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 5.0

18 September 2023

CONTRIBUTORS

Contributing organisations to this Master Protocol

Organisation
P95
FISABIO
AstraZeneca
Bavarian Nordic
GSK
Janssen
Novavax
Valneva
Pfizer

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

DOCUMENT HISTORY

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, 2021	Addressing comments from partners
2.0	February 25, 2021	Sample size section, questions on precautionary health 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 teleconferences
3.0	April 23, 2021	Addressing comments from ISC, EMA, ECDC
3.1	June 2, 2021	Minor correction to exposure definitions; submitted to the EU PAS register on 02/08/2021 (EUPAS42328)
3.2	June 15, 2021	Removing 'other hospital controls'
3.3	December 23, 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 21, 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 10, 2022	Addressing comments from partners and ISC

		Amendments: • Addition of comparator groups to objectives • Adding additional dose vaccine effectiveness to all relevant sections • Addition of contact persons list • 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 24 hours to 72 hours • Update Annex 5 (adult informed consent form) • Update Annex 6 (sample size calculations)
4.1	June 19, 2023	Amendments: • Addition of glossary • Adaptation of objectives, data analysis and sample-size sections to allow for the addition of estimation of seasonal brand-specific COVID-19 vaccine effectiveness against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients as a primary objective. Addition of relevant covariates and exposure definitions • Actualisation of sections “Rationale & Background” and “Limitations of the research methods” to current COVID-19 knowledge • Update of Data management section • Update of Quality management section • Update of section Outcomes-laboratory-confirmed SARS-CoV-2 • Removal of section “unfavourable COVID-19 positivity rates among SARI” : The described approaches were initially defined at the launch of the study, but in practise were not implementable. In place, case-control ratios are identified in risk based monitoring plan (v4.0, 19 Apr 2023) as one of the risks for central monitoring and monitored monthly for each Study Contributor. Sites are consulted if unfavourable case-control ratios are detected, to understand if these ratios are related to screening issues that need addressing or simply reflect hospitalisation trends • Addition of respiratory support in hospital severity level • Removal of precautionary health behaviour survey and associated Annex; no longer warranted based on the evolution of the pandemic

		• Removal of VAED objective and associated annex; i) data collection is challenging, ii) available data do not allow to draw any conclusions with regard to the given objective, iii) no longer warranted based on progress in COVID-19 scientific knowledge • Removal of Annex 4 (study common dataset) and Annex 5 (adult informed consent), now stand-alone documents for the COVIDRIVE study • Addition of a signature page
4.2	July 17, 2023	Addressing comments from partners
4.3	August 7, 2023	Addressing comments from ISC
4.4	August 17, 2023	Addressing comments from partners
5.0	September 18, 2023	Clean version (medical writer and quality review)

Abbreviations: COVID-19, coronavirus disease 2019; ECDC, European Centre for Disease Prevention and Control; EMA, European Medicines Agency; EU PAS register, European Union electronic register of post authorisation studies; GEE, generalised estimating equations; ICF, informed consent form; ISC, Independent Scientific Committee; RT-PCR, reverse transcriptase polymerase chain reaction; SARI, severe acute respiratory infection; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMA, transcription-mediated amplification; VAED, vaccine-associated enhanced disease; WHO, World Health Organisation.

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 EC approval of amendment Master protoco v4.0	Enrolment date of first prospective participant	Enrolment date of first retrospective participant
VAHNSI, Spain	17 Mar 2021	V2.2	01 Apr 2021	02 Nov 2022	15 Sep 2021	N/A
GTPUH, Spain	TBC	V2.0	01 Jun 2021	16 Dec 2022	20 Oct 2021	01 Jun 2021
HUVH, Spain	TBC	V2.0	01 Jun 2021	16 Dec 2022	14 Feb 2022	30 Oct 2021
CIRI-IT, Italy	TBC	V3.1	03 May 2021	28 Nov 2022	16 Nov 2021	N/A
Klinik Favoriten, Austria	20 Oct 2021	V3.1	29 Nov 2021	31 Jan 2023	04 Apr 2022	01 Jun 2021
UZA, Belgium	02 Dec 2021	V3.1	08 Dec 2021	17 Nov 2022	30 Dec 2021	01 Jun 2021
St Pierre, Belgium	25 Nov 2021	V3.1	07 Dec 2021	17 Nov 2022	01 Jun 2022	01 Jun 2021
GH Charleroi, Belgium	13 Jul 2022	V3.3	09 Aug 2022	17 Nov 2022	N/A	01 Jun 2022
Universitätsklinikum Frankfurt	06 Dec 2022	V4.0	09 Jan 2023	N/A	15 May 2023	N/A
Universitätsklinikum Ulm	23 Nov 2022	V4.0	27 Feb 2023	N/A	25 Apr 2023	N/A

Abbreviations: CIRI-IT, Centro Interuniversitario per la Ricerca sull'Influenza e le altre Infezioni; EC, ethics committee; VAHNSI, Valencia Hospital Network for the Study of Influenza and Other Respiratory Viruses (part of Fundación Fomento de la Investigación Sanitaria y Biomédica de la Comunidad Valenciana (FISABIO)); 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 coronavirus disease 2019 (COVID-19) vaccines against severe COVID-19 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 Requestors (vaccine companies) 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.

This Master Protocol has been developed by the COVIDRIVE public-private partnership (www.covidrive.eu). Current COVIDRIVE members are FISABIO (Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana, Spain), P95 (Belgium), THL (Finnish Institute for Health and Welfare, Finland), AstraZeneca (UK), CureVac (Germany), GSK (GlaxoSmithKline, 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[1], ACCESS[2]). 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 were addressed in version 3.0. Subsequent versions of this protocol were made to adapt to changes in COVID-19 epidemiology, pandemic management, and COVID-19 vaccines.

[1] ECDC/WHO-EU : European Centre for Disease Prevention and Control/World Health Organization Europe
[2] ACCESS: American COVID-19 Collaborative Enabling Seamless Science

« 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. »

« 'Brand-specific' and 'product-specific' are terms that can be used interchangeably throughout the master protocol. The appropriate term will be selected by the Study Team.»

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	*Primary objectives:* 1. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who have received the [COVID-19 vaccine dose of interest] ***« specify exposure definitions of interest e.g., Vaccinated with at least one dose, completed primary series vaccination etc. »***, compared to [selected comparator group] ***« specify comparator group».*** *Secondary objectives:* 2. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who have received the [COVID-19 vaccine dose of interest] ***« specify exposure definitions of interest e.g., Vaccinated with at least one dose, completed primary series vaccination etc. »***, compared to [selected comparator group] ***« specify comparator group[(1)]»***

	▪ 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. ▪ by number or type(s)[1] of the COVID-19 vaccine doses given prior to the last dose. *Exploratory objectives:* 3. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who have received the [COVID-19 vaccine dose of interest] ***« specify exposure definitions of interest e.g., Vaccinated with at least one dose, completed primary series vaccination etc. »***, compared to [selected comparator group] ***« specify comparator group[1]»*** ▪ by severity level[2]. ▪ by calendar time[3] ▪ by history and calendar time[3] of prior SARS-CoV-2 infection 4. To estimate the brand-specific effect of COVID-19 vaccination in SARI patients who have received the [COVID-19 vaccine dose of interest] ***« specify exposure definitions of interest e.g., Vaccinated with at least one dose, completed primary series vaccination etc. »*** on length of hospital stay (in days) due to laboratory-confirmed SARS-CoV-2 admission, compared to [selected comparator group] « specify comparator group» *[1] Only estimated if the type includes at least two brands or only the brand of interest.* *[2] Severity levels are defined by hospital outcome (ICU admission; in-hospital death) and/or respiratory support.* *[3] Calendar time periods as a proxy for periods of specific variant dominance .*
Country(ies) of study	[name 1, name 2, …]
Protocol main author(s)	[name 1, name 2, …]

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.

