id.DRIVE

Master Protocol for Study Contributors

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

A contribution of id.DRIVE,
a public-private partnership to facilitate the conduct of observational studies on infectious diseases, vaccines, related preventive measures, therapeutics, and diagnostics for infectious diseases.

Version 7.0

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https://iddrive.eu

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Abbreviations: FISABIO, Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana; P95, P95 Clinical and Epidemiology Services; GSK, GlaxoSmithKline.

DOCUMENT HISTORY

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 August 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

Version	Version date	Reason for new version
		• 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)
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)
5.0	September 18, 2023	Clean version (medical writer and quality review)
6.0	March 21, 2024	Amendments : • Updated to align with new id.DRIVE Consortium Agreement and Governance Charter • Update of covariate table to align with eCRF • Addition of vaccine misclassification and SARI incidental cases to limitations sections

Version	Version date	Reason for new version
		• Update of Annex 1 : Sample size calculations, technical specifications • Addition of Individual Case Safety Report (ICSR) form for reporting Serious Adverse Events (SAEs) to be used in case additional safety reporting as required for a specific Study Requestor. • Update to Study population section to clarify that co-enrolment in interventional trials is allowed. In case of co-enrolment, the name of the trial will be collected to allow for exclusion from specific analysis if required.
7.0	February 21, 2025	Amendments: • Update of variable table to align with eCRF • Update of statistical analysis to allow for matched analysis • Only for sites in the United Kingdom: addition of an exclusion criteria for patients who are deemed mentally incapacitated to provide informed consent (UK Mental Capacity Act 2025)

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.

BACKGROUND OF THIS MASTER PROTOCOL

This Master Protocol describes an observational 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 (Pharmaceutical company Partners) 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, endpoints, and data collection) and to mutualise healthcare providers/study site resources.

This Master Protocol has been developed by the id.DRIVE public-private partnership (https://iddrive.eu). Current id.DRIVE members are FISABIO (Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana, Spain), P95 Clinical and Epidemiology Services (Belgium), AstraZeneca (United Kingdom), Novavax (United States), and Pfizer (United States). Former members are THL (Finnish Institute for Health and Welfare, Finland), GSK (GlaxoSmithKline, Belgium), Janssen (Belgium), CureVac (Germany), Moderna (United States), Sanofi (France), Bavarian Nordic (Denmark), and Valneva (Austria). 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]) under the former COVIDRIVE Consortium Agreement. 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 former 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. The COVIDRIVE Consortium has evolved into the id.DRIVE Consortium in January 2024 and has enlarged its scope to facilitate the conduct of observational studies on infectious diseases, vaccines, related preventive measures and therapeutics for infectious diseases in Europe. This Master Protocol, as of version 6.0, is aligned with the id.DRIVE Consortium agreement for COVID-19 vaccine effectiveness studies.

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

1 TITLE PAGE

Abbreviated study title	Brand-specific COVID-19 vaccine effectiveness against severe COVID-19 disease in Europe
Full study title	Brand-specific COVID-19 vaccine effectiveness against severe COVID-19 disease in Europe - A contribution of id.DRIVE, a public-private partnership to estimate brand-specific COVID-19 vaccine effectiveness in Europe.
EMA-HMA catalogue number	EUPAS42328
Master protocol version	7.0
Date of protocol version	21 February 2025
Active substance(s)	Study Requestor COVID-19 vaccine
Study status	Observational
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, compared to selected comparator group[1]. ***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, compared to selected 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)[2] 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, compared to selected comparator group[1] ▪ by severity level[3]. ▪ by calendar time[4] ▪ by history and calendar time[4] 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 on length of hospital stay (in days) due to laboratory-confirmed SARS-CoV-2 admission, compared to selected comparator group[1] *[1] An appropriate comparator group will be defined for each objective, based on the use of the vaccine dose 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).* *[2] Only estimated if the type includes at least two brands or only the brand of interest.* *[3] Severity levels are defined by hospital outcome (ICU admission; in-hospital death) and/or respiratory support.* *[4] Calendar time periods as a proxy for periods of specific variant dominance.*
Country(ies) of study	Germany, Spain, United Kingdom and Italy. Additional countries may be included in the course of the study.

