-specific protocol will specify whether the study uses a delay of 24 hours, 48 hours or 72 hours after admission.

15.7 SARI patient identification

Depending on the study site, the SARI patient identification will be different. Hospitalised SARI patients will be identified prospectively (e.g. during consultation in the ED or during a pneumology consultation) or retrospectively by hospital database search or from respiratory samples sent to the virology laboratory.

«For every participating study site, the patient flow will be documented in detail.»

15.8 Exposure (COVID-19 vaccination)

15.8.1 Exposure definitions

« Exposure outcomes to be aligned with study objectives. »

1. Vaccinated with at least one dose: vaccinated with **at least 1 dose** of the COVID-19 vaccine brand of interest [(1)] > 14 days prior to SARI symptom onset.
2. Completed primary series vaccination: **completed a primary series** with the COVID-19 vaccine brand of interest [(1)] > 14 days prior to SARI symptom onset.

3. At least one additional COVID-19 vaccine dose: **any COVID-19 vaccine dose** with the brand of interest [(1)] given **as last dose** > 14 days prior to SARI symptom onset to subjects who previously completed a primary series with any COVID-19 vaccine(s) [(2)] [(3)].
4. Previously vaccinated but did not receive the last additional dose of interest: previously completed at least a primary series with any COVID-19 vaccine prior to SARI symptom onset, and was **eligible [(4)] to receive the last additional dose of interest but did not receive it**.
5. Recently vaccinated: vaccinated with any COVID-19 vaccine <= 14 days prior to SARI symptom onset [(5)].
6. Unvaccinated: did **not receive any COVID-19 vaccine dose.**
7. Other: additional vaccine exposure case definitions might be defined depending on the real-life use of the COVID-19 vaccines.

[(1)] The COVID-19 vaccine with brand of interest must be EMA approved.

[(2)] Throughout the protocol, additional dose refers to booster doses (1st, 2nd, 3rd…). COVID-19 vaccine dose will be classified as primary (P) or additional dose (N) by expert consensus.

[(3)] For its secondary objective, the Study Requestor may define specific exposures based on the number of COVID-19 vaccine doses and type(s) of the COVID-19 vaccine doses given prior to the last dose.

[(4)] at least 3 months since last dose.

[(5)] Recently vaccinated patients will not be considered protected by the last vaccine dose. Their data use will be specified in the statistical analysis plan. This applies to both primary series and additional doses.

15.8.2 Exposure ascertainment

Information on all prior COVID-19 vaccine doses will be collected. Vaccination status, vaccination date, dose and vaccine brand information are required. When feasible, batch number will be collected. Depending on the study site, the source for exposure ascertainment will be different and may include vaccination registry, medical records or vaccination cards. For every participating study site, the source documentation and its validity will be described in detail in the study site-specific study protocol.

Patients that cannot be classified into one of the exposure categories (i.e. vaccination status is unknown) will be excluded.

Context information on national/regional COVID-19 immunisation recommendations (priority groups by vaccine brand), SARS-CoV-2 genetic variant circulation and COVID-19 vaccine label information (including licensed age groups, contraindications, number of doses and timing between doses) will be collected.

15.9 Outcomes

15.9.1 Laboratory-confirmed SARS-CoV-2

Respiratory specimens will be collected from those patients eligible for the study and as per routine clinical practice. Only study sites where laboratory confirmation is done by RT-PCR or another RNA amplification system with similar sensitivity are eligible to participate to the study. Nasopharyngeal or oropharyngeal swabs are recommended.

For every participating study site, the testing policy and laboratory methods will be described in detail in the site-specific protocol. Information as summarised in Table 2 will be collected.

Genomic sequencing will be performed using commercially available molecular kits. At every study site with prospective data collection, preferably 100% of the vaccinated SARS-CoV-2 positive cases (i.e. vaccine failures) for the brands of interest and sufficiently large proportion of the unvaccinated SARS-CoV-2 positive cases will be sequenced. The size of this proportion will be chosen to obtain a sufficient number of COVID-19 cases with the variant of interest allowing the estimation of variant- and brand-specific CVE with an expected 95% CI length ≤70% (See Section 15.11 Sample size considerations).
For retrospective data collection sequencing data is obtained from medical records, when available.

Table 2. Key aspects of laboratory specimen collection and analysis

Study site name	[to be inserted]
Sampling strategy	[all patients, selection of patients fulfilling certain criteria,…]
Type of respiratory sample	[nasopharyngeal swab, nasal swab, oropharyngeal swab, branchoalveolar lavage fluid, sputum, other (specify)]
Blood sample	[Yes or no] serum (for serology if collected)
Type of molecular laboratory test	[RT-PCR, multiplex PCR, TMA, LAMP, other (specify)]
Name of molecular kit	[open]
PCR Ct value	[2-digit value] (optional)
PCR variant screening kit	[Positions screened in the S gene (501, 484, 417, 452, others)]
Full genome sequencing sampling strategy	[all, random sampling]
Full genome sequencing laboratory tests	[Illumina, Nanopore, other…]
Sequencing minimum nucleotide coverage	[value - minimum of 200 required]

Abbreviation: LAMP loop-mediated isothermal amplification

15.9.2 Hospitalisation due to laboratory-confirmed SARS-CoV-2: level of severity

The following three mutually exclusive categories will characterise the severity of the hospitalisation due to laboratory-confirmed SARS-CoV-2 disease:

1. Hospital admission without ICU admission and without in-hospital death
2. ICU admission without in-hospital death
3. In-hospital death

COVID-19 hospitalisation that takes place within 3 months of the first COVID-19 hospitalisation will be considered as part of the same episode.

15.9.3 Hospitalisation due to laboratory-confirmed SARS-CoV-2: Length of hospital stay

Length of hospitalisation stay is defined as the number of overnights spent at the hospital from hospital admission till hospital discharge or death.
COVID-19 hospitalisation that takes place within 3 months of the first COVID-19 hospitalisation will be considered as part of the same episode. The length of stays of the admission will be summed.

15.9.4 Critical COVID-19 disease

A critical COVID-19 disease case is defined as a COVID-19 disease case being admitted to the ICU. The clinical and laboratory characteristics of the critical COVID-19 disease cases will be described (Annex 1).

15.10 Covariates

The complete dataset can be found in Annex 4, and is summarised in Table 3. Some covariates are mandatory to collect for all participating study sites. All covariates are both being collected for prospective and retrospective subjects, if available.

Table 3. Study covariates

Covariate	Description	Mandatory
Age at hospital admission	Calculated based on date of birth and date of admission	x
Sex	Male, female	x
Chronic conditions (see Annex 2 for definitions)		
Asthma	Binary	x
Lung disease	Binary	x

Cardiovascular disease	Binary	x
Hypertension	Binary	x
Chronic kidney disease	Binary	x
Type 2 diabetes	Binary	x
Cancer	Binary	x
Immunodeficiency (or organ transplant)	Binary	x
Chronic liver disease	Binary	x
Pregnancy	Binary	x
Trimester	First, second, third	x
Body mass index (BMI)	Continuous	x
Smoking history	Never smoker, former smoker (smokefree for at least 28 days), current smoker	
Vaccination history influenza	Being vaccinated with at least one influenza vaccine within 12 months prior to SARI hospital admission	X
Vaccination history pneumococcus	Year of vaccination	x
Long-term care facility residence	Binary	
Healthcare worker	Binary	
Healthcare worker with direct contact to COVID-19 patients	Binary	
Precautionary health behavior (see Annex 3 for survey)	Participants will be asked about their precautionary health behavior (e.g. wearing face masks, using hand sanitiser, going to public places)	
Previous SARS-CoV-2 infection	Participants will be asked about prior COVID-19 tests and test results	x
Anti-SARS-CoV-2 antibody products or other drugs indicated for pre-exposure prophylaxis for SARS-CoV-2 infection within 6 months prior to hospitalisation	Binary, brand, start date of treatment	
Anti-SARS-CoV-2 antibody products or other drugs indicated for post-exposure prophylaxis for SARS-CoV-2 infection	Binary, brand, start date of treatment	

within 6 months prior to hospitalisation	
Anti-SARS-CoV-2 antibody products or antiviral drugs indicated for treatment post-symptom onset leading to the current hospitalisation	Binary, brand, start date of treatment

15.11 Sample size considerations

15.11.1 Targeted sample size

The sample size requirements and assumptions will be different for the different vaccine brands. In case the parameter settings used for these sample size calculations are very different from what is observed in the study, the sample size calculations will be updated accordingly for both interim and final analysis.

15.11.1.1 Primary vaccination

For the analysis of interest, the number of required COVID-19 cases to obtain precise estimates were obtained using a simulation-based sample size calculation. The simulation study reflects the design of the current study; a multi-site TNCC study with data from different sites combined using a meta-analytical approach (see Section 17.14 Data Analysis). Sample size calculations were performed with the number of equally sized sites being 10, the overall anticipated CVE being 80% or 90%, the control to case ratio being 3:1, 1:1 or 1:3, the overall vaccination coverage among controls being 60%, 80% or 90%, and the proportion of the vaccination coverage covered by the vaccine of interest being 10%, 25%, 50%, or 75%. For each combination of these parameters, the sample sizes for which the expected 95% CI range was ≤30% were obtained. The technical specifications of the sample size calculations are given in Appendix 6.

For various CVE, total vaccination coverages, and different proportions of the total vaccination coverage covered by the brand of interest, the number of COVID-19 cases required to meet the CI criterion are summarised in Table 4. Irrespective of the other considered parameter combinations, having at least 1,134 COVID-19 cases yields expected 95% CI ranges ≤30%. The corresponding total number of SARI cases needed to be enrolled can be found in Table 5 and having at least 2,210 SARI cases yields expected 95% CI ranges ≤30% for a control to case ratio of 1:1. As this sample size was obtained for the crude CVE instead of the adjusted CVE, it was decided to conservatively adjust the targeted sample size to 1.2 x 1,134 = 1,360 COVID-19 cases and 1.2 x 2,210 = 2,652 SARI cases.

Finally, in case the observed share of the different COVID-19 vaccine brands or the overall vaccination coverage rate observed in the study differs largely from the settings described, the sample size

calculations will be updated accordingly. The sample size might also be updated in case vaccine effectiveness estimates against specific COVID-19 genetic variants are required.

Table 4. The required number of COVID-19 cases to allow the estimation of the CVE with an expected CI length ≤30%.

			Proportion of the total vaccination coverage covered by the brand of interest			
			10%	25%	50%	75%
Anticipated crude CVE	Overall vaccination coverage	Control to case ratio	Required number of COVID-19 cases (unexposed + exposed any brand)			
80%	60%	3:1	1099	470	248	185
80%	80%	3:1	674	326	191	172
80%	90%	3:1	592	370	288	308
90%	60%	3:1	879	355	191	130
90%	80%	3:1	448	308	123	94
90%	90%	3:1	308	191	148	129
80%	60%	1:1	1105	460	255	187
80%	80%	1:1	666	330	211	172
80%	90%	1:1	608	348	286	258
90%	60%	1:1	855	363	190	128
90%	80%	1:1	440	208	127	93
90%	90%	1:1	343	203	148	128
80%	60%	1:3	**1134**	464	264	180
80%	80%	1:3	660	319	206	174
80%	90%	1:3	594	368	288	267
90%	60%	1:3	871	358	189	132
90%	80%	1:3	452	204	125	180
90%	90%	1:3	328	193	152	130

Table 5. The number of SARI cases required to allow the estimation of the CVE with an expected CI length ≤30%.

			Proportion of the total vaccination coverage covered by the brand of interest			
			10%	25%	50%	75%
Anticipated crude CVE	Overall vaccination coverage	Control to case ratio	Required number of SARI cases (unexposed + exposed any brand)			
80%	60%	3:1	4534	1857	1054	720
80%	80%	3:1	2641	1277	825	694
80%	90%	3:1	2378	1473	1150	1067
90%	60%	3:1	3484	1431	757	528
90%	80%	3:1	1806	816	500	719
90%	90%	3:1	1314	773	610	518
80%	60%	1:1	**2210**	921	510	374

80%	80%	1:1	1332	659	422	345
80%	90%	1:1	1217	697	572	517
90%	60%	1:1	1710	726	380	255
90%	80%	1:1	880	415	254	186
90%	90%	1:1	686	406	295	255
80%	50%	1:3	1465	626	330	247
80%	70%	1:3	899	435	255	230
80%	90%	1:3	789	493	384	410
90%	50%	1:3	1172	473	255	174
90%	70%	1:3	598	410	164	126
90%	90%	1:3	410	255	197	172

15.11.1.2 Primary vaccination, variants of interest

The sample size calculations for calculation of the brand-specific CVE against SARS-CoV-2 variants of interest were done in the same manner as for the sample size calculations for the primary analysis with the exception that the required sample size had to lead to an expected range of the 95% CI ≤70%. The required number of COVID-19 cases with the variant of interest ranged from 68 to 500. For the brand-specific analyses, the required number of COVID-19 cases with the variant of interest will be selected based on the observed vaccination coverage and brand proportions.

Table 6. The number of COVID-19 cases with the SARS-CoV-2 variant of interest to allow the estimation of the variant- and brand-specific CVE with an expected CI length ≤70%.

			Proportion of the total vaccination coverage covered by the brand of interest			
			10%	25%	50%	75%
Anticipated crude CVE	Overall vaccination coverage	Control to case ratio	Required number of COVID-19 cases with the variant of interest (unexposed + exposed any brand)			
80%	60%	1:1	472	203	108	84
80%	80%	1:1	276	146	92	73
80%	90%	1:1	258	164	128	120
90%	60%	1:1	506	209	114	80
90%	80%	1:1	244	128	82	68
90%	90%	1:1	208	128	93	84

15.11.1.3 Additional dose vaccination

For the additional dose objective, the following assumptions were made: an overall anticipated CVE of 70% of the comparator group, a booster relative CVE of 80% or 90%, a control to case ratio of 3:1, 1:1 or 1:3, an overall vaccination coverage among comparator group controls being 70%, 80% or 90%, a proportion of previously vaccinated subjects receiving the additional dose of 90% and the proportion of the additional dose vaccination coverage covered by the vaccine of interest being 10%, 25%, 50%, or 75% (Table 7). For each combination of these parameters, the sample sizes for which the expected 95% CI range was ≤30% were obtained. The technical specifications of the sample size calculations are given in Appendix 6.