2 TABLE OF CONTENTS

3 LIST OF TABLES

4 GLOSSARY

Term	Description
Co-coordinators	FISABIO and P95, both COVIDRIVE Partners, are appointed as Co-coordinators to jointly coordinate and manage the project.
Core Platform Partners	means the group of Partners that are not Vaccine Company Partners.
COVIDRIVE	means the public-private partnership for the estimation of brand-specific COVID-19 vaccine effectiveness in Europe organised under the Consortium Agreement.
Independent Scientific Committee (ISC)	consists of a limited number of external experts with relevant experience/expertise in the field of COVID-19 vaccine effectiveness. Scientific experts representing each of the Co-coordinators act as the secretariat of the ISC.
Partner or Participant	means a legal entity signatory of the Consortium Agreement. Partners are either Core Platform Partners or Vaccine Company Partners.
Quality Assurance and Audit Committee (QAAC)	means the committee responsible for the quality management and auditing of the Study or Studies, composed of one quality assurance expert from each Vaccine Company Partners and one quality assurance expert from the Co-coordinators. The Co-coordinators act as the secretariat of the QAAC.
Study Contributor	also referred to as “Study Site” or “Site”, is an institution that collects/owns data of interest for Studies, and that signs a Study Contributor Agreement with P95 after being selected via a study-specific selection process. The Study Contributor is part of the Study Team for the specific Study.
Study Requestor	means the Partner that requests to perform a specific Study.
Study Team (ST)	means the team that carries out the conduct of the Study and includes experts from the Co-coordinators, Study Contributors and Study Requestors. • The Restricted Study Team (Restricted ST) is made up of experts from the Co-coordinators and Study Contributors. • The Full Study Team (Full ST) is the Restricted ST plus the experts from the Study Requestors.
Vaccine Company Partner	means a Partner that is a pharmaceutical company.

5 ABBREVIATIONS

ACCESS	American COVID-19 Collaborative Enabling Seamless Science
BiPAP	Bi-level Intermittent Positive Airway Pressure
BMI	Body mass index
CCA	Complete case analysis
CHU St Pierre	Centre Hospitalier Universitaire St Pierre
CI	Confidence interval
CIOMS	Council for International Organisations of Medical Sciences
CIRI-IT	Centro Interuniversitario per la Ricerca sull'Influenza e le altre Infezioni
COVID-19	Coronavirus disease 2019
CPAP	Continuous Positive Airway Pressure
CVE	COVID-19 vaccine effectiveness
DMP	Data management plan
ECDC	European Centre for Disease Prevention and Control
ECMO	Extracorporeal membrane oxygenation
ED	Emergency department
EDC	Electronic data capture
EMA	European Medicines Agency
EU	European Union
EU PAS	European Union electronic Register of Post-Authorisation Studies
FISABIO	Fundación para Fomento de Investigación Sanitaria y Biomédica la Comunidad
GAM	Generalised additive model
GDPR	General Data Protection Regulation
GEE	Generalised estimating equations
GEP	Good Epidemiological Practice
GH Charleroi	Grand Hôpital de Charleroi
GPP	Good Publication Practice
GSK	GlaxoSmithKline
GTPUH	Germans Trias i Pujol University Hospital
HCW	Health care worker
HIV	Human immunodeficiency virus
HUVH	Hospital Universitari Vall d'Hebron
ICF	Informed consent form
ICH-E6	International Council for Harmonisation E6 on Good Clinical Practice Revision
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive care unit
ID	Identification
IEC	Independent ethics committee
IMI	Innovative Medicines Initiative
IMI-DRIVE	Innovative Medicines Initiative – Development of Robust and Innovative
IRB	Independent review board
ISC	Independent Scientific Committee
LAR	Legally acceptable representative
MAH	Marketing authorisation holder
mRNA	Messenger ribonucleic acid
NIP	National immunisation programmes
NPI	Non-pharmaceutical interventions
OR	Odds ratio
QAAC	Quality Assurance and Audit Committee

RE-MA	Random-effects meta-analysis
REML	Restricted maximum likelihood estimation
RMP	Risk management plan
RNA	Ribonucleic acid
RT-PCR	Reverse transcription polymerase chain reaction
SAP	Statistical analysis plan
SARI	Severe acute respiratory infection
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
ST	Study team
THL	Finnish Institute for Health and Welfare
TMA	Transcription mediated amplification
TNCC	Test-negative case-control design
UK	United Kingdom
US	United States
UZA	Universitair Ziekenhuis Antwerpen
VAED	Vaccine-associated enhanced disease
VAHNSI	Valencia Hospital Network for the Study of Influenza and Other Respiratory
VE	Vaccine effectiveness
WHO	World Health Organisation
WHO-EU	The WHO Regional Office for Europe

6 RESPONSIBLE PARTIES

« Complete for study-specific protocols. »

6.1 Principal Investigator

Name:
Organisation:
Address:
E-mail:

6.2 Study Requestor(s)

Name:
Organisation:
Address:
E-mail:

6.3 Study Sponsor

Name:
Organisation:
Address
E-mail:

6.4 Study Team

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

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

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

6.5 Study Contributors (sites)

Organisation:
Address:
Name investigator:
E-mail:

Organisation:
Address:
Name investigator:
E-mail:

6.6 External partner(s)/committee(s)

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

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

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

7 ABSTRACT

Background

- Since its emergence in 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a great challenge to public health with the coronavirus disease 2019 (COVID-19) waves having devastating societal impacts.
- Multiple COVID-19 vaccines and variant-adapted vaccines have received European Union (EU) marketing authorisation and are used for primary and/or booster vaccination.
- ***«For brand-specific protocol»*** [Cite vaccine product of concern, its vaccine platform, and EU market authorisation details (dates; vaccine schedule i.e., primary versus booster; target population)]. [Vaccine company] will use the COVIDRIVE partnership to conduct its future vaccine effectiveness (VE) studies as part of its European regulatory obligations.
- COVIDRIVE is a public-private partnership built upon the Innovative Medicines Initiative – Development of Robust and Innovative Vaccine effectiveness (IMI-DRIVE) project, adapting its tools and structure to the specificities of COVID-19 vaccine effectiveness (CVE). COVIDRIVE was launched in November 2020 to address the joint need to monitor COVID-19 vaccination programs for public health institutes and assess brand-specific CVE for vaccine companies as part of their regulatory obligations. COVIDRIVE started its patient recruitment in September 2021.
- This protocol details a non-interventional study to estimate the effectiveness of [COVID-19 vaccine name] against COVID-19 related hospitalisations through the COVIDRIVE partnership.