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4 GLOSSARY

Term	Description
Co-Coordinators	means FISABIO and P95, both Partners, that are the Co-coordinators.
Core Platform Partners	means the group of Partners that are not Pharmaceutical 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.
id.DRIVE	means the public-private partnership for conducting observational studies on infectious diseases, vaccines, related preventive measures and therapeutics for infectious diseases in Europe organised under the Consortium Agreement. For the avoidance of doubt, as of January 2024 COVIDRIVE became a part of id.DRIVE as described in further detail in the Governance Charter.
Independent Scientific Committee (ISC)	means the body consisting of a limited number of external experts with relevant experience/expertise in the field of infectious diseases, vaccines, related preventive measures and therapeutics for infectious diseases. Scientific experts representing each of the Co-coordinators act as the secretariat of the ISC.
Partner	means a legal entity signatory of the Consortium Agreement. Partners are either Core Platform Partners or Pharmaceutical Company Partners.
Pharmaceutical Company Partner	means a Partner that is a pharmaceutical company.
Primary Data Use	means the use of patient's data for the purpose of a single Study or multiple Studies defined prior to id.DRIVE Data Collection.
Quality Assurance and Audit Committee (QAAC)	means the committee responsible for the quality management and auditing of the Studies, composed of one quality assurance expert from each Pharmaceutical Company Partners and one quality assurance expert from the Co-Coordinators. The Co-Coordinators act as the secretariat of the QAAC.
Study Contributor	or "Study Site" or "Site", means 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.

Study Requestor	means the Partner that requests to perform a specific Study.
Study Results Publication	means a scientific publication reporting on the Study including all Study objectives identified in the individual Study protocol(s).
Study Team (ST)	means the team that carries out the conduct of the Study. For Primary Data Use Studies, the Study Team 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.

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
CI	Confidence interval
CIOMS	Council for International Organisations of Medical Sciences
CIRI-IT	Centro Interuniversitario per la Ricerca sull'Influenza e le altre Infezioni Trasmissibili
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
eCRF	Electronic Case Report Form
ECMO	Extracorporeal membrane oxygenation
ED	Emergency department
EDC	Electronic data capture
EMA	European Medicines Agency
EU	European Union
FISABIO	Fundación para Fomento de Investigación Sanitaria y Biomédica la Comunidad Valenciana
GAM	Generalised additive model
GDPR	General Data Protection Regulation
GEE	Generalised estimating equations
GEP	Good Epidemiological Practice
GH Charleroi	Grand Hôpital de Charleroi
GLM	Generalized linear model
GPP	Good Publication Practice
GSK	GlaxoSmithKline
GTPUH	Germans Trias i Pujol University Hospital
HIV	Human immunodeficiency virus
HMA-EMA	Heads of Medicines Agencies-European Medicines Agency
HUVH	Hospital Universitari Vall d'Hebron
ICF	Informed consent form
ICH-E6	International Council for Harmonisation E6 on Good Clinical Practice
ICMJE	International Committee of Medical Journal Editors
ICSR	Individual Case Safety Report
ICU	Intensive care unit
ID	Identification
IEC	Independent ethics committee
IMI	Innovative Medicines Initiative
IMI-DRIVE	Innovative Medicines Initiative – Development of Robust and Innovative Vaccine Effectiveness
IRB	Independent review board
ISC	Independent Scientific Committee
ISF	Investigator Site Files
LAR	Legally acceptable representative

MAH	Marketing authorisation holder
NA	Not Applicable
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
SAE	Serious Adverse Event
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 Viruses
VE	Vaccine effectiveness
WHO	World Health Organisation
WHO-EU	The WHO Regional Office for Europe

