



id.DRIVE

Surveillance of Respiratory Pathogens and Brand-Specific Vaccine Effectiveness in Adults Hospitalised with SARI: An Observational Study.

Protocol

Version: 3.0

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1 TITLE PAGE

Title:	id.DRIVE: Surveillance of Respiratory Pathogens and Brand-Specific Vaccine Effectiveness in Adults Hospitalised with SARI: An Observational Study.
Protocol version and date:	V3.0 02-MAR-2026
HMA-EMA catalogue number:	EUPAS1000000012
Aim	To conduct observational studies on infectious diseases including disease surveillance and/or assessment of effectiveness, impact of vaccines or therapeutics.
Sponsor:	P95 Clinical and Epidemiology Services Diestsevest 125, 3000 Leuven, Belgium

2 RESPONSIBLE PARTIES

- P95 Clinical and Epidemiology Services
- FISABIO, Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana.

3 PROTOCOL SUMMARY

Background

Continuous surveillance of viral respiratory pathogens is essential to monitor clinical and virological trends, support vaccine effectiveness (VE) studies, evaluate the impact of interventions (e.g., mass vaccination campaigns, novel therapeutics, or vaccines), guide pathogen and strain selection for vaccine development, and for epidemic and pandemic preparedness. Severe acute respiratory illness (SARI) surveillance is an international standard for monitoring influenza-associated hospital morbidity and mortality [1, 2], and was extended to the monitoring of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the coronavirus disease 19 (COVID-19) pandemic. With the generalisation of the use of multiplex assays, SARI surveillance systems can now be used to study additional respiratory pathogens.

id.DRIVE is a public-private partnership which aims to conduct observational studies on infectious diseases, vaccines, related preventive measures and therapeutics for infectious diseases (<https://iddrive.eu>). This study will leverage the id.DRIVE's Study Network to continuously monitor SARI-causing pathogens (e.g., SARS-CoV-2, influenza, and respiratory syncytial virus [RSV]), including virological and clinical trends, as well as burden of disease (e.g., pathogen-specific morbidity; in-hospital mortality). The surveillance of additional pathogens allows for study preparedness, with the potential to perform feasibility assessments for future impact and effectiveness studies within the id.DRIVE Study Network. In addition, the id.DRIVE Study Network is used to conduct (brand-specific) VE studies.

This protocol describes three study modules that all investigate the same study population and collect information via a common data collection. The surveillance module serves as the umbrella study. Extra inclusion and exclusion criteria can be applicable for the other study modules.

Research aim

Surveillance Module: To establish sentinel SARI surveillance for the continuous monitoring of the burden of disease caused by multiple viral respiratory pathogens in adults, and to assess associated virological and clinical trends.

COVID-19 VE (CVE) Module: To continuously estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in adults with SARI.

RSV VE Module: To continuously monitor VE of RSV vaccine(s) against RSV-related SARI hospitalisations in adults using a network of hospitals.

Objectives

Surveillance Module:

Primary objective:

- To calculate the proportion of laboratory samples positive for each viral respiratory pathogen of interest⁽¹⁾, among adult patients hospitalised with SARI.
- To characterise adult SARI patients (including age, gender, protective and risk factors, specific treatments, healthcare utilisation outcomes⁽²⁾), overall and by viral respiratory pathogen of interest⁽¹⁾.

Secondary objectives:

- To investigate the prevalence of co-infection with the viral respiratory pathogens of interest⁽¹⁾, in adult patients hospitalised with SARI, and the impact on healthcare utilisation outcomes⁽²⁾.
- To explore risk factors of pathogen-specific SARI⁽³⁾, healthcare utilisation outcomes⁽²⁾, and the presence of co-infection.

Exploratory objectives:

- To calculate pathogen-specific SARI incidences and describe trends in adults (by time period, country, and level of severity).
- To perform feasibility assessments for future respiratory disease studies within the id.DRIVE Study Network (e.g., effectiveness studies, impact studies).

⁽¹⁾ SARS-CoV-2, Influenza A/B, RSV A/B, Adenovirus, Parainfluenza viruses (1-4), human metapneumovirus (hMPV), human rhinovirus (HRV), human enterovirus (HEV), human coronaviruses (229E/NL63/OC43/HKU1), and human bocavirus (1-4).