Research question

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

Objectives

« Objectives can differ between the Study-Requestor-specific protocols. Objectives are to be selected, prioritised, and modified by the Study Team. An appropriate comparator group will be defined for each objective, based on the use of the vaccine of interest (e.g., unvaccinated subjects, vaccinated subjects eligible to receive the vaccine of interest following the national recommendations, vaccinated subjects considered to have waned immunity, and vaccinated subjects who have not received any COVID-19 vaccine within the season of interest). Objectives can be repeated for different exposure definitions of interest. Secondary and exploratory objectives are stratifications of the primary objectives.»

Primary:

1. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who have received the [COVID-19 vaccine dose of interest] ***« specify exposure definitions of interest e.g., Vaccinated with at least one dose, completed primary series vaccination etc. »***, compared to [selected comparator group] ***« specify comparator group».***

Secondary:

2. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who have received the [COVID-19 vaccine dose of interest] ***« specify exposure definitions of interest e.g., Vaccinated with at least one dose, completed primary series vaccination etc. »***, compared to [selected comparator group] ***« specify comparator group»***
    - 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
    - by number or type(s)[(1)] of the COVID-19 vaccine doses given prior to the last dose

Exploratory:

3. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who have received the [COVID-19 vaccine dose of interest] ***« specify exposure definitions of interest e.g., Vaccinated with at least one dose, completed primary series vaccination etc. »***, compared to [selected comparator group] ***« specify comparator group[(1)]»***
    - by severity level[(2)]
    - by calendar time[(3)]
    - by history and calendar time[(3)] of prior SARS-CoV-2 infection

4. To estimate the brand-specific effect of COVID-19 vaccination in SARI patients who have received the [COVID-19 vaccine dose of interest] ***« specify exposure definitions of interest e.g., Vaccinated with at least one dose, completed primary series vaccination etc. »*** on length of hospital stay (in days) due to laboratory-confirmed SARS-CoV-2 admission, compared to [selected comparator group] « specify comparator group»

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

[(2)] Severity levels are defined by hospital outcome (ICU admission; in-hospital death) and/or respiratory support.

[(3)] Calendar time periods as a proxy for periods of specific variant dominance.

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(s))

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

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 (≥38°C)
- shortness of breath
- sudden onset of anosmia, ageusia or dysgeusia

with symptom onset within the **last 14 days** prior to hospital admission. This SARI definition is modified from the latest ECDC case definition (specifying "suspicion of respiratory infection [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 [72 hours][(2)] of hospital admission.

[(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 selected, 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 [COVID-19 vaccine 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)].

Recently vaccinated: vaccinated with any COVID-19 vaccine <= [14] days prior to SARI symptom onset[(3)].

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

Vaccinated with any COVID-19 vaccine, waned immunity: received last COVID-19 vaccine dose **>** [6] **months prior to symptom onset**

Vaccinated with seasonal COVID-19 vaccine: **received the seasonal COVID-19 vaccine brand** of interest within the season of interest [(4)] and ≥ [14] days before symptom onset.

Unvaccinated with seasonal COVID-19 vaccine: did not receive **any COVID-19 vaccine** within the season of interest[(4)].

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) 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.

(3) 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.

(4) COVID-19 season will be defined by the Study team in alignment with ECDC and/or EMA definitions once these are made available.

Covariates

Covariates: Variables that are potential confounders and/or effect modifiers and will be *collected at all study sites* include age, gender, history of prior COVID-19 vaccinations, history of medical diagnosis for selected morbidities of interest (asthma, lung disease, cardiovascular disease, hypertension, chronic liver disease, chronic kidney disease, type I diabetes, type 2 diabetes, obesity, cancer, immunodeficiency, neurological disorders), vaccination against pathogens causing COVID-19 like symptoms (influenza, pneumococcus), calendar time, previous SARS-CoV-2 infection and smoking history.

Variables that will be *potentially additionally collected at certain study sites* include any use of anti-SARS-CoV-2 antibodies and other drugs (antibiotics, antivirals, corticosteroids, immunomodulators, other monoclonal antibodies) received either as prophylaxis or treatment for the current SARI episode, body mass index (BMI), employment as health care worker (HCW), and long-term care facility residence.

Sample size

[Sample size considerations for the primary objective(s) to be included here, including the assumptions made (vaccination coverage, absolute and/or relative vaccine effectiveness, number of study contributors), the sample-size calculation methods (simulation- or analytical-based) and the properties

of estimation procedure (e.g., 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)].

For studies with a data collection period > 1 year, an interim analysis is planned when data on a sufficient number of COVID-19 cases vaccinated with the [COVID-19 vaccine] as **«specify exposure definition(s) for primary objectives»** [exposure definition (s) primary series/additional last dose] has been collected to provide an expected [properties of estimation procedure] with the same assumptions as described above.

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).

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 confirmed COVID-19 cases when sample quality allows.

After study enrolment, 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 and effect modifiers.

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

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.

All CVE estimates will be adjusted for symptom-onset date and the confounder-adjusted CVE estimates will also be adjusted for age, gender, and number of chronic conditions. Adjustments will be achieved through inclusion of the relevant terms in the logistic regression models. Calendar time and age will be adjusted using penalized splines.

The symptom onset- and confounder-adjusted brand-specific CVE against laboratory-confirmed SARS-CoV-2 will be estimated as: VE = (1 – OR) x 100%, where *OR* denotes the symptom onset- 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.

Heterogeneity by study sites will be accounted for through using random-effects meta-analysis (RE-MA), or alternatively, when site-specific cell counts are too low (resulting in non-robust RE-MA

standard error estimates), generalized estimating equations (GEE) or generalized additive models (GAM).

For RE-MA, the CVE estimates pooled across study sites will be obtained through pooling the log-transformed site-specific estimates. 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. 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. For the GAM models, indicator variables for the different study sites will be additionally included in the logistic regression models.

Sensitivity analyses will be conducted as appropriate. A complete and detailed 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 or products of interest. **« In case the Study Requestor is an MAH»** [Interim reports and final report will be submitted to EMA and other competent regulatory bodies (e.g., Medicines and Healthcare products Regulatory Agency (MHRA), U.S. Food and Drug Administration (FDA)) 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. 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 independent ethics committee(s) (IECs) following local regulations. Informed consent will be obtained from participants/guardians as specified by the national/regional IEC.

Study limitations

Study limitations include :

- Time-varying confounders and effect modifiers: these include COVID-19 epidemic waves, SARS-CoV-2 genetic variants, levels of vaccine-induced and natural immunity in the population, non-pharmaceutical interventions, priority groups and timing of COVID-19 vaccination

programs. Their complex interplay makes it challenging to disentangle waning vaccine immunity, differences in CVE against different genetic SARS-CoV-2 variants and infection acquired immunity.