6 RESPONSIBLE PARTIES

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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.
- Pharmaceutical Company Partners will use the id.DRIVE partnership to conduct its future vaccine effectiveness (VE) studies as part of its European regulatory obligations.
- id.DRIVE is a public-private partnership. It was originally initiated under the COVIDRIVE Consortium 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. The COVIDRIVE Consortium has evolved into id.DRIVE Consortium in January 2024 and has enlarged its scope to facilitate the conduct of observational studies on infectious diseases, vaccines, related preventive measures and therapeutics for infectious diseases in Europe.
- This protocol details an observational study to estimate the effectiveness of COVID-19 vaccines against COVID-19 related hospitalisations through the id.DRIVE 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

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, compared to selected comparator group[1].

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, compared to selected 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)[2] 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, compared to selected comparator group[1]
    - by severity level[3]
    - by calendar time[4]
    - by history and calendar time[4] 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 on length of hospital stay (in days) due to laboratory-confirmed SARS-CoV-2 admission, compared to selected comparator group[1]

[1] An appropriate comparator group will be defined for each objective, based on the use of the vaccine dose 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).

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

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

[4] 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 a possible extension

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
- only for sites in the United Kingdom: deemed mentally incapacitated to provide informed consent due to a condition other than SARI, as defined by the UK Mental Capacity Act 2025

Study endpoints:

- Primary endpoint: SARS-CoV-2 detection in patients hospitalised with SARI symptoms.
- Secondary and exploratory endpoints:
  - Detection of SARS-CoV-2 genetic variants in patients hospitalised due to laboratory-confirmed SARS-CoV-2.
  - Hospitalisation due to laboratory-confirmed SARS-CoV-2 by level of severity (defined by hospital outcome; ICU admission and or in-hospital death).
  - Hospitalisation due to laboratory-confirmed SARS-CoV-2 by level of respiratory support.
  - Length of hospital stay.

Definitions:

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 (new or worsening)
- fever (≥38°C)
- shortness of breath (new or worsening)
- 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 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. after hospital admission. Study participants tested negative for SARS-CoV-2 prior to hospitalisation will be re-tested within 72 hours after hospital admission.

(1) Current countries include Germany, Italy, United Kingdom and Spain. The list of countries will be extended as the network grows.

Vaccine exposure

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).

Never vaccinated: have **never received any COVID-19 vaccine dose.**

Vaccinated with any COVID-19 vaccine **>** 6 months ago: 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.

Variables

Variables of interest that will be *collected at all study sites* include age, sex, 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 1 diabetes, type 2 diabetes, obesity, chronic haematological disorder, cancer, immunodeficiency, neurological disorders), vaccination against pathogens causing COVID-19 like symptoms (influenza, respiratory syncytial virus, pneumococcus), previous SARS-CoV-2 infection, respiratory support, ICU admission, in-hospital death, length of hospital stay, and pregnancy.

Variables that will be *potentially additionally collected at certain study sites* include treatments received prior to or during hospital admission for the current SARI episode (e.g. antibiotics, antivirals, corticosteroids, Anti-SARS-CoV-2 antibodies, immunomodulators, other monoclonal antibodies), body mass index (BMI), and long-term care facility residence.

Sample size

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. Sample size requirements will be calculated for each Study Requestor-specific protocol (for both interim and final analysis when applicable). 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, sex, 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) cubic 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), 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 independent 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. Matched cohort and matched analysis will be considered if sample size allows.