⁽²⁾ Healthcare utilisation outcomes are defined by outcome (hospitalisation without intensive care unit (ICU) admission or in-hospital death; ICU admission without in-hospital death; in-hospital death), by the need for respiratory support (none; oxygen therapy, non-invasive ventilation; invasive mechanical ventilation; ECMO), discharge destination, and length of stay.

⁽³⁾ Factors associated with an infection by pathogen of interest versus not being infected by the pathogen of interest among adult patients hospitalised with SARI.

CVE Module**Primary objective:**

- 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 the selected comparator group.

Secondary objectives:

- 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 the selected comparator group:
 - by SARS-CoV-2 genetic variants,
 - within populations of special interest (e.g., specific age groups, specific immunocompromised or chronic conditions, pregnant women),
 - by time since last COVID-19 vaccine dose,
 - by time between COVID-19 vaccine doses,
 - by number or type(s)⁽¹⁾ of the COVID-19 vaccine doses given prior to the last dose.

Exploratory objectives:

- 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 the selected comparator group:
 - by severity level⁽²⁾,
 - by calendar time⁽³⁾,
 - by history and calendar time⁽³⁾ of prior SARS-CoV-2 infection.
- 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 the selected comparator group

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

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

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

RSV VE Module**Primary objective:**

- To estimate RSV VE for brand-specific RSV vaccine against hospitalisation due to laboratory-confirmed RSV infection overall or within a specific timeframe from vaccination) in adult patients with SARI, eligible to receive the vaccine.

Secondary objectives:

- As primary objective, but stratified by/subgroup analyses among:
 - RSV subtype A and B,
 - populations of special interest (e.g., age groups, gender, chronic medical condition risk groups, immunocompetent, and with co-administered vaccines),
 - time since vaccination,
 - history and time since prior RSV infection within the last 12 months,
 - country and study site,
 - SARI severity level.

Exploratory objectives:

- Descriptive analysis of vaccinated and unvaccinated cases and controls: demographic, clinical, severity, length of hospital stay, and laboratory characteristics.

Study methods

Study design: multi-country, multi-centre, hospital-based,

- SARI-based surveillance study,
- test-negative case-control (TNCC) VE studies

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

Data collection: Prospective and retrospective

Study duration: The study provides year-round surveillance, with a study period lasting minimum 12 months with possibility to extend.

Eligibility Criteria**For all three modules:**

Adults (18 years and older) presenting at the participating hospitals during the study period who are:

- Hospitalised and meet the SARI case definition.
- Willing and able to provide informed consent, when applicable, obtained from the patient or from the patient's Legally Acceptable Representative(s) (LAR).
- Only for sites in the United Kingdom: participants are excluded if deemed mentally incapacitated to provide informed consent due to a condition other than SARI, as defined by the United Kingdom Mental Capacity Act 2005.

Additional inclusion and exclusion criteria for the VE Modules**Additional inclusion criteria CVE and RSV module:**

- Willing and able to provide the protocol-required respiratory specimen(s).
-

Additional inclusion criteria CVE module:

- Ever eligible for COVID-19 vaccination prior to hospital admission.

Additional inclusion criteria RSV module:

- Eligible to receive RSV vaccination following to their residence country/regional immunisation programme prior to hospital admission.

Addition exclusion criteria CVE module:

- COVID-19 hospitalisation within three months prior to the current admission. Hospital transfers are not considered as a prior hospitalisation
- Received last vaccine dose with other than European Medicines Agency (EMA)-approved COVID-19 vaccine brand (EMA approval status at time of hospitalisation)

Definitions

SARI case definition: A SARI 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 ($\geq 38\text{ C}^\circ$)
- 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 European Centre for Disease Prevention and Control (ECDC) case definition (specifying “suspicion of respiratory infection”) [3].

An extended SARI case definition is used at the Study Contributor site **VAHNSI only** for the surveillance module. In this extended case definition, a SARI patient is defined as a hospitalised person with a suspicion of a respiratory infection or exacerbation of underlying chronic obstructive pulmonary disease (COPD), asthma, or chronic heart failure (CHF), with the following symptoms, signs or confirmed SARI evidence: cough (new or worsening); fever ($\geq 38\text{ C}^\circ$); shortness of breath (new or worsening); sudden onset of anosmia, ageusia, or dysgeusia; runny nose (rhinorrhea), nasal congestion, or coryza; sore throat or hoarseness; sputum production (new or worsening); wheezing (new or worsening); chills or rigors; abnormal auscultatory findings suggestive of pneumonia; radiographic finding consistent with pneumonia, with symptom onset within the last 14 days prior to hospital admission. Only one symptom is required to meet the case definition.