Table 7. The required number of COVID-19 cases to allow the estimation of the relative CVE with an expected CI length ≤30%.

Anticipated crude absolute CVE of comparator group	Anticipated crude relative CVE of additional dose group	Overall vaccination coverage of comparator group	Proportion previously vaccinated subjects receiving an additional dose	Control to case ratio	Proportion of the additional dose vaccination coverage covered by the brand of interest			
					10%	25%	50%	75%
					Required number of COVID-19 cases (unexposed + exposed any brand)			
70%	80%	70%	90%	3:1	1094	650	483	1094
70%	80%	80%	90%	3:1	702	448	332	702
70%	80%	90%	90%	3:1	433	286	223	433
70%	90%	70%	90%	3:1	852	476	336	852
70%	90%	80%	90%	3:1	560	312	216	560
70%	90%	90%	90%	3:1	319	179	135	319
70%	80%	70%	90%	1:1	2485	1262	832	674
70%	80%	80%	90%	1:1	1672	884	593	498
70%	80%	90%	90%	1:1	1076	588	426	361
70%	90%	70%	90%	1:1	1972	929	552	420
70%	90%	80%	90%	1:1	1316	614	378	298
70%	90%	90%	90%	1:1	780	384	254	206
70%	80%	70%	90%	1:3	3455	1944	1490	1373
70%	80%	80%	90%	1:3	2498	1507	1198	1133
70%	80%	90%	90%	1:3	1888	1218	952	922
70%	90%	70%	90%	1:3	2504	1294	919	785
70%	90%	80%	90%	1:3	1692	950	691	604
70%	90%	90%	90%	1:3	1075	682	534	487

15.11.1.4 Interim analysis

An interim analysis is planned when data on a sufficient number of COVID-19 cases, vaccinated with the brand-specific vaccine as primary series or an additional last dose, has been collected to provide an expected 95% CI range ≤15% or a power of 50% with the same assumptions as described in the previous sections.

15.11.2 Time to number of cases

The institute for Health Metrics and Evaluation (IHME) has developed a deterministic SEIR (susceptible – exposed – infectious – recovered) compartmental framework to predict SARS-CoV-2 infections, hospitalisations and deaths for over 380 locations worldwide (http://www.healthdata.org/covid)[11].

For study planning, the continuously updated IHME projected COVID-19 hospitalisation rates will be used to predict the number of COVID-19 cases that is expected to be reached by a certain point in time, taking into account the catchment area of the study sites participating to the study. The number

of vaccinated COVID-19 cases by brand are predicted by additionally accounting for the anticipated CVE and brand-specific vaccination coverage.

15.11.3 Case-control ratio

Including more than three controls per case does not lead to a notable increase in the precision of the estimates. When possible and resource-saving, the number of controls sampled per case by calendar week will be restricted. Restricting the number of controls might be possible for some sites where SARI patients can be enrolled after their SARS-CoV-2 status is known and before they are transferred to either the COVID-19 or non-COVID-19 area within the hospital. This will be described as part of the patient flow, when applicable.

15.12 Unfavourable COVID-19 positivity rate among SARI cases

The COVID-19 positivity rate among SARI cases will be closely monitored over time. Positivity rates that are too high or too low result in an inefficient study requiring large sample sizes (SARI cases) to obtain limited precision of the vaccine effectiveness estimates. When the positivity rate is unfavourably high, changing the case capture definition (currently SARI) or enrolling other hospital controls (e.g. patients presenting to the emergency department for reasons other than SARI) will be considered, as a separate analysis. When the positivity rate is low, the weekly number of controls per case for the prospective recruitment will be restricted when possible to a maximum of three. For retrospective data, we will randomly select controls from the pool available for each study contributor and match to cases based on calendar week.

15.13 Data management

Data collection, statistical analysis and preparation of the study report are activities firewalled from vaccine companies to avoid perception of undue influence on the study report and CVE results interpretation.

15.13.1 Data management at site level

Each study site is responsible for the data collection, data validation, and data management of their participant-level study data. Depending on the study site, the data collection and source documentation will be different. For every participating study site, the data flow and data management will be documented in detail, including data collection, validation, data entry and data cleaning processes.

All pseudonymised participant-level study data will be locally transformed to the study-specific common minimum dataset (see Annex 4). The study site will perform quality checks and process any findings accordingly, with sufficient documentation to ensure transparency and reproducibility.

When the performed data quality checks are satisfactory, the study site can upload the data. (Section 15.13.2).

15.13.2 Data transfer and management at central level

The study-specific common minimum dataset will be uploaded by the study sites to a dedicated secured central server, the COVIDRIVE Research Server (CRS). The server is hosted by P95, Koning Leopold III Laan 1, 3001 Heverlee, Belgium. P95 will act as Data Processor according to the General Data Protection Regulation (GDPR) 2016/679. The data flow from the study to the CRS and extraction of results from the CRS is described in Figure 1.

1. Each data site will upload the study-specific common minimum dataset through the COVIDRIVE Electronic Data Transfer Application (EDTA), a password-protected secure web application using a secure file transfer protocol (sFTP).

2. The CRS system administrator, a certified Data Protection Officer (DPO), checks whether the data are compliant to the protocol, statistical analysis plan (SAP) and privacy regulations.
    a. If the check is satisfactory, the system administrator releases the uploaded data to the study folder accessible to the data analysts (using Remote Desktop Protocol (RDP)) and performs a data lock (the data are only readable by the data analysts and cannot be changed).
    b. If the check is not satisfactory, the system administrator reports this to the study site responsible for the data.

3. The data analysts perform the required data transformations on the data released in the study folder as per the SAP.

4. When the data transformations are finalized, the data analysts flag the resulting output files to the system administrator for extraction out of the CRS. These output files only contain aggregated summary data such as figures, tables with number of events, or estimates.

5. The system administrator checks the resulting output files flagged for extraction for compliance to the SAP.
    a. If the check is satisfactory, the resulting files are extracted out of the CRS by the system administrator using sFTP.
    b. If the check is not satisfactory, the system administrator reports this to the data analyst and requests changes to get the data into compliance with the SAP.

6. After the resulting files are extracted from the CRS, they can be used as the basis for reports, web applications and publications as per the SAP.

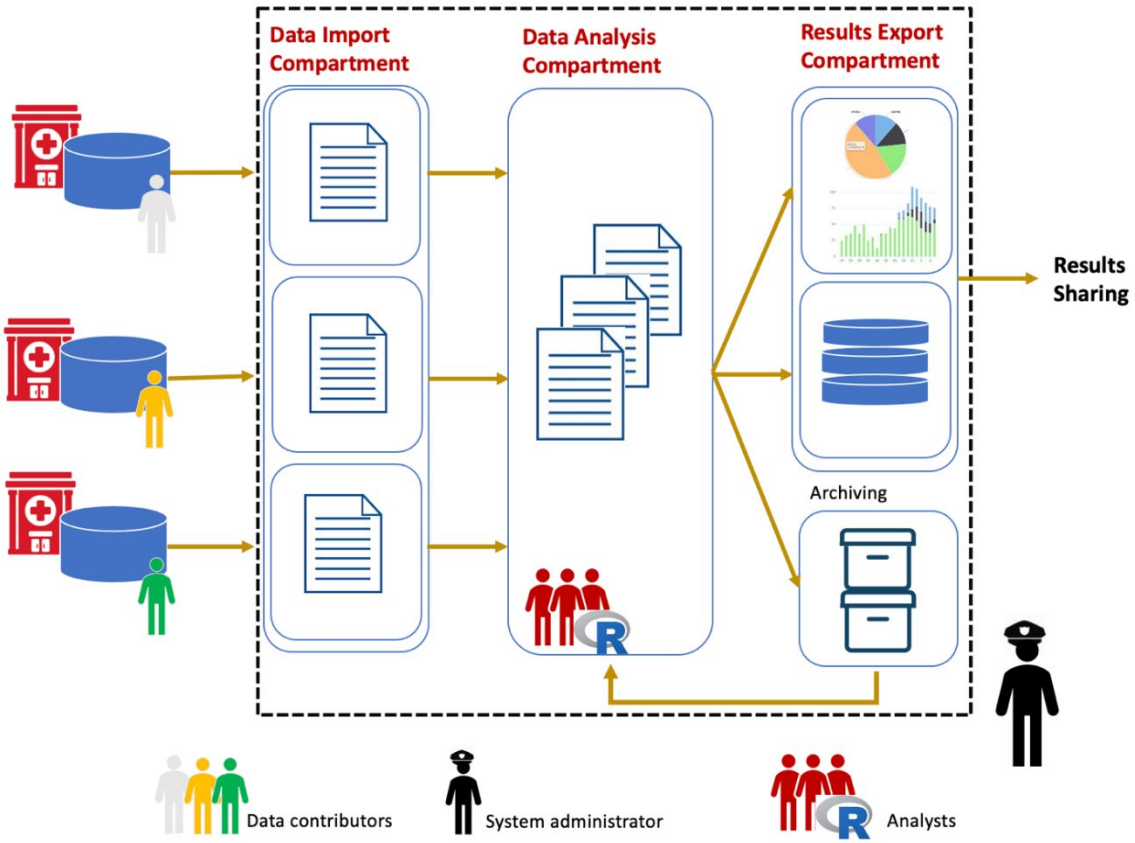

Figure 1. Data flow from study sites to the COVIDRIVE research server and beyond.

A data management plan (DMP) is written prior to the start of the data collection to describe data management at the central level. The DMP describes all functions, processes, responsibilities and specifications for data collection, data storage, quality checking, transfer, cleaning, and validation. The DMP is updated regularly.

15.14 Data analysis

A full SAP and mock report will be developed prior to the conduct of the analysis. The SAP specifies the statistical analyses to be conducted while the mock report, including tables, figures, and listings (TFL) mock shells, specifies the presentation of the results.
All statistical analyses will take place in the data analysis compartment of the CRS.

15.14.1 Description of SARS-CoV-2 dynamics and COVID-19 vaccine coverage

Context information will be provided by describing the evolution of the SARS-CoV-2 dynamics during the study period in the countries where the study sites are located. The circulating genetic variants will be described as well.

National (or regional) COVID-19 immunisation recommendations over time will be described, along with the coverage of COVID-19 vaccination, overall and by brands of interest.

Table 7. Sources for context information on circulating genetic variants and national/regional COVID-19 immunisation recommendations.

Genetic variants	
« Country 1 »	***« link »***
« Country 2 »	***« link »***
COVID-19 immunisation recommendations	
« Country 1 »	***« link »***
« Country 2 »	***« link »***

15.14.2 Attrition diagram

For every study site, an attrition diagram will be created. The attrition diagram describes the number of records excluded from the statistical analyses, by reason of exclusion. For every study site, a bar chart of the distribution of vaccine brands will be created after exclusion criteria have been applied.

15.14.3 Descriptive analysis of demographics and baseline characteristics

For every study site and brand of interest, visualisations based on the final brand-specific data for analysis will be created including:

- number of controls and COVID-19 cases (possibly by genetic variants) over time.
- distribution of covariates among cases and controls.

For every study site and brand of interest, a tabular summary based on the final brand-specific data for analysis will be created, describing the characteristics of cases and controls as predefined in the mock report. Similar visualisations and tabular summaries will be made for the combined data across study sites.

15.14.4 Statistical analyses

15.14.4.1 Site-specific CVE

For every study site, the crude and confounder-adjusted brand-specific CVE against laboratory-confirmed COVID-19 disease will be estimated as:

VE = (1 – OR) x 100%,

where *OR* denotes the crude or confounder-adjusted odds ratio, comparing the odds of vaccination among COVID-19-positive study participants to the odds of vaccination among COVID-19-negative study participants.

Confounder-adjusted CVE estimates will be derived from multivariable logistic regression models. The analysis to estimate brand-specific CVE will account for the differences in approved indications, discarding from the analysis patients for which the vaccine brand of interest is not indicated. All CVE estimates will be adjusted for calendar time.

15.14.4.2 Pooled CVE

Brand-specific CVE estimates pooled across study sites will be obtained through random-effects meta-analysis (RE-MA) on the log-transformed site-specific estimates [12], or alternatively, when cell counts are too low (i.e. resulting in non-robust RE-MA standard error estimates), Generalised Estimating Equations (GEE) will be used [13]. Cell counts are expected to be low when the vaccine effectiveness is very high and/or the proportion of the vaccination coverage covered by the brand of interest is low.

15.14.4.2.1Random effects meta-analysis

Site-specific CVE estimates by vaccine brand will be calculated and these will be pooled through a RE-MA. The main analysis will be based on this two-stage pooling methodology meaning that CVE estimates will be obtained for each site and subsequently pooled. An overview of the analysis workflow can be found in Figure 2.**Fout! Verwijzingsbron niet gevonden.**

The two-stage pooling approach has the advantage that it can easily integrate estimates from sites that cannot share patient-level data. Additionally, two-stage pooling approaches are easily understood by and communicated to researchers in the field who tend to be familiar with meta-analyses of aggregated data [14]. Finally, note that it has been shown that in most scenarios two-stage and one-stage pooling tend to lead to similar results [14-16]. To account for potential treatment effect heterogeneity, a random effect will be incorporated into the model. Potential causes of such heterogeneity could include differences at the recruitment stage, local differences in the intensity of the epidemic, etc. The most important limitations of the RE-MA approach include loss of power when there is no between-study heterogeneity as compared to a fixed-effects approach, a potential loss of power as compared to a one-stage pooling approach, and potential convergence issues when the outcome of interest is rare or the sample size of some sites is relatively small [16]. One-stage pooling is to be preferred when most, if not all, the sites have shared individual patient data; and additionally, when the number of clusters as well as the total sample size of the study are low, as this leads to more efficient estimates compared to two-stage methods. However, two-stage pooling will be performed as a sensitivity analysis.