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. 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, id.DRIVE's Independent Scientific Committee (ISC) will be consulted.
Ethical considerations
The protocol 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 outcome 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 will be performed.
- Vaccination misclassification may influence CVE estimates, in particular in studies where exposure status is based on self-reporting. In this study, exposure ascertainment will be based on multiple sources including vaccine registries, vaccination cards and medical records. Although vaccination status captured in medical records will not be validated against primary records nor verbally with the patient, misclassification will be likely limited: complete exposure data will be required for a participant to be retained in the id.DRIVE study (mandatory variables included date of administration, dose number and vaccine brand). Although the status 'unvaccinated' may be harder to ascertain, the use of COVID-19 vaccination certificates during the pandemic has led to particularly good documentation of COVID-19 vaccination in Europe through national registers and vaccine cards.
- Incidental COVID-19 hospitalisations: hospitalisations of patients with COVID-19 are considered incidental when they have another cause besides COVID-19 as primary reason for admission. Although both hospitalisations with and for COVID-19 have a positive SARS-CoV-2 test, in incidental COVID-19 hospitalisations the COVID-19 finding does not influence the need for admission. To explore the level of potential bias, data on whether a patient is an incidental case or not will be collected.
- Prior infection: Infection-acquired immunity is an effect modifier of CVE. Although information on past SARS-CoV-19 infection will be 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 substantial amendments will be included in the Heads of Medicines Agencies - European Medicines Agency (HMA-EMA) catalogue of

real world data studies. Study Results Publications will be submitted to peer-reviewed open-source international journal(s).

Updates on study progress will be posted on the id.DRIVE web site (https://iddrive.eu/).

Funding

This generic Master Protocol V7.0 has been developed by the id.DRIVE partnership, which has received funds from the following members: AstraZeneca, GlaxoSmithKline (GSK), Janssen, Novavax, Pfizer, and Valneva and leveraging public health capacity from Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana (FISABIO) and existing infrastructure at P95 Clinical and Epidemiology Services. Other partners (Pharmaceutical companies or other institutes) might join the id.DRIVE 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.

id.DRIVE partnership

id.DRIVE is an open public-private partnership. Current members are FISABIO (Spain), P95 Clinical and Epidemiology Services (Belgium), AstraZeneca (UK), Novavax (US), and Pfizer (US). Past members are Bavarian Nordic (Denmark), GSK (Belgium), Janssen (Belgium), THL (Finland), CureVac (Germany), Moderna (US), Sanofi (France), and Valneva (Austria). The partnership aims to facilitate the conduct of observational studies on infectious diseases, vaccines, related preventive measures and therapeutics for infectious diseases in Europe.

Study status

Observational

Study sponsor

P95 Clinical and Epidemiology Services

8 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. Up to 8 January 2025, the following COVID-19 vaccines were 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), Comirnaty Omicron XBB.1.5 (BioNTech and Pfizer), Comirnaty JN.1 (BioNTech and Pfizer), Comirnaty KP.2 (BioNTech and Pfizer), Spikevax bivalent Original/Omicron BA.1 (Moderna), Spikevax bivalent Original/Omicron BA.4-5 (Moderna), Spikevax JN.1 (Moderna), Nuvaxovid XBB.1.5 (Novavax), and Nuvaxovid JN.1 (Novavax).

Despite the thorough investigation of the efficacy of COVID-19 vaccines during clinical trials, it is crucial to continue evaluating how well the vaccines prevent 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 well. COVIDRIVE was 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. The COVIDRIVE Consortium has evolved into id.DRIVE Consortium in January 2024 by enlarging its scope to facilitate the conduct of

observational studies on infectious diseases, vaccines, related preventive measures and therapeutics for infectious diseases in Europe. Current id. DRIVE members are FISABIO (Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana, Spain), P95 (Belgium), AstraZeneca (UK), Novavax (US), and Pfizer (US). The Pharmaceutical Company Partners will use this partnership to conduct its future VE studies as part of its European regulatory obligations.

This protocol details an observational study to estimate the effectiveness of COVID-19 vaccine against COVID-19 related hospitalisations through the id.DRIVE 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.

9 RESEARCH QUESTIONS AND 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, compared to selected comparator group[1].

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, compared to selected 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)[2] 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, compared to selected comparator group[1]
    - by severity level[3]
    - by calendar time[4]
    - by history and calendar time[4] 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 on length of hospital stay (in days) due to laboratory-confirmed SARS-CoV-2 admission, compared to selected comparator group[1].

[1] An appropriate comparator group will be defined for each objective, based on the use of the vaccine dose 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).