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

Laboratory-confirmed infection: For each studied pathogen, a laboratory-confirmed infection is defined as a positive reverse transcription polymerase chain reaction¹ (RT-PCR) on any respiratory specimen(s) collected between 14 days prior to and up to 72 hours after hospital admission. The absence of a laboratory-confirmed infection requires all samples collected in this time frame to be negative.

¹ Or another RNA amplification system with at least the same sensitivity as RT-PCR (e.g., TMA).

Laboratory-confirmed co-infection: Laboratory-confirmed co-infection is defined as two or more laboratory-confirmed infections on any respiratory sample collected between 14 days prior to and up to 72 hours after hospital admission.

Test negative control and test-positive case:

Test positive case : patients who meets the SARI case definition AND tests positive for SARS-CoV-2 or RSV using RT-PCR or similar molecular assays, with specimens collected between 14 days up to 72 hours after hospital admission.

Test negative control : patients who meets the SARI case definition AND have all respiratory samples testing negative for SARS-CoV-2 or RSV, respectively using RT-PCR or similar molecular assays, with specimen(s) collected between 14 days prior to and up to 72 hours after hospital admission.

Alternative definitions may be explored for some sensitivity analysis.

Exposure definitions (VE modules):

CVE module:

1. Vaccinated with at least one dose: vaccinated with at least one 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 > six months ago: received last COVID-19 vaccine dose > six months prior to symptom onset⁽⁴⁾
7. Vaccinated with seasonal COVID-19 vaccine with the brand of interest⁽¹⁾: received the seasonal COVID-19 vaccine brand of interest within the season of interest⁽⁵⁾ and ≥ 14 days before symptom onset
8. Unvaccinated with seasonal COVID-19 vaccine: did not receive any COVID-19 vaccine within the season of interest⁽⁴⁾⁽⁵⁾
9. Other: additional vaccine exposure 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.

RSV VE module:

1. Vaccinated with the RSV vaccine during the study period of interest: 'Vaccinated' study participants were vaccinated with the exposure of interest (e.g., single dose/primary vaccination/at least one dose) of the RSV vaccine during the study period of interest (e.g., ever/the last 12 months), within the appropriate timeframe for the product to be effective (e.g., ≥ 15 days) prior to SARI symptom onset, where day one is the date of vaccination.
2. Unvaccinated during the study period of interest: 'Unvaccinated' study participants did not receive any RSV vaccine (investigational or licensed) during the study period of interest, (e.g., never/the last 12 months).
3. Recently vaccinated with the RSV vaccine: 'Recently vaccinated' study participants were vaccinated with the exposure of interest (e.g., single dose/primary vaccination/at least one dose) of the RSV vaccine during the study period of interest, (e.g., ever/the last 12 months) within the appropriate timeframe for the product to be ineffective, e.g., < 15 days prior to SARI symptom onset.
4. Other: Additional vaccine exposure definitions might be developed depending on the real-life use of the RSV vaccines.

Laboratory testing

Clinical specimens will be taken from all SARI patients included in the study (within 72 hours after hospital admission). To the extent possible, clinical specimens will be collected from all patients eligible for the study as part of routine clinical sampling for diagnostic work-up. However, depending on local practice, additional specimen collection for the purpose of the study may be required. The preferred respiratory specimen is a nasopharyngeal swab, however, additional respiratory specimen types are also accepted (e.g., nasal swab, oropharyngeal swab, bronchoalveolar lavage, aspirates). Specimen type will be recorded.

The respiratory specimens will be tested within the local laboratory infrastructures of the participating Study Contributors, for at least SARS-CoV-2, influenza A/B, and RSV A/B. In addition, some study contributors will additionally test for other viral respiratory pathogens such as adenovirus, parainfluenza 1-4, human metapneumovirus (hMPV), human rhinovirus (HRV), human enterovirus (HEV), human bocavirus 1-4, and human coronaviruses (229E/NL63/OC43/HKU1). This will be done by using validated RT-PCR assays, or another ribonucleic acid (RNA) amplification system with at least the same sensitivity as RT-PCR (e.g., transcription-mediated amplification [TMA]).