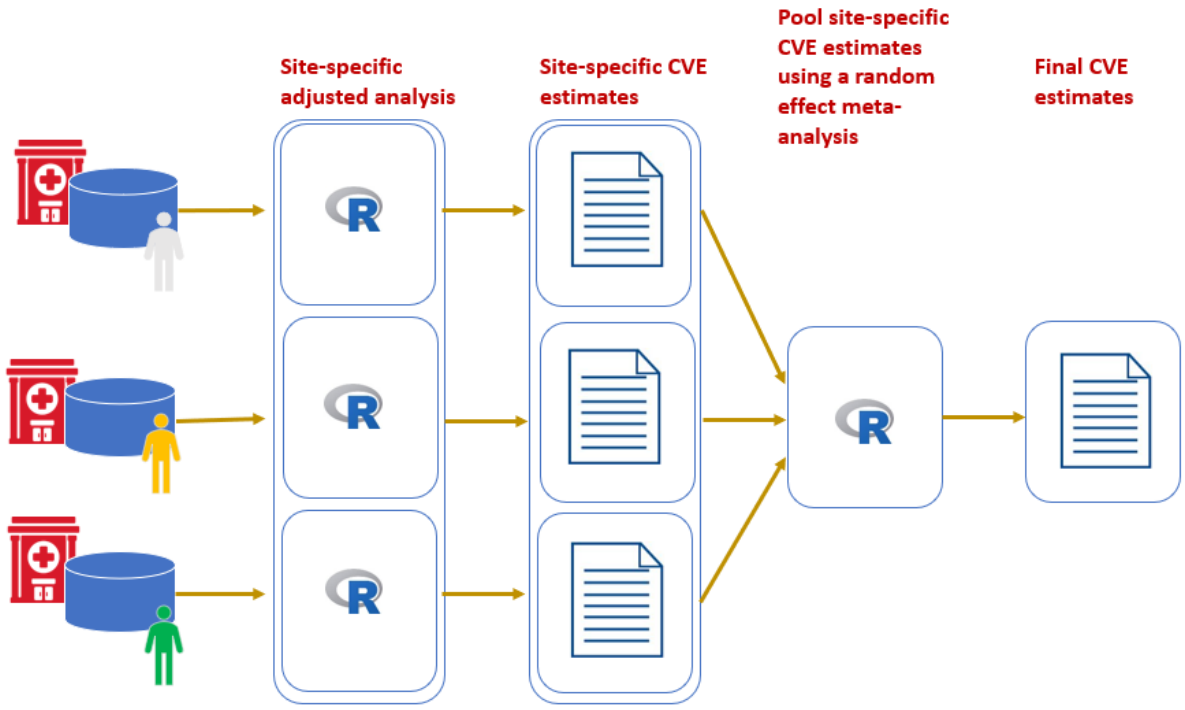

Figure 2. Analysis workflow from the site-specific datasets to the final CVE estimate.

For the RE-MA models, restricted maximum likelihood will be used to obtain the pooled meta-analyses estimates and 95% CIs [17]. The modified Hartung-Knapp correction will be used to estimate the variance of the mean effect [18]. The estimates and 95% CIs will then be back-transformed to obtain the pooled CVE estimates and 95% CI. An indication for the heterogeneity among estimates from different study sites will be obtained by calculating I^2 according to Higgins et al. [19]. For every meta-analysis performed, the potential impact of outliers and influential estimates on the pooled estimate will be evaluated. Studentised deleted residuals *r* will be used to identify outliers in the meta-analysis. The standardised DFBETAs statistic will be used to identify influential estimates [20].

15.14.4.2.2 Generalized Estimating Equations

For the GEE models, the approach for fitting logistic regression developed by Liang and Zeger [21] will be used, assuming an exchangeable correlation matrix to account for potential within-cluster homogeneity in outcomes. The robust sandwich estimator [22] will be used to estimate the standard error of the marginal effect estimates. Clusters will be defined at hospital-level or hospital network-level, depending on the similarities of the hospitals belonging to the same network.

15.14.4.3 Pooled relative CVE

The crude and confounder-adjusted brand-specific relative CVE (rVE) against hospitalisation due to laboratory-confirmed COVID-19 disease of the additional dose as compared to an appropriately selected comparator group (see below) will be estimated, as:

$$rVE = (1 - OR) \times 100\%,$$

where OR denotes the crude or confounder-adjusted odds ratio, comparing the odds of hospitalisation due SARS-CoV-2 infection among subjects receiving the last additional dose of interest, to the odds of hospitalisation due SARS-CoV-2 infection among subjects who were part of the comparator group.

All CVE estimates will be adjusted for calendar time. Confounder-adjusted CVE estimates will consider additional factors such as age, sex, and chronic conditions. Adjustments will be achieved through inclusion of the relevant terms in the logistic regression models. The smooth functions of age and symptom onset date will be modelled by penalised cubic regression splines and estimated using restricted maximum likelihood for smoothness selection [23].

Brand-specific CVE as additional dose against laboratory-confirmed COVID-19 disease will be estimated by comparing SARI patients with the additional dose (P+N doses) to SARI patients without this last additional dose (P+N-1 doses), but who are eligible to receive the last additional dose, and to unvaccinated SARI patients who are eligible to receive the additional dose (Unvacc) (Figure 3). This will be done for each P+N (P+1, P+2 etc.) separately.

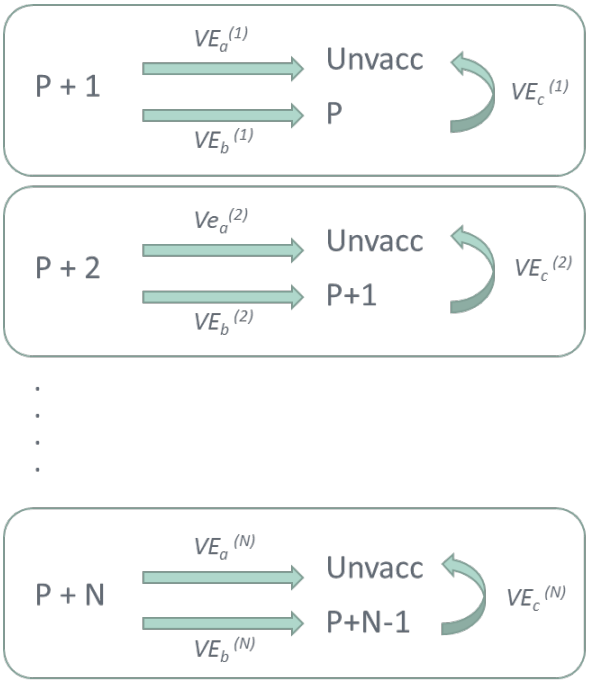

Figure 3. Estimation of CVE of N (number of) additional doses compared to unvaccinated and N-1 additional doses, in which P is primary series and all control groups are eligible for the exposure of interest.

For co-primary objective 3, a pooled VEa and VEb, representing the VE of the most recent additional dose of interest, will be obtained. For the pooled analyses, matched comparator groups will be constructed, for each SARI patient receiving a dose of the brand of interest as the most recent additional dose, selecting SARI patients who were unvaccinated or did not receive the last additional dose but who are eligible to receive the additional dose. To support the interpretation of objective 3,

also a pooled VEc across brands representing the VE of the vaccinated comparator group as compared to the unvaccinated comparator group will be presented (co-primary objective 4).

For secondary objective 3 on the time between last and additional dose analyses, two separate analyses will be performed. In the first analysis, time between doses will be treated as the exposure variable binned into categories. In the second analysis, the exposure variable will be a spline function of the time between doses with knots placed at prespecified time points.

For secondary objective 3 on the number of additional doses, the VEa and VEb will be reported by number of doses. The same will be done for VEc as to support the interpretation of secondary objective 3, as is described in secondary objective 4.

Each combination of COVID-19 vaccine dose will be classified as primary (P) or additional dose (N) by expert consensus.

15.14.4.4 Missing values

As COVID-19 status is part of the initial data collection, it is expected that exposure should be known for essentially all subjects. Data on exposure and especially the potential confounders, however, are likely to be missing for a proportion of the subjects. These data are often collected from existing medical records, vaccine registries, etc. which existed before the SARI episode, and it seems reasonable to assume that whether the data is missing is independent of the COVID-19 status during the SARI episode. Assuming that the described missing data mechanism holds, performing a complete case analysis (CCA) will not lead to biased results. The primary analysis will therefore be a CCA, dropping records with missing information for the outcome, exposure of interest or the covariates. In case >20% of the cases and controls have missing covariate information, CCA is likely to be inefficient and alternatives such as multiple imputation and augmented CCA will be explored.

15.14.4.5 Sensitivity analyses

Multiple sensitivity analyses will be performed. In case the RE-MA approach will be adopted, GEE models will be performed as sensitivity. Additional sensitivity analyses will be conducted, exploring the effect of time between symptom onset and swab data and the effects of different SARI case definitions and exclusion of subjects who have received monoclonal antibodies and other anti-SARS-CoV-2 products for either treatment or pre- or post-exposure prophylaxis prior to hospitalisation if there is significant use thereof in the population. Other sensitivity analysis might be conducted when appropriate. All sensitivity analyses will be pre-specified in the SAP.

16 QUALITY MANAGEMENT

16.1 Independent Scientific Committee

The Independent Scientific Committee (ISC) is composed of independent external experts (from organisations or institutions which are not partners of COVIDRIVE) with good expertise/experience relevant for COVID-19 vaccine effectiveness studies.

The roles and responsibilities of the ISC are the following:

- reviews and makes recommendations for study documents (protocols and SAPs)
- reviews and makes recommendations for study reports.
- reviews and formulates recommendations for the master scientific documents, which are co-developed by the COVIDRIVE partners to harmonise the CVE methodology (e.g. protocols and analyses to assess severe COVID-19 disease, long-term effectiveness, SARS-CoV-2 infection or transmission).

16.2 Quality Assurance and Audit Committee

The Quality Assurance and Audit Committee (QAAC) of COVIDRIVE is composed of quality assurance experts from COVIDRIVE vaccine companies' partners. Their mission is to evaluate the quality of the study conduct, data reporting, the analysis and report (activities firewalled from vaccine companies) in order to ensure reliable data are delivered or when necessary, identify areas for improvement.

The QAAC provides quality management recommendations for study sites and oversees any audit at the study site level if needed; the audit is subcontracted to an external qualified consultants' auditor.

Because sites participating in COVIDRIVE are not subject to the specific quality mechanisms applicable to vaccine companies as per regulatory requirements, the QAAC seeks for a reasonable and feasible mechanism to enhance the quality management. The QAAC aims to provide guidance and supports study sites to get the relevant study documentation and quality management system in place to ensure that reliable observational data are integrated into the study analysis and that activities are in place at site level to prevent, detect, correct, and control potential errors.

16.3 Monitoring

Monitoring activities include:

- Before study start, the study site will be asked to complete a quality management questionnaire to inform the study team on all aspects of the study conduct, including a description of the installed data quality management system to ensure that reliable observational data are generated and that activities are in place at the site to prevent, detect, correct, and control potential errors.

- Before study start, a site initiation visit will be organised by the study team.
- During study conduct, regular study site contacts will be organised to monitor study progress (number of cases and controls enrolled), to ensure regular data input to the COVIDRIVE Electronic Data Capture (EDC) and to discuss potential protocol deviations or other issues related to the study conduct.
- Monitoring shall occur as described in the COVIDRIVE Monitoring Plan.

The site investigators must permit any external auditor mandated by the QAAC of the COVIDRIVE partnership or Study Requestor, the IEC, auditors and representatives from regulatory authorities direct access to all study-related documents. Participant confidentiality will be protected at all times.

16.4 Data quality checks at central level

An automatic data quality check will be done during data upload to the COVIDRIVE Research Serve (CRS) via the EDTA. The data quality checks relate to compliance with the study-specific common minimum data requirements (Annex 4), the presence of duplicated records, variable formats, implausible values, inconsistencies between variables and missing values. All uploaded data will be checked again for quality by the P95 team. If data quality issues are found, the study site data responsible person will be contacted, and the data will either be corrected or discarded from further analysis. After performing the data quality checks and implementing the corrective measures, the study inclusion criteria will be applied and records with missing data in the outcome and/or exposure information will be discarded.

For every study site separately, a data quality report will be produced. This report will contain a description of the results of the quality checks performed, the amount of data that was retained for analysis after applying the inclusion criteria and graphical summaries of the retained data. The data quality report will be sent to the site for approval.

17 LIMITATIONS OF THE RESEARCH METHODS

The COVID-19 pandemic is unprecedented, unpredictable and poses challenges for the post-marketing evaluation of the COVID-19 vaccines. The following challenges and limitations for the real-world evaluation of the COVID-19 vaccines have been identified at the time of writing this protocol.

The sensitivity of the SARI case definition is imperfect and potential COVID-19 cases might not be included in the study. This will, however, not bias the CVE estimates unless vaccination affects the presentation of the SARI symptoms. Until now, it is unknown whether COVID-19 vaccination induces a milder course of disease.