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

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

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

10 RESEARCH METHODS

10.1 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.

10.2 Study Contributors (study sites)

This is a multi-country, multi-centre study, with hospital sites in Europe.

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 study sites, data will additionally be retrieved from the existing hospital databases and linked data.

When required, a site-specific protocol will be written, describing details on patient flow, data collection, laboratory tests and genomic sequencing.

10.3 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 12.3.1) but who do NOT meet the exclusion criteria (see Section 15.3.2)

AND

- are hospitalised and meet the SARI case definition (see Section 12.5.2)

Participants may be co-enrolled in interventional trials. The name of the trial will be collected, to allow for exclusion from specific analysis, where required, and will be prespecified in the SAP.

10.3.1 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)

10.3.2 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)
- Only for sites in the United Kingdom: As defined by the UK Mental Capacity Act 2025[1], patients who are deemed mentally incapacitated to provide informed consent due to a condition other than SARI will be excluded from the study.

[1] For the UK Mental Capacity Act 2025, a person is considered unable to consent if, at the time of consent, they can't make decisions for themselves because of mind or brain impairments (See ANNEX 2: PATIENTS LACKING CAPACITY).

10.4 Study period

Minimum one year with a possible extension.

10.5 Definitions

10.5.1 Hospitalised patient

Person admitted to the hospital with overnight stay. An overnight stay is defined as at least one day difference between date of presentation at the hospital and discharge

date. In case of referral to another hospital, the date of hospital admission is defined as the date of first admission.

10.5.2 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 (new or worsening)
- fever (≥38 C^0)
- shortness of breath (new or worsening)
- 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]).

10.5.3 Test-positive case

A study participant who:

- meets the **SARI** case definition (see Section 12.5.2)

  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 after hospital admission

10.5.4 Test-negative control

A study participant that:

- meets the **SARI** case definition (see Section 12.5.2)

  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 after hospital admission. Study participants tested negative for SARS-CoV-2 prior to hospitalisation will be re-tested within 72 hours after hospital admission.

10.6 SARI patient identification

Hospitalised SARI patients will be identified based on the defined SARI definition (section 12.5.2) 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.

10.7 Exposure (COVID-19 vaccination)

10.7.1 Exposure definitions

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. Never vaccinated: have never received any COVID-19 vaccine dose[4]
6. Vaccinated with any COVID-19 vaccine **>** 6 months ago: 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[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.

10.7.2 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.

10.8 Endpoints

10.8.1 Primary endpoint: laboratory-confirmed SARS-CoV-2

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. 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.

10.8.2 Secondary endpoint: SARS-CoV-2 genetic variants

Genomic sequencing will be performed using commercially available molecular kits. At every study site with prospective data collection, preferably 100% of the SARS-CoV-2 positive cases will be sequenced. For retrospective data collection, sequencing data is obtained from medical records, when available.

10.8.3 Exploratory endpoints:

10.8.3.1 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

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).

10.8.3.2 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 discharge from another COVID-19 hospitalisation will be considered as part of the same episode. The length of stays of the admission will be summed.

10.9 Variables

The complete dataset can be found in id.DRIVE Common dataset case report form and is summarised in Table 1. Some variables are collected by all participating study sites. All variables are both being collected for prospective and retrospective subjects, if available.

Table 1. The list of collected study variables with description

Variable	Description	Collected by all sites
Age at hospital admission	Calculated based on date of birth and date of admission	x
Gender assigned at birth (sex)	Male, female	x
Chronic conditions*		
Asthma	Binary	x
Lung disease	Binary	x
Cardiovascular disease	Binary	x
Hypertension	Binary	x
Chronic liver disease	Binary	x
Chronic kidney disease	Binary	x
Diabetes type 1	Binary, if yes subcategory diabetic end organ damage: No, Yes, No information	x
Diabetes type 2	Binary, if yes subcategory diabetic end organ damage: No, Yes, No information	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
Chronic haematological disorder (non-cancerous)	Binary	x
Neurological disorder	Binary	x
Pregnancy	Binary	x
Trimester	First, second, third	x