Further subtyping will be performed on specimens that test-positive for:

- RSV:
 - Subtype A and B
- Influenza:
 - Type A and B
 - Subtypes A H1, Influenza A H3

Collection of SARS-CoV-2 genetic variant information is optional. Participating sites will gather variant data to the extent possible, preferably on all confirmed COVID-19 cases when sample quality allows.

Variables of interest

Information will be collected on patient demographics (e.g. age and gender), relevant risk factors (including selected chronic conditions, such as chronic pulmonary disease, cardiovascular disease and immunodeficiency disorders, as well as for example BMI), history of previous respiratory infections, vaccination history for respiratory illnesses. In addition, health care resource use indicators associated with the current hospitalisation will be collected such as respiratory support, medications received, and ICU stay.

Data collection

After study enrolment, data will be collected from primary (e.g., laboratory results) and/or secondary data sources (e.g., vaccination registries).

Exposure status, 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). Where needed, treating physicians or other health care professionals will be contacted to obtain additional information.

Statistical analysis

Demographic and clinical characteristics of SARI patients will be reported, overall and stratified by respiratory pathogen detected (type and/or subtype).

Surveillance module:

The analysis will report counts and proportions of positive laboratory samples for each respiratory pathogen, including co-infections, with 95% exact binomial confidence intervals (CI) across key subgroups (calendar time, site, country, age, and risk groups). Co-infections will be further characterized by number and type of pathogens and associated healthcare outcomes.

Logistic regression will be used to explore risk factors (age, gender, chronic conditions) for pathogen-specific SARI hospitalisation, healthcare use, and co-infections, with stratified analyses by age, gender, chronic conditions, and immunodeficiency status.

Where feasible, pathogen-specific SARI incidence rates will be estimated using percent positivity and hospital catchment population data. When exact catchment populations are unknown, other sources of information will be pursued. Incidence will be reported across calendar time, sites, countries, and age groups. Time trends will be explored treating calendar time as a categorical variable and as a continuous variable using penalised smoothing splines.

VE modules:

Descriptive analyses will be performed to describe the study population, the evolution of the SARS-CoV-2 dynamics, RSV subtypes and the COVID-19 and RSV vaccination coverage for the brands of interest. VE is calculated as $(1 - OR) \times 100\%$, where OR denotes the (exposure) odds ratio, comparing the confounder-adjusted odds of vaccination among test positive cases to the odds of vaccination among test negative controls. VE estimates will be adjusted for symptom-onset date at minimum, and additionally the following confounders – age, gender, and comorbidities (e.g. number of chronic conditions). Confounder adjustments are usually achieved through the inclusion of relevant terms in the logistic regression models, with (penalised) spline terms for

calendar time and/or age. Other potential covariates may be identified and included in the model using predefined model building procedures.

Generalised estimating equation (GEE) logistic regression models accounting for potential intra-cluster correlation [4] among subjects from the same Study Contributor will be employed to compute the confounder-adjusted OR with a predefined working correlation matrix. The uncertainty around the estimated ORs will be calculated using a robust sandwich estimator, yielding a consistent and asymptotically normal estimator [5]. Matching will be considered if sample size allows. Sensitivity analyses will be conducted as appropriate.

Sample size

Surveillance:

To estimate the proportions of laboratory samples testing positive for each targeted viral respiratory pathogen with the desired level of precision, several scenarios were assessed, considering prevalences ranging between 4-15% and enrolment of 4,000 to 10,000 SARI patients. Based on feasibility assessments and previous recruitment trends in the past years, the anticipated sample size is expected to provide proportion estimates with adequate precision.

VE Modules:

The sample size calculation depends on the case-control ratio, overall vaccination coverage, share of the different vaccine brands and anticipated VE. Hence, the expected sample size will be different for various vaccine brands. In case the parameter settings used for sample size calculations are very different from what is observed in the study, the sample size calculations will be updated accordingly.

Data management

Data collected at Study Contributors will be checked for quality and transferred to a dedicated, secured central server hosted by P95. A data management plan (DMP) will be written prior to the start of the data collection. The DMP will describe all functions, processes, responsibilities, specifications for data collection, cleaning, and validation.

Reporting

Study progress is tracked through a centralized dashboard, enabling real-time monitoring of milestones and key indicators. Progress reports can be developed regularly to provide structured updates, while comprehensive study reports may be prepared upon request from study sponsors or requestors.