As for other epidemiological study designs, the results from TNCC study designs can be biased due to misclassification of disease status using diagnostic assays with imperfect sensitivity and specificity. Low sensitivity and low specificity are expected to bias the CVE estimates downwards with the bias resulting from low specificity being more substantial than the bias from low sensitivity [24]. To minimise misclassification bias, laboratory confirmation based on RT-PCR or another RNA amplification system with at least the same sensitivity and specificity is required for the current study. The specificity of RT-PCR for the diagnosis of COVID-19 is high (>99.5%) while its sensitivity depends on various factors, including timing of sampling, type of specimen and sampling technique. In hospitalised patients, the clinical sensitivity of PCR decreased with days post symptom onset with >90% clinical sensitivity during the first 5 days after symptom onset and 70%-71% from days 9 to 11 [25]. Also, the sensitivity is higher for lower respiratory samples than for upper respiratory tract samples [26], and a good sampling technique is required to obtain better results. To explore any potential bias due to disease misclassification, information on type of specimen will be collected and sensitivity analyses regarding time between symptom onset and swabbing will be performed. Guidance on collecting and handling specimens for the diagnosis of COVID-19 will be given as part of study staff training.

The SARS-CoV-2 positivity rates within the SARI patients varies over time with the observed positivity rates since the start of the COVID-19 pandemic ranging from 20% to 80% (FISABIO, personal communication), implying that the potential case to control ratio would vary from 1:4 to 4:1 depending on calendar time. Future SARS-CoV-2 positivity rates in SARI patients are difficult to predict as they depend on both the successfulness of the COVID-19 vaccination programmes and the circulation of other respiratory pathogens. In case-control studies, the ideal number of controls is typically 1 to 3 times the number of cases [27]. To allow optimising the case-control ratio conditional on calendar time (with the latter being an important confounder in CVE studies), we allow for the possibility to 1) sample other hospital controls or modify the case capture definition in case the positivity rate would be high, and – when feasible and resource saving–- to 2) restrict the number of controls per case in case the positivity rate would be low.

Confounding is a substantial concern for real-world studies on the effectiveness of COVID-19 vaccines.

As a result of the huge demand for COVID-19 vaccines and initially limited vaccine supplies, most European countries prioritised the vaccination of elderly people, residents and personnel in long-term

care facilities, healthcare workers, social care personnel and persons with certain comorbidities [28]. The presence of such vaccination priority groups is an important potential source of confounding in COVID-19 vaccine effectiveness studies. In addition, the uptake of vaccination may be highest among individuals who adhered most strongly to NPIs (i.e. subjects exhibiting precautionary health behaviour such as wearing face masks, using hand sanitiser, avoiding public places) and consequently have a lower propensity of natural infection and immunity. As naturally acquired immunity may be strongly protective against re-infection (~90%) [29], lack of precautionary health behaviour (~previous SARS-CoV-2 infection) might be an important potential confounder as well. An alternative bias mechanism might be that subjects feel protected once vaccinated and relax the precautionary health measures that were taken prior to vaccination. In addition, propensity towards vaccination in general might also act as a confounder when, for example, subjects more likely to be vaccinated against COVID-19 are also more likely to be vaccinated against influenza and/or against pneumococcal infection (e.g. as is the case for healthcare workers, risk groups and persons with a positive attitude towards vaccination). Joint vaccination against COVID-19, influenza and/or pneumococcal infection might bias the results of TNCC studies as such joint vaccination will affect both the probability that the subject becomes a case as well as the probability that the subject becomes a control. Another potential important confounder is ethnicity and socio-economic background. It is well established that some minority ethnic groups have a higher risk of confirmed SARS-CoV-2 infection and higher risk of developing critical COVID-19 disease given exposure, even after accounting for socio-economic variables [30]. When these groups are also less likely to be vaccinated, the vaccine effectiveness estimates will be overestimated. Finally, CVE studies are strongly subject to time-varying confounding as both the COVID-19 vaccination coverage and the SARS-CoV-2 infection pressure and virulence will co-vary over time.

Pre-existing immunity is a factor influencing vaccine effectiveness estimates. Prior natural infection is a typical reason for pre-existing immunity, however prior infections may be undocumented. A careful interpretation of all time-related effects will be warranted.

An important potential effect modifier of the effectiveness of the COVID-19 vaccines is frailty. Frailty has been shown to affect older adults's responses to vaccines for infections such as influenza, shingles and pneumococcus [31]. Frailty is a multi-dimensional construct, including physical, psychological, and social dimensions. Frailty is age- and disease-associated, changes over time and is characterised by a strong inter-personal variation. There is currently no consensus on how to define and how to best measure frailty. Methods include questionnaires, performance measures, electronic health care database algorithms or any combination of these. As the study population of our study is the general population and given the complexity of measuring frailty, we do not measure frailty as such. Rather we will collect information on variables that are known to be strongly related to frailty, including age, BMI, long-term care facility residence and chronic conditions including cancer and immunodeficiency.

Finally, sample size estimations for brand-specific CVE estimates are challenging as they strongly depend on the SARS-CoV-2 attack rate and the brand-specific vaccination coverage, with both parameters being difficult to predict. Sample size requirements will further increase for estimating effectiveness against COVID-19 disease by genetic variants. Although our study covers a wide network of hospital across Europe, obtaining sufficient sample to obtain accurate estimates is a primordial challenge.

18 ETHICAL AND REGULATORY CONSIDERATIONS, RETENTION OF DATA AND OF BIOLOGICAL SAMPLES

18.1 Guiding principles

To ensure the quality and integrity of research, this study will be conducted under the International Ethical Guidelines on Epidemiological Studies issued by the Council for International Organisations of Medical Sciences (CIOMS, 2009), Good Epidemiological Practice (GEP), the ethical principles that have their origins in the Declaration of Helsinki and any applicable national laws, regulations and guidelines.

This is an observational study without medical intervention or change in the clinical and diagnostic capacity. Therefore, there is no direct benefit to the participants. Nevertheless, there are important potential societal benefits derived from this vaccine effectiveness study. Effective COVID-19 vaccines are key to ending the pandemic and preventing potential future resurgence. Close monitoring of the effectiveness of COVID-19 vaccines is essential to guide decision-making regarding vaccine marketing approval, optimisation of vaccination programmes and future COVID-19 vaccine development.

18.2 Ethics approval

The site-specific protocols will be submitted to relevant ethics committee(s) following local regulations and the declaration of Helsinki. Copies of the appropriate approvals will be collected from each site and archived according to the local regulations, but at least for 5 years. The only exception is where the study is part of an ongoing routine program evaluation required by a 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.

18.3 Informed consent

Written informed consent will be obtained from all participants/guardians as specified by the national/regional ethics committee, if applicable. The following information should be specified in the informed consent form (ICF) (Annex 5): who is responsible for the study, aim of the study, nature of processed data, purposes of processing, purpose of the use of the data including potential future use of the data to advance knowledge on vaccines, recipients of possible data transfers, rights of the study participants, and consequences of not accepting the informed consent. Specific consent procedures may be needed for patients in poor health conditions (e.g. oral witnessed consent, consent by next of kin) or for children (assent). If informed consent will not be required, the reason will be stated.

18.4 Independent Ethics Committee/Institutional Review Board

Consistent with local regulations and prior to enrolment of participants at a given site, the study protocol together with its associated documents (e.g., ICF) will be submitted by the study site to the responsible Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for its review. Participant enrolment will not start before the study site has obtained written confirmation of a favourable opinion/approval from the relevant central or local IRB/IEC. The study site will promptly and before first participant enrolment inform the study team that ethical approval has been granted. The IRB/IEC will be asked to provide documentation of the date of the meeting at which the favourable opinion/approval was given that clearly identifies the study, the protocol version, and the ICF version reviewed.

Before implementation of any substantial changes to the protocol, protocol amendments will also be submitted to the relevant IRB/IEC in a manner consistent with local regulations. It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and ICFs, and other relevant documents, if applicable, from their local IRB/IEC and provide documentation of approval to the study team.

Should the study be terminated early for any unanticipated reason, the investigator will be responsible for informing the IRB/IEC of the early termination.

18.5 Participant's confidentiality

Data will be pseudonymised at the site-level prior to data transfer to P95. All parties will ensure protection of participants´ personal data and will not include participant names on any study forms, reports, publications, or in any other disclosures, except where required by law. In accordance with local regulations in each of the countries, participants will be informed about data handling procedures and asked for their consent. Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing participant data. Every effort will be made to protect participant confidentiality according to Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons regarding the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation; GDPR).

18.6 Changes to the protocol

Changes to the protocol will be documented in written protocol amendments. Such protocol changes will be discussed and agreed upon with the study team prior to their implementation. Major (i.e., substantial, significant) amendments will usually require submission to the relevant IRB/IEC for approval or favourable opinion and to the relevant regulatory authorities, if applicable. In such cases, the amendment will be implemented only after approval or favourable opinion has been obtained.

Minor (non-substantial) protocol amendments, including administrative changes, will be filed at each participating study site and will be submitted to the relevant IRB/IEC or regulatory authorities where required by pertinent regulations.

18.7 Data re-use

Data can be re-used for additional analysis to advance the knowledge on SARI and its prevention or treatment following a set of principles defined and approved by the COVIDRIVE partnership including the following :

- The data request application be submitted and approved by the COVIDRIVE ISC
- The data can only be used for relevant scientific research and as pre-defined in the data access application/protocol when approved by the COVIDRIVE ISC
- The data requestor will only be provided access to the data as needed for the purposes set out in the data access application/protocol approved by the COVIDRIVE ISC
- The data will remain at all times at the P95 server.

19 STUDY MANAGEMENT AND LOGISTICAL ASPECTS

This study will be performed by the study site investigator(s), with guidance, input, review, and approval of the study team, including development of materials, recruitment, training and management of sites, electronic data capture and data management and analysis.

The investigator(s) and all study staff will conduct the study in compliance with the final version of this protocol. The rights, safety and well-being of the participants are the most important considerations and prevail over the interests of science and society. All personnel involved in the conduct of this study must be qualified by education, training, and experience to perform their tasks.

19.1 Study investigators at hospital level

Each investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the International Ethical Guidelines on Epidemiological Studies issued by the CIOMS (CIOMS, 2009), GEP, the ethical principles that have their origins in the Declaration of Helsinki and any applicable national laws, regulations and guidelines.

2. Personally conduct or supervise the staff who will assist with the protocol.

3. Ensure that study-related procedures including study-specific (non-routine/non-standard panel) screening assessments are NOT performed on potential participants, prior to the receipt of written approval from relevant governing bodies/authorities.

4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.

5. Secure prior approval of the study and any changes by an appropriate IEC and competent authority.

6. Ensure that the IEC will be responsible for initial review, continuing review, and approval of the protocol.

7. Ensure that requirements for informed consent, as outlined in ICH-E6 (R2) 4.8 [32] and local regulations, are met.

8. Obtain valid informed consent from each participant and document the date of consent in the participant's medical chart. Valid informed consent is the most current version approved by the IEC.

9. Prepare and maintain adequate case histories of all persons enrolled into the study, including laboratory results, etc., and maintain these data for a minimum of 2 years, or upon agreement

with the Sponsor. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

10. Allow possible inspection and copying by the regulatory authority of GEP-specified source documents.

11. Review and provide a signature as approval of the content of the epidemiological study report.

19.2 Training

Investigators and data collectors will be trained on the study protocol before the start of the study. They will receive the protocol and study training material.

19.3 Data capture

The data will be collected using an EDC system as described in the Data Management Plan.

19.4 Retention

To enable evaluations and/or audits from regulatory authorities or others, the site investigator(s) agree(s) to keep documents and data relating to the study in an orderly manner in a secure Study file, which will be available for audits/inspections, for a period of at least 10 years after the end of the study or longer according to local requirements and legislation. Documents to be archived include the participant enrollment log and the signed ICFs. In the event that archiving of the file is no longer possible at the site, the site/investigator will be instructed to notify the study team. The investigator must contact the sponsor before destroying any study related documentation. It is the responsibility of the sponsor to inform the study site of when these documents no longer need to be retained.

Biological specimen might be collected for future research. Retention, storage, and access rights will be pre-defined and described as appropriate.

19.5 Discontinuation of study participation/Withdrawal from the study

Participation in the study is strictly voluntary. A participant has the right to withdraw from the study at any time and for any reason. All attempts should be made to determine the underlying reason for the discontinuation/withdrawal and, if possible, the primary underlying reason should be recorded. Data collected up to the time of consent withdrawal will be considered for the analysis.

19.6 Study termination

The study team reserves the right to terminate the study at a specific study site at any time. Reasons for terminating the study include but are not limited to the following:

- The study site does not respond to study management requests.
- Repeated protocol deviations/poor protocol compliance.

20 REPORTING AND DISSEMINATION OF RESULTS

20.1 Study protocol

The study protocol and final study report will be posted on the EU PAS register: (http://www.encepp.eu/encepp/studiesDatabase.jsp).

20.2 Management and reporting of adverse events/adverse reactions

This is a non-interventional epidemiological study for assessing the effectiveness of routine COVID-19 vaccination. The study sites conducting the study should follow local requirements as regards the submission of cases of suspected adverse reactions to the competent authority in the country where the reaction occurred.

20.3 Progress, interim and final reports

Progress reports will be provided every two months since enrolment of the first participant. Progress reports will provide an overview of the number of cases, number of controls, number of study participants vaccinated with any COVID-19 vaccine brand and number of study participants vaccinated with the COVID-19 vaccine brand of interest.

Interim analysis for a specific CVE objective will be performed as soon as a prespecified number of COVID-19 cases required for the brand-specific CVE estimates is reached. The progress reports will be used to monitor these required number of COVID-19 cases.

A final study report will be written for each of the individual COVID-19 vaccine brands of interest. When the Study Requestor is a MAH, the COVIDRIVE ISC will review the study report and the written comments by the vaccine company requestor. The ISC will provide recommendations for the integration of the vaccine company requestor comments. The interim and final reports will be submitted to the EMA by [Study Requestor] to meet regulatory requirements. This process is further described in the Governance Charter.