Variable	Description	Collected by all sites
Body mass index (BMI)	Binary ("data available yes or no"). If yes, numerical, continuous	
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 respiratory syncytial virus	Binary. If yes, date of vaccination	
Vaccination history pneumococcus	Binary. If yes year of vaccination	x
Long-term care facility residence[§]	Binary	
COVID-19 prior episode	Binary	x
Month and year of most recent prior COVID-19 episode	Month and year	x
Respiratory support	No respiratory support, Oxygen therapy Non-invasive ventilation, Invasive mechanical ventilation, Extracorporeal membrane oxygenation (ECMO), No information	
Admission to ICU	Binary. If yes, date of admission, date of discharge.	
In-hospital death	Binary. If yes, date of in-hospital death	
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	

[*] *Definitions for each chronic conditions are specified in the id.DRIVE Common dataset case report form*
[§] *At VAHNSI, long-term care facility residents are excluded*
Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; HIV, human immunodeficiency virus; ICU, intensive care unit; SARI, severe acute respiratory infection; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

10.10 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.

Sample size requirements will be calculated for each Study Requestor-specific protocol (for both interim and final analysis when applicable). 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.

10.11 Data management

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

10.11.1 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.

10.11.2 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 id. DRIVE Research Server.

10.12 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.

10.12.1 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.

10.12.2 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.

10.12.3 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.

10.12.4 Statistical analyses

All CVE estimates will be adjusted for symptom onset date and the confounder-adjusted CVE estimates will also be adjusted for age, sex, 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) cubic 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. Potential intra-cluster between subjects from the same Study Contributors will be accounted for by using generalised estimating equations (GEE), generalized additive models (GAM), or random effects meta-analysis models (RE-MA) when individual data from some Study Contributors cannot be obtained to perform the analysis due to certain data restriction conditions.

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 directly derive Study Contributor-specific CVE estimates. As an alternative, Study Contributor-specific CVE estimates can be obtained by performing analysis using patient-level data from that specific Study Contributor only.

10.12.4.1 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 independent correlation matrix to account for potential within-cluster homogeneity in outcomes. An independent working correlation matrix is recommended over an exchangeable working correlation structure as the later might introduce bias if there are cluster based confounding and/or informative cluster sizes present [16, 17]. The robust sandwich estimator [18] will be used to estimate the standard error of the marginal effect estimates. Clusters will be defined at Study Contributor level.

10.12.4.2 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).

10.12.4.3 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].

10.12.4.4 Matching

Matched cohort (for example, four test-negative controls up to one test-positive case) and matched analysis will be considered if sample size allows.

10.12.4.5 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 12.7.1. 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.

10.12.4.6 Missing values

Data on exposure and especially the potential confounders may 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.

10.12.4.7 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, the effect of additional endpoint definitions (e.g. exclusion of subjects with vaccine-preventable viruses from the test-negative control group), the effect of confounding by correlation between vaccination behaviour against other vaccine-preventable pathogens (by adjusting additionally for the vaccination status of other vaccine-preventable viruses in logistic regression models), 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.

11 QUALITY MANAGEMENT

11.1 Independent Scientific Committee

The Independent Scientific Committee (ISC) is composed of independent external experts (from organisations or institutions which are not partners of id.DRIVE) with good expertise/experience relevant for id.DRIVE studies on infectious diseases, vaccines, related preventive measures and therapeutics for infectious diseases in Europe.

The roles and responsibilities of the ISC are the following:

- reviews and makes recommendations for Master Scientific Documents (Study Master protocols and SAPs),
- reviews and makes recommendations for Study reports.

11.2 Quality Assurance and Audit Committee

The Quality Assurance and Audit Committee (QAAC) of id.DRIVE composed of one quality assurance expert of each Pharmaceutical Company Partner and one quality assurance expert of the Co-Coordinators. 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.