For studies with a data collection period > 1 year, an interim analysis is planned when data on a sufficient number of COVID-19 cases vaccinated with the COVID-19 vaccine has been collected. Interim analysis are planned after each season, however other triggers could also be applied.

Ethical considerations

The protocol will be submitted to relevant ethics committee(s) following local regulations. Informed consent will be obtained from participants/guardians as specified by the national/regional ethics committee.

Study limitations

Surveillance Module:

- Catchment populations from sentinel surveillance sites may differ from the national population, limiting generalisability of findings.
- RT-PCR sensitivity varies by specimen type, timing, number of specimens collected, operator technique, and pathogen [6, 7], potentially leading to under-ascertainment of infections.
- RT-PCR provides high specificity, however detection of viral nucleic acid may reflect past infection rather than the aetiology of the current SARI episode.
- The use of different RT-PCR assays across Study Contributors may affect the comparability of laboratory results between sites or with other surveillance systems.
- Multiple different SARI definitions are currently in use in epidemiological surveillance, potentially limiting comparability of our results with other studies. We apply an (extended) ECDC SARI case definition. However, sensitivity analyses will be performed using alternative SARI-case definitions (e.g., WHO SARI definition, WHO extended SARI definition, and modified ECDC SARI case definitions).

VE Modules:

- There are several time-varying confounders and effect modifiers. Their complex interplay makes it challenging to disentangle waning vaccine immunity, differences in VE against different genetic variants/strains, and infection acquired immunity.
- Misclassification of outcome status: 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.
- Vaccination misclassification may influence VE estimates.
- Prior infection: Infection-acquired immunity is an effect modifier of VE. Although information on past SARS-CoV-2 and RSV infection is collected in this study, prior infection may be undocumented (e.g., asymptomatic disease).
- Unaccounted confounders: these include ethnicity, socio-economic status, and frailty. In general, results from this study will be highly specific to its population, and this will need to be carefully considered when generalising or comparing results.

Dissemination

The study protocol and its substantial amendments will be posted on the id.DRIVE website (<https://iddrive.eu>) and included in 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).

Funding

The id.DRIVE Study Network has been funded by current and previous Pharmaceutical Company Partners of the id.DRIVE consortium. Other partners (pharmaceutical companies or public institutions) may join the id.DRIVE consortium as per id.DRIVE Consortium Agreement and participate in the study's funding. All funding will be transparently acknowledged in study communications.

id.DRIVE consortium

id.DRIVE is a not-for-profit open public-private partnership to facilitate the conduct of observational studies on infectious diseases, vaccines, related preventive measures, therapeutics, and diagnostics for infectious diseases in Europe and beyond.

Study Sponsor

P95 Clinical and Epidemiology Services

Study status

Observational

4 MILESTONES

Milestone	Date
Registration of study protocol in the HMA-EMA catalogue of real world data studies	February 2024 (Protocol V1.0) August 2025 (Protocol V2.0) August 2026 (Protocol V3.0)
Start of data collection	Surveillance Module: 04 August 2024 CVE Module: 01 May 2021 RSV VE Module: 01 September 2024
End of data collection	30 August 2027, with possibility to extend
Registration of study results in the HMA-EMA catalogue of real world data studies	Results will be registered after study finalization, depending on extensions.

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6 VERSION HISTORY

Version	Date	Description of changes
1.0	21 March 2024	Creation of first version of the Surveillance study protocol
2.0	23 April 2025	Include extended SARI case definition for VAHNSI Update protocol according to updated eCRF Include secondary objective 'risk factor assessment' Remove 'samples are tested for at least COVID-19, RSV and Influenza' Include option for retrospective data collection in Study Contributors with late set-up Only for sites in the United Kingdom: add an exclusion criteria for patients who are deemed mentally incapacitated to provide informed consent (United Kingdom Mental Capacity Act 2025)
3.0	02 March 2026	This protocol v3.0 describes three study modules that investigate the same study population and collect information via a common data collection: • Surveillance module: Surveillance study of respiratory pathogens in adults hospitalised for SARI • CVE module Brand-specific COVID-19 vaccine effectiveness against severe COVID-19 disease • RSV VE module Brand-specific respiratory syncytial virus vaccine effectiveness The vaccine effectiveness studies for COVID-19 (Brand-specific COVID-19 vaccine effectiveness against severe COVID-19 disease in Europe, EUPAS42328) and RSV (Brand-specific respiratory syncytial virus vaccine effectiveness in Europe, EUPAS1000000035) have been included into this study protocol as specific modules. The surveillance module serves as the umbrella study and the study title was changed to "Surveillance of Respiratory Pathogens and Brand-Specific Vaccine Effectiveness in Adults Hospitalised with SARI: An Observational Study." Amendments: • The detailed list of variables is now only described in the annotated case report form (CRF), annexed to the protocol. • Extension of inclusion criteria for the RSV study to all adults. • Removal of information on participating Study Contributor to allow additional sites to join/leave later.