- Misclassification of disease status: SARS-CoV-2 RT-PCR assays have a high specificity and sensitivity, and the risk of disease misclassification bias is minimised. However, RT-PCR sensitivity is influenced by several factors, including operator sampling technique, type of specimen, and timing of sampling. To explore any potential bias due to disease misclassification, sensitivity analyses regarding time between symptom onset and swabbing are performed.
- Prior infection: Infection-acquired immunity is an effect modifier of CVE. Although information on past SARS-CoV-19 infection is collected in this study, prior infection may be undocumented (e.g., asymptomatic disease).
- Unaccounted confounders: these include ethnicity, socio-economic status and frailty. In general, results from this study will be highly specific to its population, and this will need to be carefully considered when generalising or comparing results.

Dissemination

This generic Master 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 V5.0 has been developed by the COVIDRIVE partnership, which has received funds from AstraZeneca, Bavarian Nordic, CureVac, GlaxoSmithKline (GSK), Janssen, Moderna, Novavax, Sanofi, and Valneva, leveraging public health capacity from Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana (FISABIO) and the Finnish institute for Health and Welfare (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), AstraZeneca (UK), Bavarian Nordic (Denmark), GSK (Belgium), Janssen (Belgium), Novavax (US), Valneva (Austria) and Pfizer (US) . Past members are THL (Finland), CureVac (Germany), Moderna (US), Sanofi (France). 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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8 AMENDMENTS AND UPDATES

« To complete as appropriate »

Version	Version date	Reason for new version
[Version Number]	[Date]	[Text]

9 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]

10 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

11 SPONSOR SIGNATURE PAGE

Study title: [title]

Protocol number: [number]

Sponsor:

_____
Print name

_____ _____
Signature Date

_____
Print name of institution or practice and location

12 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 rapidly spread to different parts of China and an increasing number of countries worldwide. On 12 March 2020 the World Health Organisation (WHO) declared the SARS-CoV-2 outbreak a global pandemic. By [1 June 2023], more than 275 million COVID-19 cases and [2 million] COVID-19 deaths had been recorded in the European region [1]. On 5 May 2023, more than 3 years into the pandemic, the WHO declared the end of global emergency status of COVID-19 [2], but disease burden persists as the pandemic evolves to endemicity.

The development of safe and effective vaccines is key in containing the SARS-CoV-2 pandemic. As of [1 June 2023], the following COVID-19 vaccines are authorised for use in the EU: Comirnaty (BioNTech and Pfizer), COVID-19 Vaccine Valneva, Nuvaxovid (Novavax), Spikevax (Moderna), Vaxzevria (AstraZeneca), Jcovden (Janssen), VidPrevtyn Beta (Sanofi Pasteur) and Bimervax (HIPRA) [3]. The COVID-19 adapted vaccines authorised for use are Comirnaty Original/Omicron BA.1 (BioNTech and Pfizer), Comirnaty Original/Omicron BA.4-5 (BioNTech and Pfizer), Spikevax bivalent Original/Omicron BA.1 (Moderna) and Spikevax bivalent Original/Omicron BA.4-5 (Moderna) *« update list accordingly »*.

« For brand-specific protocol » [Short paragraph with summary of characteristics of vaccine product of concern, clinical trial data (safety and efficacy) and European Medicines Agency (EMA) market authorisation details (dates, vaccine schedule i.e., primary verses booster, target population)]. Despite the thorough investigation of the efficacy of [COVID-19 vaccine name] during clinical trials, it is crucial to continue evaluating how well the vaccine prevents disease under real-world conditions once used as part of the national immunisation programmes (NIPs). Questions that are typically unanswered by clinical trials and that remain to be evaluated by real-world effectiveness studies include duration of vaccine protection and waning of immunity, vaccine effectiveness (VE) against disease by specific and newly emerging SARS-CoV-2 strains, VE against severe COVID-19, and VE in special risk groups such as immunocompromised or subjects with chronic conditions.

In its guidance 'Consideration on core requirements for Risk Management Plans (RMPs) of COVID-19 vaccines', the EMA recommends Marketing Authorisation Holders (MAH)s to include VE studies and make use of existing EU efforts that could provide brand-specific data reliably and timely [4]. COVIDRIVE, a public-private partnership launched in November 2020, fits this recommendation. COVIDRIVE is leveraging DRIVE, a VE platform and Innovative Medicines Initiative (IMI) project that has provided 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 (Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana, Spain), P95 (Belgium), THL (Finnish institute for Health and Welfare, Finland), AstraZeneca (UK), Bavarian Nordic (Denmark), CureVac (Germany), GSK (GlaxoSmithKline, Belgium), Janssen (Belgium), Moderna (US), Novavax (US), Sanofi (France) and Valneva (Austria) *«update list accordingly»*. [Vaccine

company] will use this partnership to conduct its future VE studies as part of its European regulatory obligations.

This protocol details a non-interventional study to estimate the effectiveness of [COVID-19 vaccine name] against COVID-19 related hospitalisations through the COVIDRIVE partnership. Studying the effectiveness against COVID-19 hospitalisations is prioritised as 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. 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.

COVIDRIVE developed the initial version of the study outline of this protocol in parallel to the development of similar protocols by other initiatives [5-7]. 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.

13 RESEARCH QUESTIONS AND OBJECTIVES

« Objectives can differ between the Study Requestor-specific protocols. Objectives are to be selected, prioritised, and modified by the Study Team. An appropriate comparator group will be defined for each objective, based on the use of the vaccine of interest (e.g., unvaccinated subjects, vaccinated subjects eligible to receive the vaccine of interest following the national recommendations, vaccinated subjects considered to have waned immunity, and vaccinated subjects who have not received any COVID-19 vaccine within the season of interest). Objectives can be repeated for different exposure definitions of interest. Secondary and exploratory objectives are stratifications of the primary objectives.»

Primary:

1. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who have received the [COVID-19 vaccine dose of interest] ***« specify exposure definitions of interest e.g., Vaccinated with at least one dose, completed primary series vaccination etc. »***, compared to [selected comparator group] ***« specify comparator group ».***

Secondary:

2. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who have received the [COVID-19 vaccine dose of interest] ***« specify exposure definitions of interest e.g., Vaccinated with at least one dose, completed primary series vaccination etc. »***, compared to [selected comparator group] ***« specify comparator group »***
    - 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
- by number or type(s)[1] of the COVID-19 vaccine doses given prior to the last dose

Exploratory:

3. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who have received the [COVID-19 vaccine dose of interest] ***« specify exposure definitions of interest e.g., Vaccinated with at least one dose, completed primary series vaccination etc. »***, compared to [selected comparator group] ***« specify comparator group[1]»***
    - by severity level[2]
    - by calendar time[3]
    - by history and calendar time[3] of prior SARS-CoV-2 infection

4. To estimate the brand-specific effect of COVID-19 vaccination in SARI patients who have received the [COVID-19 vaccine dose of interest] ***« specify exposure definitions of interest e.g., Vaccinated with at least one dose, completed primary series vaccination etc. »*** on length of hospital stay (in days) due to laboratory-confirmed SARS-CoV-2 admission, compared to [selected comparator group] «specify comparator group»

[1] Only estimated if the type includes at least two brands or only the brand of interest.

[2] Severity levels are defined by hospital outcome (ICU admission; in-hospital death) and/or respiratory support.