The QAAC seeks to develop and sustain a reasonable and feasible mechanism to support quality management together with P95 as the Study Sponsor of the Studies.

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.

11.3 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 id.DRIVE 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 id.DRIVE Monitoring Plan.

The Study Contributor investigators must permit any external auditor mandated by the QAAC of the id.DRIVE 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.

11.4 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.

12 LIMITATIONS OF THE RESEARCH METHODS

The COVID-19 pandemic was unprecedented, unpredictable and continues to pose 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[19]. 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 [20]. Although information on past SARS-CoV-2 infection will be 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 [21], 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 that will be collected in the present study.

Misclassification of outcome 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 [22, 23], risk of disease misclassification bias is minimised. However, RT-PCR sensitivity is influenced by several factors, including operator sampling technique, type of specimen [24], and timing of sampling - with sensitivity peaking during the first 4 to 5 days after symptom onset before showing a gradual decline [25-28]. 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 [29]. 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 [27]. 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.

Vaccination misclassification may influence CVE estimates, in particular in studies where exposure status is based on self-reporting [30]. In this study, exposure ascertainment will be based on multiple sources including vaccine registries, vaccination cards and medical records. Although vaccination status captured in medical records will not be validated against primary records nor verbally with the patient, misclassification will likely be limited: complete exposure data will be required for a participant to be retained in the id.DRIVE study (mandatory variables included date of administration, dose number and vaccine brand). Although the status ‘unvaccinated’ may be harder to ascertain, the use of COVID-19 vaccination certificates during the pandemic has led to particularly good documentation of COVID-19 vaccination in Europe through national registers and vaccine cards. In Germany there is no vaccine registry available, and paper vaccination cards are used for documentation. In some cases, the vaccination card may not be available as a physical document at the time of hospital admission, thus, provision of the vaccination data card may be foreseen by relatives, which can be challenging. In addition, there is a chance of incomplete data because of unreadable handwriting on vaccination cards. Therefore, misclassification of vaccination status may be greater for data collected in German sites.

Incidental COVID-19 among SARI hospitalisations could be a potential source of bias. In general, hospitalisations of patients with COVID-19 are considered incidental when they have another cause besides COVID-19 as likely primary reason for admission [31, 32]. To explore the level of potential bias, data on whether a patient is an incidental case or not will be collected.

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 [33]. 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 [34]. 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.

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

13.1 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) [35], Good Epidemiological Practice (GEP) [36], 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.

13.2 Ethics approval

The protocol 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.

13.3 Informed consent

A good readability was prioritised when writing the Master ICF. The 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.

13.4 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.

13.5 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).

13.6 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.

13.7 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. For this secondary use of data the id.DRIVE governance principles will be respected as detailed in the id.DRIVE Governance Charter. The Governance Charter can be made available by the Co-Coordinators upon written request.

14 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.

14.1 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 [35], GEP [36], 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 [37] 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.

14.2 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.

14.3 Data capture

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

14.4 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.

14.5 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.

14.6 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

15 REPORTING AND DISSEMINATION OF RESULTS

15.1 Study protocol

The study protocol and final study report will be included in the Heads of Medicines Agencies-European Medicines Agency (HMA-EMA) catalogue of real world data studies.

15.2 Management and reporting of adverse events/adverse reactions

This is an observational 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.

In case additional safety reporting is required for a specific Study Requestor, only Serious Adverse Events (SAEs) related to the receipt of the investigational products, of which the Study Contributors becomes aware, will be reported to the Study Requestor. The Individual Case Safety Report (ICSR) form for reporting SAEs is provided in the Investigator Site Files (ISF).

15.3 Progress, interim and final reports

Progress reports will be provided every two months since enrolment of the first participant to the Study Requestors. 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.

A final study report will be written for each of the individual COVID-19 vaccine brands of interest. The id.DRIVE ISC will review all study reports (interim and/or final, as applicable) and the written comments by the Study Requestor. The ISC will provide recommendations for the integration of the Study Requestor comments. The study report(s) (interim and/or final, as applicable) will be submitted to the EMA by the MAH to meet regulatory requirements. This process is further described in the id.DRIVE Governance Charter.