20.4 Publication

Study contributors (sites) may publish their own data independently from COVIDRIVE upon informing COVIDRIVE and acknowledgement of funding. Co-authorship will be defined following the ICMJE (International Committee of Medical Journal Editors) criteria and the Good Publication Practice (GPP). All publications will be open-access.

21 FUNDING

This study is partially funded by [Study Requestor].

The following study sites (hospitals) receive additional funding from other sources:

Study site (hospital)	Additional funding source

Study sites (hospitals) not listed did not receive additional funding. In those sites, the study is solely funded by [Study Requestor].

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ANNEX 1: VACCINE-ASSOCIATED ENHANCED DISEASE (VAED)

VAEDs are modified and severe presentations of clinical infections affecting individuals exposed to a wild-type pathogen after having received a prior vaccine against the same pathogen [1]. VAED has been observed in the past following administration of measles and RSV vaccines [2]. VAED is a theoretical concern for COVID-19 vaccines, based on observations from other respiratory viruses and from animal models of highly pathogenic coronaviruses [3]. While the underlying potential mechanisms for VAED are unclear, VAED always involves a memory response primed by vaccination and appears to target the same organs as wild-type infections [3]. Particular concerns include the potential for (inactivated whole-virus) vaccines to elicit antibody-dependent enhancement (ADE) of infection or vaccine-associated enhanced respiratory disease (VAERD) upon SARS-CoV-2 infection [4], although neither has been observed in clinical trials so far. Studying VAED on an individual patient level is challenging, as no confirmatory tests to diagnose VAED exist, and distinguishing vaccine failure from VAED among vaccinees is difficult.

VAED may be studied on a population level by comparing the occurrence and presentation of severe disease among vaccinated and non-vaccinated patients. VAED through ADE is postulated to occur with low levels of neutralising antibodies, and where non-neutralising or poorly neutralising antibodies increase the subsequent viral entry into cells, thereby intensifying the infection [5]. The effect of waning antibody titers after vaccination on ADE is unknown [6]. If neutralising antibodies wane over time, an association between time since vaccination and the risk of developing severe disease may be observed. Therefore, CVE should be studied against different levels of COVID-19 disease severity by time since vaccination.

Further information on VAED including possible pathophysiologic pathways is provided by Munoz et al. [3].

[1] World Health Organization. COVID-19 vaccines: safety surveillance manual. Available from: https://apps.who.int/iris/handle/10665/338400
[2] Polack FP. Atypical measles and enhanced respiratory syncytial virus disease (ERD) made simple. Pediatric research. 2007;62:111-5. DOI: 10.1203/PDR.0b013e3180686ce0
[3] Munoz FM, Cramer JP, et al. Vaccine-associated Enhanced Disease: Case Definition and Guidelines for Data Collection, Analysis, and Presentation of Immunization Safety Data. Vaccine. 2021;39(22):3053-3066. DOI: 10.1016/j.vaccine.2021.01.055
[4] Rostad CA and Anderson EJ. Optimism and caution for an inactivated COVID-19 vaccine. The Lancet Infectious Diseases. 2021;21(5):581-582. DOI: 10.1016/S1473-3099(20)30988-9.
[5] Karthik K, Senthilkumar TMA, et al. Role of antibody-dependent enhancement (ADE) in the virulence of SARS-CoV-2 and its mitigation strategies for the development of vaccines and immunotherapies to counter COVID-19. Human Vaccines & Immunotherapeutics. 2020;16:3055-60. DOI: 10.1080/21645515.2020.1796425
[6] Kim JH, Marks F, Clemens JD. Looking beyond COVID-19 vaccine phase 3 trials. Nature medicine. 2021:205-211. DOI: 10.1038/s41591-021-01230-y

The following form should be used to capture clinical and laboratory features of patients with critical COVID-19 disease admitted to the ICU.

Section A: clinical features

Please complete the tables below concerning the patient's condition during ICU stay.

During ICU admission, did the patient have any measurements at rest of:		**If yes, please provide the following details:**
a respiratory rate ≥ 30 per minute?	☐ No ☐ Yes	
an oxygen saturation ≤ 93% on room air?	☐ No ☐ Yes	
a systolic blood pressure < 90 mmHg or a diastolic blood pressure < 60 mmHg?	☐ No ☐ Yes	
fever ≥ 39.3°C?	☐ No ☐ Yes	Total number of days:
a heart rate ≥ 125 beats per minute?	☐ No ☐ Yes	

During ICU admission, did the patient ever require:		**If yes, please provide the following details:**
non-invasive supplemental oxygen?	☐ No ☐ Yes	Total number of days:
respiratory ventilator support or ECMO[1]?	☐ No ☐ Yes	Total number of days:
treatment with vasopressors?	☐ No ☐ Yes	Total number of days:

During ICU admission, did the patient exhibit signs or symptoms of new/worsening dysfunction in any of the following categories?

Gastrointestinal disorders		
Acute liver failure	☐ No	☐ Yes
Acute renal failure	☐ No	☐ Yes
Renal replacement therapy	☐ No	☐ Yes
Neurological disorders		

[1] Extracorporeal membrane oxygenation

Encephalopathy	☐ No	☐ Yes			
Convulsions/seizures	☐ No	☐ Yes			
Meningitis	☐ No	☐ Yes			
Altered level of consciousness	☐ No	☐ Yes			
Guillain-Barre Syndrome	☐ No	☐ Yes			
Cerebrovascular stroke	☐ No	☐ Yes			
Other	☐ No	☐ Yes	If yes, specify:		
Respiratory disorders					
Acute respiratory distress syndrome (ARDS)	☐ No	☐ Yes			
Pneumonia	☐ No	☐ Yes	If yes, radiological confirmation?	☐ No	☐ Yes
Acute respiratory failure	☐ No	☐ Yes			
Other	☐ No	☐ Yes	If yes, specify:		
Cardiac disorders					
Myocardial infarction	☐ No	☐ Yes			
Arrhythmia (new onset)	☐ No	☐ Yes			
Ischemic heart disease	☐ No	☐ Yes			
Myocarditis, pericarditis	☐ No	☐ Yes			
Stress cardiomyopathy	☐ No	☐ Yes			
Microangiopathy	☐ No	☐ Yes			
Other	☐ No	☐ Yes	If yes, specify:		
Vascular disorders					
Deep vein thrombosis	☐ No	☐ Yes			
Pulmonary embolus	☐ No	☐ Yes			
Limb ischemia	☐ No	☐ Yes			
Vasculitis	☐ No	☐ Yes			
Thrombocytopenia	☐ No	☐ Yes			
Other	☐ No	☐ Yes	If yes, specify:		
Others					
Multi-organ failure	☐ No	☐ Yes	If yes, specify:		
Multisystem inflammatory syndrome	☐ No	☐ Yes			

Section B: laboratory features

Please provide the **clinically significant** laboratory results **at** ICU admission.

Date of sampling:	**[dd/mm/yyyy]**

Test type/name	Clinically significant results?	Provide details for clinically significant results only
Creatinine	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
Bilirubin	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
Platelet count	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
Lymphocytes (i.e. CD4, CD8 counts)	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
Cytokines	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
Procalcitonin	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
C-reactive protein	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
Ferritin	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
Lactate dehydrogenase (LDH)	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
D-dimer	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
Prothrombin time (PT)	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
Partial thromboplastin time (PTT)	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
International Normalized Ratio (INR)	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
Fibrinogen	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:

Test type/name	Clinically significant results?	Provide details for clinically significant results only
PaO2/FiO2	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
PaCO2	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
pH	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
SpO2/FiO2	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:

Section C: other measurements

Please provide **clinically significant** laboratory, histopathological, and/or radiological results during ICU stay.

Test type/name	Clinically significant results?	Provide details for clinically significant results only
Histopathology/ immunopathology of organs involved	☐ Yes ☐ No ☐ Unknown	Date(s): Results:
Diagnostic imaging (Magnetic Resonance Imaging, Computed Tomography, Ultrasound, Doppler, etc.)	☐ Yes ☐ No ☐ Unknown	Test Date Result
Other relevant results	☐ Yes ☐ No ☐ Unknown	Test Date Result w/units

ANNEX 2: CHRONIC CONDITIONS

Covariate		Definition
Chronic conditions		
	Asthma	• **Any of the following diagnostic codes (ICD-10):** J45, J46 • **INCLUDING**: predominantly allergic asthma, nonallergic asthma, status asthmaticus, acute severe asthma • **EXCLUDING:** acute severe asthma, chronic asthmatic (obstructive) bronchitis, chronic obstructive asthma, eosinophilic asthma, lung diseases due to external agents
	Lung disease	• **Any of the following diagnostic codes (ICD-10):** A15-16, A19, A31.0, B33.4, E84.0, J40-44, J47, J60-70, J80-84, J85-86, J90-91, J92.9, J93-94, J95-99 • **INCLUDING:** tuberculosis (pulmonary, miliary, but not that of other systems), atypical mycobacteria, cystic fibrosis, chronic obstructive pulmonary disease (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
	Cardiovascular disease	• **Any of the following diagnostic 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 and large vessels 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.
	Hypertension	• **Any of the following diagnostic codes (ICD-10):** I10, I11.9, I12, I13.1, I13.9, I15 • **INCLUDING**: essential (primary) hypertension, secondary hypertension • **EXCLUDING:** hypertensive heart/renal disease with (congestive) heart failure
	Chronic liver disease	• **Any of the following diagnostic codes (ICD- 10):** B18, B19, K70.1-4, K70.9, K71.1, K71.3, K71.4, K71.6-9, K72.1,

		K72.9, K73, K74, K75.2, K75.4, K75.8, K75.9, K76.1, K76.2, K76.5, K76.6, K76.9 • **INCLUDING:** all conditions of the liver that are chronic or likely to have chronic sequelae • **EXCLUDING:** acute liver disease, liver cancer/metastasis, liver transplant
	Chronic kidney disease	• **Any of the following diagnostic 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
	Type 2 diabetes	• **Any of the following diagnostic codes (ICD-10):** E11 • **INCLUDING:** non-insulin dependent diabetes mellitus (adult-onset, maturity-onset, nonketotic, stable, type II, non-insulin-dependent diabetes of the young)
	Cancer	• **Any of the following diagnostic codes (ICD- 10):** C00-97, D37-48, Z85, Z92.3, Z92.6 • **INCLUDING:** all malignant neoplasms (both solid and haematologic) with potential to metastasise, either in treatment, active follow-up, 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.
	Immunodeficiency (or organ transplant)	• **Any of the following diagnostic codes (ICD-10):** B20-B24, D80–84, D89, Z94 • **INCLUDING:** human immunodeficiency virus (HIV) infections, immunodeficiencies and organ transplants, iatrogenic immunodeficiencies (systemic treatment of more than two weeks duration, in the three months preceding symptom onset, with any of the following: corticosteroid (≥20 mg prednisolone daily or equivalent), ciclosporin, tacrolimus, mycophenolate, methotrexate, azathioprine, tumor necrosis factor alpha (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)

ANNEX 3: SURVEY ON PRECAUTIONARY HEALTH BEHAVIOUR[1]

During the last three months,

It really bothers me when people sneeze without covering their mouth
- 0= strongly disagree
- 1= undecided
- 2= strongly agree

I avoid touching door handles and staircase railings at public locations
- 0= strongly disagree
- 1= undecided
- 2= strongly agree

I dislike wearing a face mask
- 0= strongly agree
- 1= undecided
- 2= strongly disagree

I want people's temperature to be taken before they enter public places
- 0= strongly disagree
- 1= undecided
- 2= strongly agree

I don't mind going to very crowded places
- 0= strongly agree
- 1= undecided
- 2= strongly disagree

I would self-isolate myself at home if needed
- 0= strongly disagree
- 1= undecided
- 2= strongly agree

I frequently use hand sanitiser and/or wash my hands after shaking someone's hand
- 0= strongly disagree
- 1= undecided
- 2= strongly agree

I avoid going to public places
- 0= strongly disagree
- 1= undecided
- 2= strongly agree

[1] Olapegba PO, Iorfa SK, Kolawole SO, Oguntayo R, Gandi JC, Ottu IFA, Ayandele O. Survey data of COVID-19-related Knowledge, Risk Perceptions and Precautionary Behavior among Nigerians. Data Brief. 2020 May 8;30:105685. doi: 10.1016/j.dib.2020.105685. PMID: 32391411; PMCID: PMC7206440.