[3] Calendar time periods as a proxy for periods of specific variant dominance.

14 RESEARCH METHODS

14.1 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.

14.2 Study Contributors (study sites)

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

The participating study sites are either individual hospitals or hospital networks. The data collection will be a prospective data collection from primary and secondary data sources, and in some sites, data will additionally be 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	Study Contributor (study site, location)	Hospital population	No. of hospital beds/ICU beds
« complete »				

Abbreviations: ICU, intensive care unit; [abbreviations for the hospitals]

14.3 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 14.3.1) but who do NOT meet the exclusion criteria (see Section 15.3.2)

AND

- are hospitalised and meet the SARI case definition (see Section 14.6.2)

14.3.1 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)

14.3.2 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)

14.4 Study period

« Modify as appropriate »

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

14.5 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., transcription-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 or by level of Respiratory support severity levels.
- Length of hospital stay.

Exploratory outcomes are further explained in Section 14.9.

14.6 Definitions

14.6.1 Hospitalised patient

Person 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.

14.6.2 SARI patient (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 (≥38 C^{o})
- shortness of breath
- sudden onset of anosmia, ageusia or dysgeusia

with symptom onset within the **last 14 days** prior to hospital admission. This SARI definition is modified from the latest ECDC case definition (specifying "suspicion of respiratory infection. [6].

14.6.3 Test-positive case

A study participant who:

- meets the **SARI** case definition (see Section 14.6.2)

  AND

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

(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.

14.6.4 Test-negative control

A study participant that:

- meets the **SARI** case definition (see Section 14.6.2)

  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 [72 hours][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.

14.7 SARI patient identification

Hospitalised SARI patients will be identified based on the defined SARI definition (section 14.6.2) either prospectively (e.g., during consultation in the emergency department (ED) or at admission to infectious disease or internal medicine ward) or retrospectively by hospital database search or from respiratory samples sent to the virology laboratory.

14.8 Exposure (COVID-19 vaccination)

14.8.1 Exposure definitions

« Exposure outcomes to be selected and 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)]
4. Recently vaccinated: vaccinated with any COVID-19 vaccine, with the brand of interest[(1)] <= 14 days prior to SARI symptom onset[(3)]
5. Unvaccinated: did **not receive any COVID-19 vaccine dose**[(4)]
6. Vaccinated with any COVID-19 vaccine with the brand of interest[(1)], waned immunity: received last COVID-19 vaccine dose **>** [6] **months prior to symptom onset**[(4)]
7. Vaccinated with seasonal COVID-19 vaccine with the brand of interest[(1)]: **received the seasonal COVID-19 vaccine brand** of interest within the season of interest[(5)] and ≥ [14] days before symptom onset
8. Unvaccinated with seasonal COVID-19 vaccine: did not receive **any COVID-19 vaccine** within the season of interest[(4)(5)]
9. 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)] 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.

[(3)] 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.

[(4)] Participants in this comparator group should be eligible to receive the COVID-19 vaccine dose of interest. Eligibility criteria will be defined by the Study Team and based on National recommendations.

[5] COVID-19 season will be defined by the Study team in alignment with ECDC and/or EMA definitions once these are made available.

14.8.2 Exposure ascertainment

Information on all prior COVID-19 vaccine doses will be collected. Vaccination status, vaccination date, dose and vaccine brand information are required. 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.

14.9 OutcomesSection

14.9.1 Laboratory-confirmed SARS-CoV-2

To the extent possible, clinical specimens will be collected from the patients eligible for the study as part of routine clinical sampling for diagnostic work-up. However, depending on local practice, additional sampling for the purpose of the study may be required. 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 used for testing.

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 a 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.

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

SARI severity levels:

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

« Additional severity levels may be defined by Study team, based on data availability, and are to be clearly stated here e.g., ICU admission without ICU death, ICU admission with ICU death »

Respiratory support severity levels:

The following categories, provided from low to high severity, will complement the SARI severity levels. The highest level of respiratory support required during the hospital stay will define the respiratory support severity level.

1. None;
2. Oxygen therapy (e.g., nasal cannula, mask);
3. Non-invasive ventilation (ventilatory support without tracheal intubation; e.g., high-flow nasal oxygen, Continuous Positive Airway Pressure (CPAP) or Bi-level Intermittent Positive Airway Pressure (BiPAP));
4. Invasive mechanical ventilation (ventilatory support with tracheal intubation);
5. Extracorporeal membrane oxygenation (ECMO).

14.9.3 Hospitalisation due to laboratory-confirmed SARS-CoV-2: length of hospital stay

Length of hospitalisation stay is defined as the number of overnights (date of discharge > date of admission) 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.

14.10 Covariates

The complete dataset can be found in COVIDRIVE Common dataset case report form and is summarised in
Table 2. Some covariates are collected by all participating study sites. All covariates are both being collected for prospective and retrospective subjects, if available.

Table 2. Study covariates and health care use.

Covariate	Description	Collected by all sites
Age at hospital admission	Calculated based on date of birth and date of admission	x
Gender assigned at birth	Male, female	x

Chronic conditions*		
Asthma	Binary	x
Lung disease	Binary	x
Cardiovascular disease	Binary	x
Hypertension	Binary	x
Chronic kidney disease	Binary	x
Diabetes type 1	Binary	x
Diabetes type 2	Binary	x
Obesity	Binary	x
Cancer	Binary. If yes, specification of subcategories: solid tumour, haematological cancer, no information. If solid tumour or hematological cancer is yes, further specification of cancer type to be selected from list.	x
Immunodeficiency (or organ transplant)	Binary. If yes, specification of subcategories: Solid organ transplant, Hematopoietic stem cell transplantation, Primary immunodeficiency, Advanced or untreated HIV infection, Iatrogenic immunodeficiency, other	x
Neurological disorders	Binary	x
Pregnancy	Binary	x
Trimester	First, second, third	x
Body mass index (BMI)	Continuous	
Smoking history	Never smoker, former smoker (smokefree for at least 28 days), current smoker	x
Vaccination history COVID-19	Being vaccinated with at least one COVID-19 vaccine during the COVID-19 vaccination campaign/season prior to campaign/season as defined in the vaccine exposure definition of interest	x
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	
COVID-19 prior episode	Binary	x
Month and year of prior COVID-19 episode	Month and year	x
Respiratory support	None, high-flow oxygen therapy, invasive ventilation, extra corporeal membrane oxygenation (ECMO), other	x
Length of hospital stay	Days, continuous	x
Treatments received during hospital stay for the management of SARI episode	Antibiotics, Antiviral drug(s), Corticosteroid(s), Immune-modulator(s), Anti-SARS-CoV-2 antibodies , Other monoclonal antibodies, None of the above. Brand name if anti-SARS-CoV-2 antibodies received during hospital stay	
Treatments received prior to hospital admission for the management of current SARI episode	Antibiotics, Antiviral drug(s), Corticosteroid(s), Immune-modulator(s), Anti-SARS-CoV-2 antibodies , Other monoclonal antibodies, None of the above. Brand name if anti-SARS-CoV-2 antibodies received during hospital stay	
Medicinal product for the prevention of SARS-CoV-2 (pre- or post-exposure prophylaxis) in the 6 months prior to current hospitalisation	Binary. If yes, type (Antiviral drug, Anti-SARS-CoV-2 antibodies, Other), brand and date (month/year) if SARS-CoV-2 monoclonal antibody	

**Definitions for each chronic conditions are specified in the COVIDRIVE Common dataset case report form*

14.11 Sample size considerations

The technical considerations for the calculation of the targeted samples sizes are detailed in Annex 1 **« The sample size requirements strongly depend on the objectives (primary vaccination, booster vaccination, seasonal vaccination), on case-control ratio, overall vaccination coverage and share of the different vaccine brands. As such, the sample size requirements and assumptions will be different for each vaccine brands and defined by the Study Team. »**

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 with the progress reports.