15.4 Publication

Scientific publication(s) of the study results will be prepared. 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.

Study Contributors are allowed to develop publications based on their raw patient-level data or cleaned pseudonymized patient-level data collected in the scope of the id.DRIVE Study following the id.DRIVE Governance Charter.

16 FUNDING

id.DRIVE is a public-private partnership funded by the Pharmaceutical Company Partners and leveraging health capacities from public partners and sites. This generic Master Protocol has been developed by the id.DRIVE partnership, which has received funds from AstraZeneca, Bavarian Nordic, CureVac, GSK, Janssen, Moderna, Novavax, Pfizer, 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 (Pharmaceutical Companies or other Institutions) may join the id.DRIVE partnership at later stages. Cost sharing principles are defined in the id.DRIVE Consortium governance charter. The execution of the brand-specific study will be further funded by the Pharmaceutical Company Partners requesting the study.

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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 than 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 [38].

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

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

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 [38].

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 Contributors as 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 Contributors, 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 Contributor-specific CVEs for all exposures. The subsequent section describes how

the CVE are varied across the Study Contributors 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 $P(exposure\ x|case) = \mathrm{OR}_x * \frac{(1-c)P_x}{c} * P(unexposed|case)$.

Simulating Study Contributor -specific CVE

Effect of primary series vaccination

To incorporate the expected between-site heterogeneity, for each Study Contributor 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 [39]. 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.
- The site-specific expected OR on the log-scale 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.
- The expected OR on the log-scale of the treatment effect is estimated 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 considered as clusters and the variances are calculated using a robust sandwich estimator.
- The estimated log OR and the corresponding CI are then back-transformed to obtain an estimate of the mean overall (r)CVE and its 95% CI.
- 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.
- The expected OR on the log-scale of the treatment effect is estimated using a logistic regression model with the disease status as the outcome and the exposure as a covariate.
- The estimates are obtained using the GLM/GAM method in which the sites are considered as fixed effects.
- The estimated log OR and the corresponding CI are then back-transformed to obtain an estimate of the mean overall (r)CVE and its 95% CI.
- 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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ANNEX 2: PATIENTS LACKING CAPACITY

According to the UK Mental Capacity Act 2005 (c. 9) Part 1, a person is considered to lack mental capacity in relation to a matter if at the material time he is unable to make a decision for himself in relation to the matter because of an impairment of, or a disturbance in the functioning of, the mind or brain. For the purpose of this study, a patient is considered to lack capacity if, at the time of consenting for the study, they are unable to fully understand, retain, or process the information necessary to make an informed decision about their participation in the study because of this mental impairment or disturbance due to a condition other than SARI. For these patients, consent from the next of kin cannot be used, and they will therefore be excluded from the study. The following aspects need to be considered when assessing the participant's mental capacity:

- A lack of mental capacity cannot be established merely by reference to a person's age or appearance, or a condition of his/her, or an aspect of his/her behaviour, which might lead others to make unjustified assumptions about his/her mental capacity.
- A person is unable to make a decision for himself/herself if he/she is unable to:
    a) understand the information relevant to the decision,
    b) retain that information,
    c) use or weigh that information as part of the process of making the decision, or
    d) communicate his/her decision (whether by talking, using sign language or any other means).
- A person is not to be regarded as unable to understand the information relevant to a decision if he/she is able to understand an explanation of it given to him/her in a way that is appropriate to his/her circumstances (using simple language, visual aids, different language or any other means).
- The fact that a person is able to retain the information relevant to a decision for a short period only does not prevent him/her from being regarded as able to make the decision. The information relevant to a decision includes information about the reasonably foreseeable consequences of:
    a) deciding one way or another,
    b) failing to make the decision.

For avoidance of doubt, patients who temporarily lack mental capacity only due to SARI (e.g., who are in coma in intensive care unit), can still be included in the study.