ANNEX 4: STUDY-SPECIFIC COMMON MINIMUM DATASET

Nr	Variable name		Description	Additional info	Variable format	Values/coding	Mandatory
SITE IDENTIFICATION							
	idsite		Site identifier		Text	As described in the Study Plan	X
	country		Country identifier		Text	As described in the Study Plan	X
PATIENT IDENTIFICATION							
	idpatient		Patient identifier	Identifier also contains country and site identifier	Text	As described in the Study Plan	X
	sex		Sex		Numeric (categorical)	1=Male 2=Female X=Sex-neutral	X
	ageyears		Age in years at admission		Numeric		X
ADMISSION DATA							
	onsetdate		Date of first symptom onset		DD/MM/YYYY	Date within the study period	X
	admissiondate		Date of hospitalisation	First point of contact (arrival at Emergency Department)	DD/MM/YYYY	Date within the study period	X
	SARI		SARI patient		Numeric (categorical)	0=No	x

						1=Yes 9999=No information	
	fever		History of fever or measured fever >= 38°C		Numeric (categorical)	0=No 1=Yes 9999=No information	x
	cough		Cough		Numeric (categorical)	0=No 1=Yes 9999=No information	x
	shortbreath		Shortness of breath		Numeric (categorical)	0=No 1=Yes 9999=No information	x
	anos_dysg		Sudden onset of anosmia, ageusia or dysgeusia		Numeric (categorical)	0=No 1=Yes 9999=No information	x
INCLUSION/EXCLUSION CRITERIA							
	vacc_eligible		Eligible for COVID-19 vaccination at time of hospitalisation		Numeric (categorical)	0=No 1=Yes	
	comm		Communication with patient/Legally Authorised Representative		Numeric (categorical)	0=No 1=Yes 8888=Not applicable	X
	consent		Consent/assent given		Numeric (categorical)	0=No 1=Yes 8888=Not applicable	X
	Consentwho1		If consent is given, who gives the consent?		Numeric (categorical)	0=Patient 1=Legally Authorised Representative 8888=Not applicable	X
	Consentwho2		If consent is given, who gives the consent?	In case consent/assent needs to be given by both Parent/tutor/guardian and young patient	Numeric (categorical)	0=Patient 1= Legally Authorised Representative 8888=Not applicable	X

	consentdate		Date of consent given		DD/MM/YYYY	Date within the study period 8888 = Not applicable	X
	prior_hosp		COVID-19 hospitalisation within 3 months prior to the current admission (excl hospital transfers)		Numeric (categorical)	0=No 1=Yes 9999=No information	X
	contra_swab		Contra-indication for swabbing		Numeric (categorical)	0=No 1=Yes 9999=No information	X
	other_last_vacc		Received last vaccine dose with other than EMA-approved COVID-19 vaccine brand		Numeric (categorical)	0=No 1=Yes 9999=No information	X
COVID-19 VACCINATION HISTORY							
	contra_vacc		Any contraindication for SARS-CoV-2 vaccination	Based on locally used criteria	Numeric (categorical)	0=No 1=Yes 9999=No information	X
	covvaccany1		Received SARS-CoV-2 vaccination dose 1		Numeric (categorical)	0=No 1=Yes 9999=No information	X
	covvaccbrand1		Vaccine brand dose 1		Numeric (categorical)	0 = Vaxzevria ® (AstraZeneca) 1= Janssen (Johnson & Johnson) 2 = Comirnaty® (Pfizer) 3 = Spikevax (Moderna) 4 = Other 5= Nuvaxovid (Novavax) 6= Spikevax bivalent Original/Omicron BA.1 7=Comirnaty Original/Omicron BA.1 8=COVID-19 Vaccine Valneva 9999 = No information	X
	covvaccdate1		Date of SARS-CoV-2 vaccination dose 1		DD/MM/YYYY		X
	covvaccany2		Received SARS-CoV-2 vaccination dose		Numeric (categorical)	0=No	X

			2			1=Yes 9999=No information	
	covvaccbrand2		Vaccine brand dose 2		Numeric (categorical)	0 = Vaxzevria ® (Astrazeneca) 1= Janssen (Johnson & Johnson) 2 = Comirnaty® (Pfizer) 3 = Spikevax (Moderna) 4 = Other 5= Nuvaxovid (Novavax) 6= Spikevax bivalent Original/Omicron BA.1 7=Comirnaty Original/Omicron BA.1 8=COVID-19 Vaccine Valneva 9999 = No information	X
	covvaccdate2		Date of SARS-CoV-2 vaccination dose 2		DD/MM/YYYY		X
	covvaccany3		Received SARS-CoV-2 vaccination dose 3		Numeric (categorical)	0=No 1=Yes 9999=No information	X
	covvaccbrand3		Vaccine brand dose 3		Numeric (categorical)	0 = Vaxzevria ® (Astrazeneca) 1= Janssen (Johnson & Johnson) 2 = Comirnaty® (Pfizer) 3 = Spikevax (Moderna) 4 = Other 5= Nuvaxovid (Novavax) 6= Spikevax bivalent Original/Omicron BA.1 7=Comirnaty Original/Omicron BA.1 8=COVID-19 Vaccine Valneva 9999 = No information	X
	covvaccdate3		Date of SARS-CoV-2 vaccination dose 3		DD/MM/YYYY		X
	covvaccany4		Received SARS-CoV-2 vaccination dose		Numeric (categorical)	0=No	X

			4			1=Yes 9999=No information	
	covvaccbrand4		Vaccine brand dose 4		Numeric (categorical)	0 = Vaxzevria ® (Astrazeneca) 1= Janssen (Johnson & Johnson) 2 = Comirnaty® (Pfizer) 3 = Spikevax (Moderna) 4 = Other 5= Nuvaxovid (Novavax) 6= Spikevax bivalent Original/Omicron BA.1 7=Comirnaty Original/Omicron BA.1 8=COVID-19 Vaccine Valneva 9999 = No information	X
	covvaccdate4		Date of SARS-CoV-2 vaccination dose 4		DD/MM/YYYY		X
	covvaccanyx		Received SARS-CoV-2 vaccination dose x + 1 (additional dose numbers will be added following real-life use of COVID-19 vaccine doses)		Numeric (categorical)	0=No 1=Yes 9999=No information	X
	covvaccbrandx		Vaccine brand of dose x + 1		Text		X
	covvaccdatex		Date of SARS-CoV-2 vaccination dose x + 1		DD/MM/YYYY		X
	covvacsource		Source of the COVID-19 exposure information		Numeric (categorical)	1=registry 2=medical record 3= vaccine card 9999=No information	X
COMORBIDITIES/RISK FACTORS							
	asthma		Asthma	Diagnostic codes and definitions can be found in Annex	Numeric (categorical)	0=No 1=Yes 9999=No information	X

				2			
	lungdis		Lung disease	Diagnostic codes and definitions can be found in Annex 2	Numeric (categorical)	0=No 1=Yes 9999=No information	X
	cardiovasc		Cardiovascular diseases	Diagnostic codes and definitions can be found in Annex 2	Numeric (categorical)	0=No 1=Yes 9999=No information	x
	hypertens		Hypertension	Diagnostic codes and definitions can be found in Annex 2	Numeric (categorical)	0=No 1=Yes 9999=No information	X
	liverdis		Chronic liver disease	Diagnostic codes and definitions can be found in Annex 2	Numeric (categorical)	0=No 1=Yes 9999=No information	X
	rendisease		Chronic renal disease	Diagnostic codes and definitions can be found in Annex 2	Numeric (categorical)	0=No 1=Yes 9999=No information	X
	type2diabetes		Diabetes	Diagnostic codes and definitions can be found in Annex 2	Numeric (categorical)	0=No 1=Yes 9999=No information	X
	cancer		Cancer	Diagnostic codes and definitions can be found in Annex 2	Numeric (categorical)	0=No 1=Yes 9999=No information	X
	immuno		Immunodeficiency or organ transplant	Diagnostic codes and definitions can be found in Annex 2	Numeric (categorical)	0=No 1=Yes 9999=No information	x
OTHER RISK FACTORS							
	pregnancy		Pregnancy	Any trimester at symptom onset	Numeric (categorical)	0=No 1=Yes 9999=No information	X

	pregn_trim		Pregnancy trimester		Numeric (ordinal)	0=Not applicable 1=First trimester 2=Second trimester 3=Third trimester 9999=No information	X
	bmi		Body mass index		Numeric	10 to 55 or 9999=No information	X
	smoking		Smoking status (cigarettes, cigars, pipe, hookah, vaping, e-cigarettes). Not counting exclusively chewing tobacco or snus.	Never-smoker: <100 cigarettes during their lifetime. Ex-smoker: has smoked ≥100 cigarettes over lifetime but has stopped ≥3 months ago. Occasional smoker: has smoked ≥100 cigarettes over lifetime and has still smoked in the 3 months preceding symptom onset, but not daily. Daily smoker: has smoked ≥100 cigarettes over lifetime and smokes daily.	Numeric (categorical)	0=Never-smoker 1=Ex-smoker 2=Occasional smoker 3=Daily smoker 9999=No information	
	ltcf_res		Is the patient a long-term care facility resident		Numeric (categorical)	0=No 1=Yes 9999=No information	
	hcw		Is the patient a healthcare worker		Numeric (categorical)	0=No 1=Yes 9999=No information	
	hcw_patient		Is the patient a healthcare worker with direct contact to patients		Numeric (categorical)	0=No 1=Yes 9999=No information	

	hcw_covid		Is the patient a healthcare worker with direct contact to COVID-19 patients		Numeric (categorical)	0=No 1=Yes 9999=No information	
	hcw_ltcf		Is the patient a healthcare worker working in long-term care facility		Numeric (categorical)	0=No 1=Yes 9999=No information	
	prev_covid		COVID-19 prior to current episode	I had a previous episode of COVID-19 more than 2 months ago	Numeric (categorical)	0=No 1=Yes, clinical diagnosis only 2=Yes, laboratory-confirmed	
PRECAUTIONARY HEALTH BEHAVIOR & VACCINATION ATTITUDE				***As measured through a precautionary health survey, by summing scores on questions detailed below***			
	prehb_sneeze		Sneeze	It really bothers me when people sneeze without covering their mouth	Numeric (categorical)	0=strongly disagree 1=undecided 2=strongly agree	
	prehb_touch		Touch	I avoid touching door handles and staircase railing at public locations	Numeric (categorical)	0=strongly disagree 1=undecided 2=strongly agree	
	prehb_mask		Face mask	I dislike wearing face mask because of the way it looks and/or feels	Numeric (categorical)	0=strongly agree 1=undecided 2=strongly disagree	
	prehb_crowd		Crowds	I don’t mind going to very crowded places	Numeric (categorical)	0=strongly agree 1=undecided 2=strongly disagree	
	prehb_isolate		Self-isolate	I would self-isolate myself at home if needed	Numeric (categorical)	0=strongly disagree 1=undecided 2=strongly agree	

	prehb_sani		Hand sanitiser	I frequently use hand sanitiser and/or wash my hands after shaking someone's hand	Numeric (categorical)	0=strongly disagree 1=undecided 2=strongly agree	
	prehb_public		Public places	I avoid going to public places	Numeric (categorical)	0=strongly disagree 1=undecided 2=strongly agree	
LABORATORY							
	swabdate		Date of swabbing		DD/MM/YYYY	Date within the study period. In case of multiple tests with at least 1 positive test result within 14 days prior to hospital admission, take the swab date corresponding to the first positive test result. In case all test results are negative, take the earliest swab date within 14 days prior to hospital admission.	X
	virus1		Laboratory result: SARS-CoV-2		Numeric (categorical)	0=SARS-CoV-2 negative 1=SARS-CoV-2 positive 9999=No information	X
	virus2		Laboratory results: coinfection (in addition to SARS-CoV-2)		Numeric (categorical)	0=No coinfection 1=coinfection 9999=No information	X
	virus1_ext		Laboratory result: pathogen	Alternative to Q49 when multiple pathogens are tested	Numeric (categorical)	0=Negative 1=SARS-CoV-2 2=influenza 3=RSV 4=pneumococcus 5=Other 9999=No information	X

	virus2_ext		Laboratory result: In case of coinfection, second pathogen involved	Alternative to Q50 when multiple pathogens are tested	Numeric (categorical)	0=No coinfection 1=SARS-CoV-2 2=Influenza 3=RSV 4=Pneumococcus 5=Other 9999=No information	X
	sequenced		Tested for genetic variants		Numeric (categorical)	0=No 1=Yes 9999=No information	
	variant_pangolin		Pangolin lineage name		Alfanumeric (categorical)	Example: B.1.117	
	EPI_ISL_nr		GISAID identification number		Alfanumeric	Example: EPI_ISL_412974	
ADDITIONAL HOSPITALISATION DATA							
	icu		ICU admission		Numeric (categorical)	0=No 1=Yes 9999=No information	X
	death		In-hospital death		Numeric (categorical)	0=No 1=Yes 9999=No information	X
	discharge_date		Date of discharge or death		DD/MM/YYYY	Date within the study period	X
OTHER VACCINATIONS							
	fluvacc		Being vaccinated with at least one influenza vaccine within 12 months prior to SARI hospital admission		Numeric (categorical)	0=No 1=Yes 9999=No information	X
	fluvaccdate		Date of influenza vaccination		DD/MM/YYYY		X
	pneumovacc		Received any pneumococcal vaccination	Any time	Numeric (categorical)	0=No 1=Yes 9999=No information	X
	pneumovaccdate		Year of pneumococcal vaccination	Latest dose	YYYY		X
TREATMENTS							

	pre_prophylaxis_6mo		Having received anti-SARS-CoV-2 antibody products or other drugs indicated for pre-exposure prophylaxis for SARS-CoV-2 infection within 6 months prior to current hospitalisation		Binary	0=No 1=Yes 9999=No information	
	pre_prophylaxis_brand		Brand of latest received anti-SARS-CoV-2 antibody product or other drugs indicated for pre-exposure prophylaxis for SARS-CoV-2 infection		Numeric (categorical)	0=Kineret (anakinra)* 1=Regkirona (regdanvimab) 2=RoActemra (tocilizumab) 3=Ronapreve (casirivimab / imdevimab) 4=Veklury (remdesivir) 5=Xevudy (sotrovimab) 6=Evusheld (tixagevimab / cilgavimab) 7=Lagevrio (molnupiravir) 8=Paxlovid (PF-07321332 / ritonavir) 9=Other	
	pre_prophylaxis_date		Date of treatment start latest received anti-SARS-CoV-2 antibody product or other drugs indicated for pre-exposure prophylaxis for SARS-CoV-2 infection		DD/MM/YYYY		
	post_prophylaxis_6mo		Having received anti-SARS-CoV-2 antibody products or other drugs indicated for post-exposure prophylaxis for SARS-CoV-2 infection within 6 months prior to current hospitalisation		Binary	0=No 1=Yes 9999=No information	
	post_prophylaxis_brand		Brand of latest received anti-SARS-CoV-2 antibody product or other drugs indicated for post-exposure prophylaxis for SARS-CoV-2 infection		Numeric (categorical)	0=Kineret (anakinra)* 1=Regkirona (regdanvimab) 2=RoActemra (tocilizumab) 3=Ronapreve (casirivimab / imdevimab) 4=Veklury (remdesivir) 5=Xevudy (sotrovimab)	

						6=Evusheld (tixagevimab / cilgavimab) 7=Lagevrio (molnupiravir) 8=Paxlovid (PF-07321332 / ritonavir) 9=Other	
	post_prophylaxis_date		Date of treatment start latest received anti-SARS-CoV-2 antibody product or other drugs indicated for post-exposure prophylaxis for SARS-CoV-2 infection		DD/MM/YYYY		
	post_symptom		Having received anti-SARS-CoV-2 antibody products or antiviral drugs indicated for treatment post-symptom onset leading to current hospitalisation		Binary	0=No 1=Yes 9999=No information	
	post_symptom_brand		Brand of received anti-SARS-CoV-2 antibody products or antiviral drugs indicated for treatment post-symptom onset prior leading to current hospitalisation		Numeric (categorical)	0=Kineret (anakinra)* 1=Regkirona (regdanvimab) 2=RoActemra (tocilizumab) 3=Ronapreve (casirivimab / imdevimab) 4=Veklury (remdesivir) 5=Xevudy (sotrovimab) 6=Evusheld (tixagevimab / cilgavimab) 7=Lagevrio (molnupiravir) 8=Paxlovid (PF-07321332 / ritonavir) 9=Other	
	post_symptom_date		Date of treatment start anti-SARS-CoV-2 antibody products or antiviral drugs indicated for treatment post-symptom onset leading to current hospitalisation		DD/MM/YYYY		

ANNEX 5: ADULT INFORMED CONSENT FORM, AND CHILD ASSENT & PARENT INFORMED CONSENT

Study participant information

for participation in an epidemiological study to measure the effectiveness of COVID-19 vaccines

Dear Sir/ Madam,

You are receiving this letter because you have been hospitalised with Severe Acute Respiratory Infection (SARI)[1] and you are being asked to take part in a medical scientific study. Participation is voluntary. It is not a clinical trial, so you will not receive any investigational medicines or vaccines – we will just collect and analyse data (observational study). To participate in the study, your written consent is required.