14.11.1 Targeted sample size, final analysis

«*Sample size considerations for the primary objective(s) are to be included here, including the assumptions made (vaccination coverage, absolute and/or relative vaccine effectiveness, number of study contributors), the sample-size calculation methods (simulation- or analytical-based), the properties of estimation procedure (e.g., expected lower half width of the 95% CI of the CVE ≤15% or expected power of at least 80% to detect a CVE significantly different from 0) »

«Include table(s) with interim targeted sample size estimates.»

14.11.2 Targeted sample size, interim analysis

For studies with a data collection period > 1 year, an interim analysis is planned when data on a sufficient number of COVID-19 cases vaccinated with the [COVID-19 vaccine] as **« specify exposure definition(s) for primary objectives »** [exposure definition(s)] has been collected to provide an expected [properties of estimation procedure] with the same assumptions as described above.

« Include table(s) with interim targeted sample size estimates »

14.11.3 Time to number of cases

For actively recruiting COVIDRIVE Study Contributors, time to number of cases will be estimated using prior recruitment rates. For new Study Contributors, time to number of cases will be predicted based on their number of hospital beds, population coverage and/or estimated SARI recruitment as communicated during their feasibility assessments.

14.12 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.

14.12.1 Data management at Study Contributor level

Each study site is responsible for the data collection and data management of their participant-level study data. Depending on the study site, the data collection and source documentation will be different. Source documentation for each variable is collected during a site initiation visit.

14.12.2 Data flow

1. The Study Contributor collects the data and enters/uploads it in the Castor® EDC.
2. The Study Sponsor validates the data, raises applicable queries and the Study Contributor responds to data queries by updating or confirming the data.

3. The Study Sponsor imports the data from all participating Study Contributors in a secure environment using the EDC system's export functionality.
4. The Study Sponsor transforms all data to generate the output as pre-specified in the Statistical Analysis Plan (SAP) within the secure environment.

P95 reviews the imported variables on a bi-weekly basis. These data review checks are detailed in the Data Validation Plan.

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. All statistical analyses will be conducted in the COVIDRIVE Research Server.

14.13 Data analysis

A SAP will be developed prior to the conduct of the analysis. The SAP specifies all statistical analyses to be conducted, and will include tables shells and mock figures.

14.13.1 Context information

Context information will be provided in study reports by describing the circulating SARS-CoV-2 variants during the study period in the countries (or regions) where the Study Contributors are located. National (or regional) COVID-19 immunisation recommendations over time will be described, along. The external data sources used to describe the SARS-CoV-2 viral distribution, vaccination coverage, and immunisation recommendations will be specified in the SAP.

14.13.2 Attrition diagram

The study report will include an attrition diagram. The attrition diagram describes the number of records excluded from the statistical analyses, by reason of exclusion.

14.13.3 Descriptive analysis of demographics and baseline characteristics

For every 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 SARS-CoV-2 genetic variants) over time
- distribution of covariates among cases and controls

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 SAP.

14.13.4 Statistical analyses

All CVE estimates will be adjusted for symptom onset date and the confounder-adjusted CVE estimates will also be adjusted for age, gender, and number of chronic conditions. Adjustments will be achieved through inclusion of the relevant terms in the logistic regression models. Calendar time and age will be adjusted using penalised splines. The CVE against laboratory-confirmed SARS-CoV-2 will be estimated as:

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

where *OR* denotes the symptom onset- 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.

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.

Heterogeneity between Study Contributors may exist due to differences at the recruitment, local differences in the intensity of the epidemic and healthcare practices. Heterogeneity by Study Contributors will be accounted for by using random-effects meta-analysis models (RE-MA), or alternatively, when site-specific cell counts are too low (resulting in non-robust RE-MA standard error estimates), generalised estimating equations (GEE) or generalized additive models (GAM).

The RE-MA has the advantage that it can easily integrate estimates from Study Contributors that cannot share patient-level data. Additionally, RE-MA provides direct estimates of the Study Contributor-specific CVE. Furthermore, the RE-MA is intuitively understood by and communicated to researchers in the field [8]. The most important limitations of the RE-MA approach include loss of power, and potential convergence issues when the outcome of interest is rare or the sample size of some Study Contributors is relatively small [9]. GEE or GAM are preferred when most, if not all, the Study Contributors have shared individual patient data. In most circumstances, GEE will be more efficient than GAM at the cost of not allowing to derive Study Contributor-specific CVE estimates.

14.13.4.1 Random effects meta-analysis (RE-MA)

CVE estimates pooled across Study Contributors will be obtained through RE-MA on the log-transformed Study Contributor-specific estimates [10]. Restricted maximum likelihood will be used to obtain the pooled meta-analyses estimates and 95% CIs [11]. The modified Hartung-Knapp correction will be used to estimate the variance of the mean effect [12]. 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 Contributors will be obtained by calculating I^2 according to Higgins et al. [13]. 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 [14].

14.13.4.2 Generalized estimating equations (GEE)

For the GEE models, the approach for fitting logistic regression developed by Liang and Zeger [15] will be used, assuming an exchangeable correlation matrix to account for potential within-cluster homogeneity in outcomes. The robust sandwich estimator [16] will be used to estimate the standard error of the marginal effect estimates. Clusters will be defined at Study Contributor level.

14.13.4.3 Generalised additive model (GAM)

For GAM, the multivariable logistic regression models will additionally include a fixed effect for each of the Study Contributors to account for heterogeneity between Study Contributors. The coefficients of the logistic regression models will be estimated using restricted maximum likelihood estimation (REML).

14.13.4.4 Absolute and relative CVE

When the comparator group consists of unvaccinated subjects, the term absolute CVE will be used. When the comparator group consists of subjects considered to be partially protected by vaccination (e.g., vaccinated subjects considered to have waned immunity), the term relative CVE will be used.

Depending on the usage of the vaccine brand of interest, the most appropriate comparator group(s) will be used. Potential comparator groups are:

- unvaccinated subjects,
- vaccinated subjects eligible to receive the vaccine of interest following the national recommendations,
- vaccinated subjects considered to have waned immunity, and
- vaccinated subjects who have not received any COVID-19 vaccine within the season of interest.

Exposure definitions for these comparator groups are defined in section 14.8.1. A rationale for the selection of the appropriate comparator group(s) will be given and each time, the interpretation of the CVE results will be done in the light of the comparator group used to calculate the CVE estimates.

14.13.4.5 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 >10% 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.