Version	Date	Description of changes
		• Study period changed to include possibility of further extension. • Background and limitation section have been updated with most recent information. • Updates to statistical methods and sample size collection sections based on information from the previous year. • SARS-CoV-2 genetic sequencing included as an optional component of the study.

See Annex 2 for version history for the CVE and RSV VE study protocols.

7 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 and beyond 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.
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 Network	means the network of Study Contributors and potential new Study Contributors who have expressed interest to conduct Studies.
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.

8 LIST OF ABBREVIATIONS

Abbreviation	Definition
BiPAP	Bi-level intermittent positive airway pressure
BMI	Body mass index
CCA	Complete case analysis
CHF	Chronic heart failure
CI	Confidence interval
CIOMS	Council for International Organisations of Medical Sciences
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CPAP	Continuous positive airway pressure
CRF	Case report form
CVE	Covid-19 vaccine effectiveness
DALY	Disability-adjusted life year
DMP	Data management plan
ECDC	European Centre for Disease Prevention and Control
ECMO	Extracorporeal membrane Oxygenation
ED	Emergency department
EMA	European Medicines Agency
EU	European Union
FISABIO	Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana.
GAM	Generalised additive models
GDPR	General data protection regulation
GEE	Generalised estimating equation
GEP	Good epidemiological practice
GPP	Good publication practice
HEV	Human enterovirus
HMA-EMA	Heads of Medicines Agencies - European Medicines Agency
hMPV	Human metapneumovirus
HRV	Human rhinovirus
ICF	Informed consent form
ICMJE	International committee of medical journal editors
ICU	Intensive care unit
IEC	Independent ethics committee
IRB	Independent review board
ISC	Independent scientific committee
LAR	Legally acceptable representative
LRTI	Lower respiratory tract infection
ML	maximum likelihood
NPI	Non-pharmaceutical interventions
OR	odds ratio
QAAC	Quality assurance and audit committee
RADT	Rapid antigen detection test
RE-MA	Random effects meta-analysis models
REML	Restricted maximum likelihood
RNA	ribonucleic acid,
RT-PCR	Reverse transcription polymerase chain reaction

Abbreviation	Definition
RSV	Respiratory syncytial virus
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
TMA	Transcription mediated amplification
TNCC	Test-negative case-control
VAHNSI	Valencia Hospital Surveillance Network for the Study of Influenza and Other Infectious Diseases
VE	Vaccine effectiveness
WHO	World Health Organization

9 RATIONALE AND BACKGROUND

Lower respiratory tract infections (LRTIs) remain a major global cause of morbidity and mortality. The latest, pre-COVID report on LRTIs by the Global Burden of Disease Study showed that LRTIs resulted in almost 66 million hospitalisations worldwide and caused 2.4 million deaths in people of all ages in 2016, accounting for 4.4% of all-cause mortality. A total of 91,844,600 disability-adjusted life years (DALYs) were estimated to have been attributable to LRTIs in 2016 [8]. LRTIs can be caused by a broad array of pathogens, including various respiratory viruses such as influenza A and B, SARS-CoV-2, RSV, adenovirus, and parainfluenza viruses. While these infections frequently cause mild illness, they can also lead to severe disease requiring hospitalisation, particularly among older adults and individuals with underlying conditions.

SARS-CoV-2 continues to circulate globally, and although incidence has declined from pandemic peaks, COVID-19 remains an important contributor to respiratory morbidity and mortality as its circulation adopts more predictable endemic patterns. Vaccination is the primary tool for preventing severe outcomes; however, viral evolution and waning immunity underscore the need for continued assessment of real-world VE. VE studies are essential for evaluating durability of protection, effectiveness against circulating and emerging variants, and performance in high-risk groups such as older adults, immunocompromised individuals, and people with chronic conditions. As vaccine formulations are updated, sustained VE monitoring remains crucial for reducing the burden of COVID-19 morbidity and mortality.