Before you decide whether you want to take part in this study, you will be informed about it. Please take your time to read the information below and ask the study doctor if you have any questions. You can also discuss it with your partner, friends, or family.

1. General information about the study

This study was designed by COVIDRIVE (a public-private partnership[2] to estimate brand-specific COVID-19 vaccine effectiveness in Europe) and it is being conducted in various hospitals in Europe. The pharmaceutical industry (vaccine manufacturers)[2] covers the costs of the study, and the study sponsor (responsible for the oversight of the study) is an independent private research company: P95 (www.p95.com). P95 is specialised in epidemiology (the study of how often diseases occur in different groups of people and why) and pharmacovigilance (drug safety).

2. Background for the research

In December 2019, an outbreak of respiratory disease occurred in Wuhan City in the Hubei Province, China. The novel coronavirus was named 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2), while the disease associated with it is referred to as COVID-19. Following the identification of SARS-CoV-2 and its global spread, large epidemics of COVID-19 occurred in Europe. In response to this, European countries implemented large-scale unprecedented nonpharmaceutical interventions such as closure of schools and national lockdowns. Data collected by the European Centre for Disease

[1] Severe Acute Respiratory Infection (SARI) is a respiratory infection presenting with at least one of the following symptoms: cough, fever, shortness of breath, sudden onset of anosmia (loss of smell), ageusia (loss of taste) or dysgeusia (distorted sense of taste).
[2] Current COVIDRIVE members are listed on www.covidrive.eu.

Prevention and Control (ECDC) from 31 countries showed in early February 2021 that almost 20,000,000 COVID-19 cases and almost 500,000 COVID-19 related deaths had been recorded in the European Union (EU) since the start of the pandemic.

The development of safe and effective vaccines is key in containing the SARS-CoV-2 pandemic. At the end of 2020, the first COVID-19 vaccines were granted conditional marketing authorisation in the EU by the European Medicines Agency (EMA), followed by more approvals in 2021. One of the prerequisites for a vaccine to be authorised is that the vaccine manufacturer studies the safety and effectiveness of it, not just in the development phase, but also after the authorisation, i.e., when the vaccine is used in the population.

3. Purpose of the research

The purpose of this study is to evaluate how well the COVID-19 vaccines prevent COVID-19 disease under real-world conditions once these vaccines are being used as part of the national immunisation programs in the EU.

Questions that are typically unanswered by clinical trials (i.e., in the development phase of the vaccine) and that remain to be evaluated by real-world evidence studies include e.g., the long-term vaccine effectiveness, effectiveness against disease caused by specific and newly emerging SARS-CoV-2 strains, effectiveness against *severe* COVID-19 disease and effectiveness in special risk groups such as immunocompromised subjects. This knowledge is very valuable for public health decision-making on immunisation strategies.

4. Type of research intervention

This is a 'non-interventional' study to estimate the effectiveness of COVID-19 vaccines against COVID-19 related hospitalisations. Non-interventional (or 'observational') means that you will not be given any investigational medicines or vaccines as part of this study. It also means that no interventions (such as blood sampling, imaging, …) other than those part of your standard care will be performed for the study.

The study is a multi-centre, hospital-based, 'case-control' study[3]. Case-control means that the study is based on a group of SARI patients with a positive COVID-19 test ('cases') and a group of SARI patients with a negative COVID-19 test ('controls'). Data will be collected through a wide network of hospitals located in more than ten different European countries.

[3] Scientific description of the study design: 'An observational study to measure the brand-specific COVID-19 vaccine effectiveness against severe COVID-19 disease in Europe: A multi-centre, hospital-based, case-control study using a test-negative case-control design'

5. What will be expected of you?

The study does not require additional visits or assessments other than those required during hospitalisation for a patient with SARI. The study doctor or nurse may however ask you some questions or will provide you with a short questionnaire to measure your precautionary health behavior in the context of the pandemic. This questionnaire will take not more than 5 minutes to fill out.

Your responsibilities as a study participant include the following:

- tell the truth about your medical history, vaccination history and current conditions,
- complete the questionnaire(s) upon request of the study doctor,
- agree to be contacted by the study team as necessary, by telephone or through writing,
- allow your general practitioner to be contacted by the study team to obtain additional information about your health or vaccination history required for this study,
- tell the study doctor about any health problems you have during the study, and
- tell the study doctor if you wish to withdraw from the study (see also below).

6. If you do not want to participate, or would like to stop participating in the study

You are participating in this study on a voluntary basis, and you have the right to withdraw your consent for any reason. You do not need to state a reason for this. Please contact your study doctor if you wish to withdraw your consent. If you withdraw your consent, the personal data already collected up to the date of your withdrawal will be retained (i.e., it will be used for the research). This is to guarantee the validity of the study. But from the date you withdraw and onwards, no new information about you will be collected.

The decision whether to participate in this study or not will not have any negative impact on the quality of care during or after your hospitalisation or on the relationship with your treating doctor(s).

7. Confidentiality: Use and storage of your personal data and biological samples

<u>Use and storage of your personal data</u>

To run the study properly, we need to collect personal information about you and your health. The personal data collected can be reused for additional analysis and for purposes dedicated to advancing the knowledge on SARI, its prevention, or treatments.

The necessary personal data include:

- your age and gender,
- your medical history (including any chronic conditions or previous SARS-CoV-2 infection),
- your body mass index (BMI),
- your smoking history,
- if you are pregnant: your due date,
- results of the tests and examinations you have during your SARI hospitalisation,
- your vaccination history,
- your precautionary health behaviour in the context of the pandemic,

- whether you are a long-term care facility resident, and
- whether you are a healthcare worker and if so, if you are in direct contact with SARS-CoV-2 patients.

COVIDRIVE is responsible for your personal information. All results resulting from the research described in this document are property of the sponsor. The collection, transfer, and processing of personal data from patients participating in this study will be performed in accordance with [the country law of DD-MM-YYYY][4]. Your identity will never leave the hospital, i.e., only the study doctor and study staff shall know who you are. Before your personal data are transferred to P95 for analysis, they will be pseudonymised, i.e., your personal information (e.g., name, age, and sex) is removed from the data and a code is placed instead of your name. Only your study doctor and study staff will have the key to the code. Your pseudonymised data will be stored on a dedicated and secured central server by P95 in two different European locations (main location and back-up location). Your personal data will be stored for at least 10 years after study end.

To check the quality of the study, your not-yet-pseudonymised personal data or information from your medical file (information relevant to this study) may be inspected by people other than the study staff. This could happen in a 'study quality audit' or a 'study quality monitoring visit'. This access to personal data takes place under the supervision of the study doctor and the inspectors are bound by professional secrecy or by means of a confidentiality agreement. Inspectors may be:

- personnel designated by the sponsor (monitors and auditors),
- inspectors from the competent Health Authorities from around the world,
- an independent audit group, or
- persons appointed by the Ethics Committee (a committee that has approved the study before it was allowed to start).

Use and storage of biological samples

A respiratory sample (e.g., nose swab or tracheal aspirate) will be taken, processed, and stored as part of the standard hospital care, to determine whether you have been infected with SARS-CoV-2 or another pathogen. This sample will be analysed as part of the study.

As scientific progress in infectious respiratory diseases is constant, we would like to, with your consent, store the remainders of the sample for a maximum of 3 years for purposes of genomic characterisation (study of the genetic material) of the pathogen.

8. Your rights if you decide to participate

As mentioned above, you may withdraw from the study at any time without giving any reason, even if you have previously agreed to participate. Your decision will not affect your relationship with the investigator or your treating physician, or the quality of your future medical care.

[4] the protection of natural persons with regard to the processing of personal data and the European General Data Protection Regulation (GDPR), effective from May 25, 2018

You have the right to ask the study staff which personal data are collected about you and what they are used for in this study. You have the right to:

- access and check these personal data,
- receive the collected personal data,
- ask for correction of your personal data if they are incorrect,
- restrict the processing of your personal data,
- oppose the processing of your personal data, and
- withdraw your consent to the processing of your personal data. Your personal data already collected prior to your withdrawal will be retained to avoid misinterpretation of study results.

9. Benefits and risks of participation in this study

Since this is a non-interventional study, and all biological sample analyses and medical procedures are part of the standard medical care for your condition, **your participation in this study does not pose any health risk.**

[For Belgium ICF, and to be confirmed for new countries, add the following required paragraph: We will do everything to ensure confidentiality and the protection of your personal data. Nevertheless, a risk of data breach can never be completely ruled out. The study doctor has purchased insurance in the event that you suffer any harm as a result of your participation in this study].

Participation in this study will not bring you any personal benefits. If you participate, you will contribute to a better understanding about COVID-19 disease and the effectiveness of new COVID-19 vaccines (which will help us to understand how good these vaccines work).

10. Sharing the results

After study closure, a description and the results of this study will be published in specialised medical journals. A copy of the scientific publication(s) can be obtained from the study doctor or the study staff. A description of the study will also be available on www.covidrive.eu and in the European Union electronic Register of Post-Authorisation Studies (EU PAS register). The information that will be made publicly available will be anonymised, i.e., it will not include any information that can identify you.

11. Do you have any questions

If you have any questions, please contact the study doctor or study nurse. If you have any complaints about the study, you can discuss this with your study doctor, but if you would rather not do that, you can contact the complaints committee at your hospital.

[contact details study doctor]

[contact details study nurse]

[contact details complaints committee of the hospital]

Adult Informed Consent

Research title:
A study to measure the brand-specific COVID-19 vaccine effectiveness against severe COVID-19 disease in Europe: A multi-centre, hospital-based, case-control study with test-negative controls (test-negative case-control design)

I, the undersigned, declare that

- I have been informed of the nature, purpose, duration, possible benefits, and risks of the study and that I know what is expected of me,
- I have read the 'Study participant information for participation in an epidemiological study to measure the effectiveness of COVID-19 vaccines',
- I have had enough time to think about this and to talk to a person of my choice, such as my doctor or a family member,
- I have been able to ask any questions that came to my mind, and I have received clear answers to my questions,
- I understand that my participation in this study is voluntary and that I am free to discontinue my participation in this study without affecting my relationship with the therapeutic team in charge of my health,
- I understand that personal data will be collected about me during my participation in this study and that the study doctor and the sponsor ensure the confidentiality of this personal data in accordance with [country] law,
- [For Belgium ICF, and to be confirmed for new countries, add the following required paragraph:
  I understand that the study doctor has insurance in case I am harmed as a result of my participation in this study],
- I understand that if I participate in this study, I will not incur any costs other than those related to the ongoing treatment of my disease,
- I agree to the processing of my personal data in accordance with the modalities described in the section on ensuring confidentiality. I also consent to the transfer to and processing of my pseudonymised data in European countries other than [country],
- I agree that my personal data may be used and shared by the sponsor and other researchers for future research, as described in the 'Study participant information for participation in an epidemiological study to measure the effectiveness of COVID-19 vaccines', provided that the research is dedicated to advancing the knowledge on SARI, its prevention, or treatments.
- I agree that my doctor or other health care professionals will be contacted if necessary to obtain additional information about my health, and that

- I have received a copy of the 'Study participant information for participation in an epidemiological study to measure the effectiveness of COVID-19 vaccines' and my signed Informed Consent Form.

I, the undersigned, understand that

- as mentioned in Section 7 in the 'Study participant information for participation in an epidemiological study to measure the effectiveness of COVID-19 vaccines' above, the sponsor may want to use my study data for other research and development activities (and associated scientific publications). These research purposes must be approved by a recognised [country] ethics committee.

  (check the appropriate box)

  ☐ **I agree**
  ☐ **I do *not* agree**

  that anonymised data about me obtained in this study may be used for other research purposes and development activities.

I, the undersigned patient, agree to participate voluntarily in the study.

First name (study participant)	Family name (study participant)
Your signature	Date of signature

If a witness/interpreter is present:

I, the undersigned *(check the appropriate box)*

☐ **witness**

☐ **interpreter**

declare that

- I have been present throughout the process of providing information to the participant,
- information about the objectives and procedures of the study have been adequately provided to the study participant, and that
- the participant is likely to have understood the study and that participation in the study is voluntary for him/her.