14.13.4.6 Sensitivity analyses

Multiple sensitivity analyses will be performed. In case the RE-MA approach will be adopted, GEE or GAM models might be performed as sensitivity analysis. Additional sensitivity analyses can be conducted, such as exploring the effect of time between symptom onset date and swab date 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. All sensitivity analyses will be pre-specified in the Study Requestor-specific SAP.

15 QUALITY MANAGEMENT

15.1 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 CVE 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, and
- 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, long-term effectiveness, SARS-CoV-2 infection, or transmission).

15.2 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 Contributor and oversees any audit at the Study Contributor level if needed; the audit is subcontracted to an external qualified consultants' auditor.

Because Study Contributors 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's mission is to provide, at the partnership level, guidance on implementation, conduct, monitoring and quality assurance of the Studies, as well as to ensure that data quality is in line with the Study request and to, when necessary and to the extent possible, identify areas for improvement 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.

15.3 Monitoring

Monitoring activities include:

- Before study start, the Study Contributor will be asked to complete a quality management questionnaire to inform the Study Team on all aspects of the study conduct.
- Before study start, a site initiation visit will be organised by the Study Team.

- During study conduct, regular Study Contributor 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) system 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 Study Contributor investigators must permit any external auditor mandated by the QAAC of the COVIDRIVE partnership or the 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.

15.4 Data quality checks at central level

Programmed checks are run on Castor®-extracted data and the identified data issues are manually queried in Castor® every two weeks. After the Study Contributor responds to the queries by updating or confirming the data entered in Castor®, P95 closes the queries. Per agreement, the identified data issues are also sent in an MS Excel document to the corresponding Study Contributors. All the queries should be closed before database lock.

16 LIMITATIONS OF THE RESEARCH METHODS

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

As a result of the huge demand for COVID-19 vaccines and initially limited vaccine supplies, most European countries prioritised the vaccination of high-risk groups, including elderly people, residents in long-term care facilities, healthcare workers, social care personnel and persons with certain chronic conditions[17]. The presence of such vaccination priority groups is an important source of potential confounding in CVE studies. Other time-varying confounders and effect modifiers include COVID-19 epidemic waves, SARS-CoV-2 genetic variants, levels of vaccine-induced and natural immunity in the population, non-pharmaceutical interventions (NPIs), and timing of COVID-19 vaccination programs, each with regional differences to take into consideration. The complex interplay between these time-varying factors makes it particularly challenging to disentangle waning vaccine immunity, differences in CVE against different genetic SARS-CoV-2 variants, and infection acquired immunity.

Infection-acquired immunity is protective against re-infection, however, subject to waning and an effect modifier of CVE. Hybrid immunity, a combination of both infection-acquired and vaccine-induced immunity, may provide the most protective profile against severe disease [18]. Although information on past SARS-CoV-2 infection is collected in this study, prior infection may be undocumented and/or misclassified, particularly with clinical-based diagnosis (false negatives due to asymptomatic disease; false positives where unspecific flu-like symptoms were caused by another pathogen) and in the absence of serological results. Prior infection may also be a source of confounding, as it may influence the decision to be vaccinated.

Although the TNCC study design reduces unmeasured confounding due to general health care-seeking behaviour [19], specific health-related practices may act as confounders. Firstly, the uptake of vaccination may be highest among individuals who adhere 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. Conversely, being vaccinated or having had a previous SARS-CoV-2 infection may lead to a feeling of security resulting in relaxing of precautionary health behaviour and increasing the risk of SARS-CoV-2 exposure. Additionally, it is expected that 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., common target groups for vaccination such as elderly and other high-risk groups and/or persons with a positive attitude towards vaccination). Simultaneous vaccination against COVID-19, influenza and/or pneumococcal infection may bias results, affecting the person´s risk of having SARI, i.e., both the probability that the person becomes a case as well as the probability that he/she becomes a control. Prior and simultaneous vaccinations for influenza and pneumococcal diseases are covariates collected in the present study.

Misclassification of disease status due to diagnostic test inaccuracy can also be a source of bias. As SARS-CoV-2 RT-PCR assays have a high specificity and sensitivity [20, 21], risk of disease misclassification bias is minimised. However, RT-PCR sensitivity is influenced by several factors,

including operator sampling technique, type of specimen [22], and timing of sampling - with sensitivity peaking during the first 4 to 5 days after symptom onset before showing a gradual decline [23-26]. If disease misclassification by a diagnostic tool is non-differential (i.e., independent of exposure status), low test accuracy is expected to bias the CVE estimates downwards, with the bias resulting from low specificity being more substantial than the bias resulting from low sensitivity [27]. If disease misclassification is differential (i.e., dependent of exposure status), the bias may occur in either direction. For SARS-CoV-2 RT-PCR, the decline in test sensitivity with increasing time since symptom-onset appears to be faster in vaccinated cases compared to in unvaccinated [25]. This could lead to a greater number of false negatives among vaccinated when sampling is delayed and would result in an overestimation of CVE. To explore any potential bias due to disease misclassification, sensitivity analyses regarding time between symptom onset and swabbing will be performed in this study. Information on sample handling by study staff is not collected in this study. However, to ensure a good testing procedure, guidance on collecting and handling specimens for the diagnosis of COVID-19 is given as part of study staff training.

Several potential confounders are unaccounted for in this study. These include ethnicity and socio-economic status. It is well established that some ethnic minority groups have a higher risk of confirmed SARS-CoV-2 infection and higher risk of developing critical COVID-19 upon a given exposure, even after accounting for socio-economic variables [28]. When these groups are also less likely to be vaccinated, the CVE estimates will be overestimated. Moreover, TNCC studies are restricted to the inclusion of persons who have access to health care services or will be hospitalised, so results may not be generalisable to those that would have a different threshold for seeking hospitalisation, such as the most disadvantaged groups with poor access to care or nursing home residents. In general, results from this study will be highly specific to its population, and this will need to be carefully considered when generalising or comparing results.

Another important potential effect modifier of CVE not measured in this study is frailty. Frailty has been shown to affect immune responses in older adults to vaccines for infections such as influenza, shingles and pneumococcus [29]. Frailty is age- and disease-associated, changes over time and is characterised by strong inter-personal variation. There is currently no consensus on how to define and how to best measure frailty. 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 collect information on variables that are known to be strongly related to frailty, including age, BMI, long-term care facility residence and chronic conditions.

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 and evolving over time. Sample size requirements will further increase as vaccine market-shares becomes further fragmented with the increasing number of available COVID-19 vaccine products. Although our study covers a wide network of hospitals across Europe, obtaining sufficient samples to obtain accurate estimates for primary and secondary objectives may be a challenge.

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

17.1 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) [30], Good Epidemiological Practice (GEP) [31], 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. Therefore, there is no direct benefit to the participants. Nevertheless, there are important potential societal benefits derived from this VE 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.

17.2 Ethics approval

The Study Contributor-specific protocols will be submitted to relevant independent ethics committee(s) (IECs) following local regulations and the declaration of Helsinki. Copies of the appropriate IEC approvals will be collected from each Study Contributor 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 IECs. In these cases, a statement that no formal approval from an IEC is required is sufficient.

17.3 Informed consent

A good readability was prioritised when writing the Master ICF. The Study Contributor-specific ICF will always be translated to local language. Written informed consent will be obtained from all participants/guardians as specified by the national/regional IEC, if applicable. The following information should be specified in the informed consent form (ICF): 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.

17.4 Independent ethics committee/Institutional review board

Consistent with local regulations and prior to enrolment of participants at a given Study Contributor, the study protocol together with its associated documents (e.g., ICF) will be submitted by the Study Contributor to the responsible institutional review board (IRB)/IEC for its review. Participant enrolment will not start before the Study Contributor has obtained written confirmation of a favourable opinion/approval from the relevant central or local IRB/IEC. The Study Contributor 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 Study Contributor 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 Study Contributor investigator will be responsible for informing the IRB/IEC of the early termination.

17.5 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).

17.6 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 Contributor and will be submitted to the relevant IRB/IEC or regulatory authorities where required by pertinent regulations.

17.7 Secondary data use

The data generated as part of this study may be used for future research related to the expansion of the knowledge, prevention and control of infectious diseases and may be provided to third parties for correlative endpoints or secondary use. For this secondary use of data the COVIDRIVE governance principles will be respected. The guiding principles for secondary data use are detailed in the COVIDRIVE Governance Charter and available on the COVIDRIVE website https://covidrive.eu/governance/.

18 STUDY MANAGEMENT AND LOGISTICAL ASPECTS

This study will be performed by the Study Contributor investigator(s), with guidance, input, review, and approval of the Study Team, including development of materials, recruitment, training, management of network sites, electronic data capture, data management and analysis. More information can be found in the Governance charter.

The Study Contributor 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.

18.1 Study investigators at hospital level

Each Study Contributor 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 [30], GEP [31], 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. For an informed consent to be valid, the most recent version approved by the IEC is to be used.

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 Study Contributor 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.

18.2 Training

Study Contributor 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.

18.3 Data capture

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

18.4 Retention

To enable evaluations and/or audits from regulatory authorities or others, the Study Contributor 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 enrolment log and the signed ICFs. In the event that archiving of the file is no longer possible at the Study Contributor, the Study Contributor/investigator will be instructed to notify the Study Team. The Study Contributor investigator must contact the Sponsor before destroying any study-related documentation. It is the responsibility of the Sponsor to inform the Study Contributor of when these documents no longer need to be retained.

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

18.5 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, without any negative impact on the quality of care or on the relationship with the treating doctor(s). 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.

18.6 Study termination

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

- the Study Contributor does not respond to study management requests
- repeated protocol deviations/poor protocol compliance

19 REPORTING AND DISSEMINATION OF RESULTS

19.1 Study protocol

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

19.2 Management and reporting of adverse events/adverse reactions

This is a non-interventional epidemiological study for assessing the effectiveness of routine COVID-19 vaccination, based on primary and secondary data collection. Treatments, vaccines and pharmaceutical prevention will be collected as part of secondary data collection (registries and/or patient files), therefore no adverse events or adverse reactions are collected. The Study Contributors 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.

19.3 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. ***«To include 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 COVIDRIVE Governance Charter.

19.4 Publication

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

20 FUNDING

This study is partially funded by [Study Requestor].

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

Study Contributor (study site, hospital)	Additional funding source

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

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22 SIGNATURE PAGE

Document title: [internal full study title]

Version label: [version number of study protocol]

[Company name] (Study Requestor):

Print name

Signature Date

Print name of company name

P95 (Sponsor COVIDRIVE):

Print name of COVIDRIVE Principal Investigator

Signature Date

Print name of institution

ANNEX 1: SAMPLE SIZE CALCULATIONS, TECHNICAL SPECIFICATIONS

Sample size calculation

The goal of the sample size calculations is to calculate the minimally required sample size that ensures desirable properties of the VE estimates. Examples of desirable properties are the expected length of the 95%CI, the expected lower half width of the 95% CI or power to detect statistical significance of a pre-specified effect size. Two approaches to sample size calculations have been developed; analytical and simulation-based. While analytical methods do have the advantage of computational speed, simulation-based methods are sometimes developed to closer mimic the actual study design and proposed analytical approaches at the cost of requiring additional parameter assumptions.

Analytical approach: power and minimal detectable VE

The power is the likelihood of statistical significance when there is a true effect while the minimal detectable VE is the smallest VE that can be detected as significantly greater than zero in a given study using hypothesis testing. The power and minimal detectable VE can be derived from the 2x2 table of interest cross-tabulating the expected number of cases and controls with the expected number of subjects within the relevant exposure group and within the appropriate comparator group.

Particularly, to derived the power for case-control studies, first calculate

$$M = \left|\frac{(\lambda - 1)(P - 1)}{1 + (\lambda - 1)P}\right|,$$

and

$$p_c^* = \frac{P}{r + 1}\left(\frac{r\lambda}{1 + (\lambda - 1)P} + 1\right),$$

where λ is the relative risk, P is the exposure prevalence and r is the case-control ratio. Then, the power can be derived from

$$z_\beta = \frac{\frac{MP\sqrt{nr}}{\sqrt{r+1}} - z_\alpha\sqrt{(r+1)\ p_c^*\ (1 - p_c^*)}}{\sqrt{\frac{\lambda P(1-P)}{[1 + (\lambda - 1)P]^2} + r\ P\ (1 - P)}},$$

where z_α and z_β are critical values for the standard normal distribution [1].

The minimal detectable VE for a case-control study is estimated as

$$VE_{MD} = 1 - RR_{MD(RR<1)}, \qquad (1)$$

where $RR_{MD(RR<1)}$ is the minimal detectable approximate relative risk (RR) in an case-control study, if RR < 1, or

$$RR_{MD(RR<1)} \cong 1 + \frac{-b - \sqrt{b^2 - 4a(r+1)}}{2a}, \quad (2)$$

where

$$a = r\gamma^2 - \frac{N r\gamma(1-\gamma)}{\left(\frac{z_\alpha}{2}+z_\beta\right)^2 (r+1)} \quad ; b = 1 + 2r\gamma,$$

for 'cases to controls' ratio *r*, coverage γ, total number of subjects N, and where z_α and z_β are the standard normal z-scores for the type I and type II error rates [1].

For case-control studies with multiple exposure categories (k > 2), 3 generic exposure categories exist: (1) the exposure group of interest, (2) the appropriate comparator group and (3) other exposure groups not relevant for the comparison, resulting in a 3x2 cross table. Starting from the assumptions on the case-control ratio and on the proportions of subjects belonging to each of the 3 exposure categories (derived from assumptions on brand-specific vaccination coverage, overall vaccination coverage and vaccination history), the relative cell frequencies of the 2x2 table of interest can be derived, based on which all parameters required for sample size calculations are derived.

Simulation-based approach

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 contributes 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 [2]. 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.

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 model/generalized additive model (GLM/GAM)

- 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 fixed effects logistic regression model with the disease status as the outcome and the exposure as a covariate is fitted.
- 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 parameter settings, a total of 500 simulations are recommended. On empirical basis, this number of simulation runs leads to stable Monte Carlo CIs 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.

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