I also certify that, as an impartial witness, I am not related in any way to the sponsor or the investigator.

First name (witness/interpreter)	Family name (witness/interpreter)
Your signature	Date of signature

If a Legally Authorised Representative of the study participant is present:

I, the undersigned Legally Authorised Representative, declare that

- I have been present throughout the process of providing information to the participant,
- information about the objectives and procedures of the study have been adequately provided, and that
- the participant is likely to have understood the study and that participation in the study is voluntary.

First name (Legally Authorised Representative)	Family name (Legally Authorised Representative)
Your signature	Date of signature

Attending study doctor:

I, the undersigned treating study doctor, or his/her representative, declare that

- I have provided the necessary information regarding this study orally as well as a copy of the information document to the participant.

I confirm that no pressure has been placed on the participant to get him/her to agree to participate in the study and I am willing to answer any additional questions.

First name (study doctor/representative of the study doctor)	Family name (study doctor/representative of the study doctor)
Job title (representative of the study doctor)	
Your signature	Date of signature

Child Informed Assent and Parent Informed Consent

Research title:
A study to measure the brand-specific COVID-19 vaccine effectiveness against severe COVID-19 disease in Europe: A multi-centre, hospital-based, case-control study with test-negative controls (test-negative case-control design)

I, the undersigned child, declare that

- this study has been explained to me (how long the study takes, why this study is done, all risks and discomforts and what is expected of me),
- my mom, dad or the person taking care of me knows about this study and they want me to be in it if I want to,
- I have had enough time to think about taking part in this study and I could also talk to others if I wanted to (for example friends, other family member, treating doctor, …),
- I could ask all my questions and I have received clear answers to my questions,
- I understand that I can choose to participate or to not participate in this study and I know that I can stop whenever I like,
- I understand that information about me will be collected and that it will be treated confidentially,
- I understand that I should tell my mom, dad or the person taking care of me and the study doctor immediately if I think any harm is caused to me,
- I agree to my treating doctor(s) being informed of my participation in this study and that they may be asked to provide more health information about me, and that
- I understand that I need to cooperate in this study and follow the instructions of the study doctor or study team.

First name (study participant)	Family name (study participant)
Your signature	Date of signature

Mother/father/guardian/Legally Authorised Representative:

I, the undersigned parent, guardian, or Legally Authorised Representative, declare that

- I have been informed of the nature, purpose, duration, possible benefits, and risks of the study and that I know what is expected of my child,
- I have read the the 'Study participant information for participation in an epidemiological study to measure the effectiveness of COVID-19 vaccines',
- I have had enough time to think about this and to talk to a person of my choice, such as my doctor or a family member,
- I have been able to ask any questions that came to my mind, and that I have received clear answers to my questions,
- I understand that my child's participation in this study is voluntary and that I am free to discontinue my child's participation in this study without affecting my and my child's relationship with the therapeutic team in charge of his/her health,
- I understand that personal data will be collected about my child during his/her participation in this study and that the study doctor and the sponsor ensure the confidentiality of these data in accordance with [country] law,
- [For Belgium ICF, and to be confirmed for new countries, add the following required paragraph:
  I understand that the study doctor has insurance in case any harm would result from my child's participation in this study],
- I understand that if my child participates in this study, it will not incur any costs other than those related to the ongoing treatment of his/her disease,
- I agree to the processing of my child's personal data in accordance with the modalities described in the section on ensuring confidentiality and I consent to the transfer to and processing of his/her pseudonymised data in European countries other than [country],
- I agree that my child's personal data may be used and shared by the sponsor and other researchers for future research, as described in the 'Study participant information for participation in an epidemiological study to measure the effectiveness of COVID-19 vaccines', provided that the research is dedicated to advancing the knowledge on SARI, its prevention, or treatments.
- I agree that my child's doctor or other health care professionals will be contacted if necessary to obtain additional information about my child's health,
- I have received a copy of the 'Study participant information for participation in an epidemiological study to measure the effectiveness of COVID-19 vaccines' and Informed Consent Form.

I, the undersigned, understand that

- as mentioned in Section 7 in the 'Study participant information for participation in an epidemiological study to measure the effectiveness of COVID-19 vaccines' above, the sponsor may want to use my child´s study data for other research and development activities (and associated scientific publications). These research purposes must be approved by a recognised [country] ethics committee.

  (check the appropriate box)

  ☐ **I agree**

  ☐ **I do *not* agree**

  that anonymised data about my child obtained in this study may be used for other research purposes and development activities.

I, the undersigned parent, guardian, or Legally Authorised Representative, agree that my child participates in the study.

First name (Mother/father/guardian/Legally Authorised Representative)	Family name (Mother/father/guardian/Legally Authorised Representative)
Your signature	Date of signature

If a witness/interpreter is present:

I, the undersigned (check the appropriate box)

☐ **witness**

☐ **interpreter**

declare that

- I have been present throughout the process of providing information to the participant and his/her parent/guardian/Legally Authorised Representative,
- information about the objectives and procedures of the study have been adequately provided,
- the participant and his/her parent/guardian/ Legally Authorised Representative are likely to have understood the study and that the study is voluntary.

I also certify that, as an impartial witness, I am not related in any way to the sponsor or the investigator.

First name (witness/interpreter)	Family name (witness/interpreter)
Your signature	Date of signature

Attending study doctor:

I, the undersigned study doctor, or his/her representative, declare that

- I have provided the necessary information regarding this study orally as well as a copy of the 'Study participant information for participation in an epidemiological study to measure the effectiveness of COVID-19 vaccines' to the study participant and his/her parent/guardian/Legally Authorised Representative.

I confirm that no pressure has been placed on the participant or his/her parent/guardian/Legally Authorised Representative to get him/her to agree to study participation and I am willing to answer any additional questions.

First name (study doctor/representative of the study doctor)	Family name (study doctor/representative of the study doctor)
Job title (representative of the study doctor)	
Your signature	Date of signature

ANNEX 6: SAMPLE SIZE CALCULATIONS, TECHNICAL SPECIFICATIONS

Sample size calculation

To guide the study design and study site selection, several sample size calculations were performed. The goal of the sample size calculations was to ensure that the study will be able to obtain precise CVE estimates. As analytical sample size formulas for the different pooling methodology are not readily available, a simulation approach was utilised.

Aims and objectives

The goal of the simulation studies is to calculate the required sample size that ensures that the estimation procedure has certain desirable properties. Examples of such properties are:

- expected length of the 95% CI of the CVE ≤30%
- expected lower half width of the 95% CI of the CVE ≤15%
- power of at least 80% to detect a CVE significantly different from 0

Data generation workflow

Notation

Before describing the data generation workflow, the following parameters which act as input for the model have to be defined:

1. $CVE_{x,overall}$: the overall CVE of exposure x, the corresponding odds ratio is $OR_{x,overall} = 1 - \frac{CVE_{x,overall}}{100}$.
2. $c = P(unexposed|control)$: proportion of unexposed subjects among the controls
3. $P_x = P(exposure\ x|exposed, control)$: brand share of exposure x among the exposed
4. r: ratio of cases to control (that is, number of cases per one control)

General set-up

In each simulation run, a dataset is constructed by combining data generated for a number of individual sites. We will denote the total number of study sites with k and the total sample size as N. Additionally, it is assumed that each site consists of the same number of subjects, i.e. $\frac{N}{k}$. In order to allow for variability in the underlying vaccine effects across study sites, the CVE can be different from site to site. In the next section, it is described how data for one site is generated given the study site-specific CVEs for all exposures. The subsequent section describes how the CVE are varied across the study sites to introduce between-site variability.

Simulating data at the site level

For each site, $\frac{N}{k} \times \frac{r}{1+r}$ cases and $\frac{N}{k} \times \frac{1}{1+r}$ controls are simulated. The vaccine exposure status for the controls is generated from a multinomial distribution with the probability of being unexposed equal to c and the probability of being exposed to brand x equal to $(1-c)P_x$.

For each $\frac{N}{k} \times \frac{r}{1+r}$ of the cases, the vaccine exposure status is then generated from a multinomial distribution with the probability of being unexposed equal to success probability of $P(unexposed|case) = \frac{1}{1+\sum_x \mathrm{OR}_x * \frac{(1-c)P_x}{c}}$ and the probability of being exposed to brand x equal to $P(exposure\ x|case) = \mathrm{OR}_x * \frac{(1-c)P_x}{c} * P(unexposed|case)$.

Inserting these probabilities in the formula of the OR gives us:

$$\frac{\frac{P(exposure\ x|case)}{P(unexposed|case)}}{\frac{P(exposure\ x|control)}{P(unexposed|control)}} = OR_{x,site}$$

confirming that the underlying odds ratio of this simulation scheme is equal to the Study Contributor (i.e. site-specific) OR for exposure x.

Simulating study site-specific CVE

Effect of primary series vaccination

To incorporate the expected between-site heterogeneity, for each study site a site-specific odds ratio ($OR_{x,site}$) was generated from a log-normal distribution with a median of $1 - \frac{CVE_{x,overall}}{100}$ and variance on the log scale of 0.05. The value of the variance parameter on the log scale was selected to be 0.05 as it introduced an amount of between-site heterogeneity and was in line with the heterogeneity seen in a previous database study[1]. Note that decreasing the value of this parameter lead to a decrease in the sample size requirements. The expected value of the CVE over the sites is then equal to $100 \times \left(1 - \exp\left(\log\left(1 - \frac{CVE_{x,overall}}{100}\right) + \frac{0.05}{2}\right)\right)$.

Effect of additional dose vaccination

The overall effect of the exposure corresponding to vaccination with a primary series and an additional dose is generally derived from the vaccine effectiveness of the primary series and the relative vaccine effectiveness of the additional dose, $rCVE_{additional\ dose\ vs\ primary}$, using the following relation

$$CVE_{additional\ dose} = 100 \times \left(1 - \left(1 - \frac{rCVE_{additional\ dose\ vs\ primary}}{100}\right)\left(1 - \frac{CVE_{primary\ series}}{100}\right)\right).$$

To incorporate the expected study heterogeneity of the effect of an additional dose, the same procedure as for the primary series is used.

[1] Thompson, M.G., Stenehjem, E., Grannis, S., et al. *Effectiveness of Covid-19 Vaccines in Ambulatory and Inpatient Care Settings.* N Engl J Med, 2021. **385**(15): p. 1355-1371. DOI: 10.1056/NEJMoa2110362.

Estimates and data obtained for each simulation

For each simulated dataset, an estimate of the (r)CVE and the corresponding 95% CI is obtained using one of the following procedures:

Two-stage pooling / random-effects meta-analysis (RE-MA)

- The simulated dataset is restricted to represent the data of interest. In the case of the CVE, this means only the data on the exposure of interest and unvaccinated subjects is retained. For the rCVE calculations, only the data of subjects receiving the comparator and the additional dose is retained.
- The site-specific log OR of the (relative) treatment effect is calculated using a logistic regression model with the disease status as the outcome and the exposure status as a covariate.
- The site-specific log OR estimates are combined using a random-effects meta-analysis (RE-MA) model. More particularly, the log OR estimates are combined using the Hartung-Knapp-Sidik-Jonkman estimator to obtain an estimate of the median overall log OR and the corresponding two-sided 95% CI.
- The pooled log OR and the corresponding CI are then back-transformed to obtain an estimate and 95% CI of the median overall CVE.
- The overall CVE estimate and the length of the CI are stored for each simulation.

Generalized estimation equations (GEE)

- The simulated dataset is restricted to represent the data of interest. In the case of the CVE, this means only the data on the exposure of interest and unvaccinated subjects is retained. For the rCVE calculations only the data of subjects receiving the comparator and the additional dose is retained.
- The average log OR of the treatment effect is calculated using a logistic regression model with the disease status as the outcome and the exposure as a covariate. The estimates are obtained using the GEE method in which the sites are treated as clusters and the variances are calculated using a robust sandwich estimator.
- The average log OR and the corresponding CI are then back-transformed to obtain an estimate and 95% CI of the mean overall (r)CVE.
- The overall (r)CVE estimate and the length of the CI are stored for each simulation.

Generalized linear mixed model (GLMM)

- The simulated dataset is restricted to represent the data of interest. In the case of the CVE, this means only the data on the exposure of interest and unvaccinated subjects is retained. For the rCVE calculations only the data of subjects receiving the comparator and the additional dose is retained.
- A mixed effects logistic regression model with the disease status as the outcome and the exposure as a covariate is fitted. The mixed effects model includes both a random intercept

as well as a random treatment effect. An estimate of the mean overall (r)CVE is obtained using the method of Hedeker[2].

- The log OR and the corresponding CI are then back-transformed to obtain an estimate and 95% CI of the mean overall (r)CVE.
- The overall (r)CVE estimate and the length of the CI are stored for each simulation.

Number of simulations performed

For each combination of the study characteristics of interest, 500 simulations were performed. 500 simulations were performed as empirically this was seen to lead to Monte Carlo CIs with a range small enough for our purposes while limiting the computational burden.

Summary measures of the simulation study

For each combination of the study characteristics, the measure of interest is obtained from the 500 simulations, e.g.

- The expected range of the 95% CI is defined as the mean range of the CI obtained from the 500 simulations.
- The expected lower half width of the 95% CI is defined as the mean lower half width of the CI obtained from the 500 simulations.
- The expected power to detect a CVE significantly different from 0 is defined as the proportion of the CI's that do not include 0.

For each measure, 95% Monte Carlo CIs were constructed based on the respective Monte Carlo standard errors observed in the simulations.

[2] Hedeker, D., du Toit, S.H.C., Demirtas, H., et al. *A note on marginalization of regression parameters from mixed models of binary outcomes.* Biometrics, 2018. **74**(1): p. 354-361. DOI: 10.1111/biom.12707