Alongside COVID-19, influenza and RSV also remain major contributors to seasonal respiratory morbidity and mortality in adults. Influenza was estimated to have caused over 54 million disease episodes worldwide in 2017, with over 145 000 deaths and the highest hospitalisation rates consistently observed among older adults [9]. RSV is also increasingly recognised as an important cause of severe respiratory disease in older adults, with morbidity often comparable to or exceeding that of influenza and COVID-19 [10]. However, evidence on clinical features, management, outcomes, and health care utilisation of RSV in older adults remains limited, and RSV-associated hospitalisations in this group are likely underestimated because of under-ascertainment, contributing to uncertainty in burden estimates [7, 11]. Recently approved vaccines for RSV include Arexvy, Abrysvo, and mResvia and complement existing vaccines targeting COVID-19, influenza, pneumococcal disease, and pertussis. Several new and combination vaccines, including candidates covering influenza, RSV, SARS-CoV-2, and hMPV, are also in development.

Since the end of the COVID-19 public health emergency, circulation of other respiratory viruses has rebounded, with seasonal influenza and RSV activity now matching or exceeding pre-pandemic levels [12, 13, 10]. This resurgence highlights the importance of strengthened surveillance to monitor disease burden, characterise epidemiologic trends, and support VE evaluations. Sentinel surveillance for SARI provides timely patient-level data and has become an international standard for monitoring influenza-associated morbidity and mortality [14]. During the COVID-19 pandemic, SARI surveillance was expanded to include SARS-CoV-2, and the ECDC case definition was modified to remove fever as a required symptom, increasing system sensitivity, an approach particularly appropriate for pathogens such as RSV, for which afebrile

presentation is common among older adults [3]. The widespread adoption of multiplex PCR diagnostics, following ECDC recommendations [15], also now enables SARI platforms to capture multiple respiratory pathogens concurrently. These systems have supported numerous influenza and CVE studies, and have the potential to expand VE assessments to additional pathogens.

id.DRIVE is a public-private partnership built upon DRIVE² [16] and COVIDRIVE monitoring CVE since September 2021 ([Home - IDDRIVE](#)). Using SARI data collected across Europe, COVIDRIVE was conducting brand-specific CVE studies for market authorisation holders as part of their European regulatory obligations, with methodological alignment across the different post-authorisation studies. Leveraging its expertise in influenza and CVE studies, the partnership expanded its scope of research to become an infectious disease study platform with primary focus on viral respiratory disease in adults.

This protocol describes three study modules that investigate the same study population and collect information via a common data collection. The surveillance module serves as the umbrella study. The study aims per module are listed below.

- **Surveillance Module:** To establish sentinel SARI surveillance for the continuous monitoring of the burden of disease caused by multiple viral respiratory pathogens in adults, and to assess associated virological and clinical trends
- **CVE Module:** To continuously estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in adults with SARI.
- **RSV VE Module:** To continuously monitor VE of RSV vaccine(s) against RSV-related SARI hospitalisations in adults using a network of hospitals.

² DRIVE is an Innovative Medicines Initiative (IMI) project that has provided yearly brand-specific influenza vaccine effectiveness estimates to the EMA.

10 OBJECTIVES **Surveillance Module**

10.1.1 Primary objectives

- To calculate the proportion of laboratory samples positive for each viral respiratory pathogen of interest⁽¹⁾, among adult patients hospitalised with SARI.
- To characterise adult SARI patients (including age, gender, protective and risk factors, specific treatments, and healthcare utilisation outcomes⁽²⁾), overall and by viral respiratory pathogen of interest⁽¹⁾.

10.1.2 Secondary objectives

- To investigate the prevalence of co-infection with the viral respiratory pathogens of interest⁽¹⁾, in adult patients hospitalised with SARI, and the impact on healthcare utilisation outcomes⁽²⁾.
- To explore risk factors of pathogen-specific SARI⁽³⁾, healthcare utilisation outcomes, and the presence of co-infection.

10.1.3 Exploratory objectives

- To calculate pathogen-specific SARI incidences and describe trends in hospitalised adults (by time period, country, and level of severity).
- To perform feasibility assessments for future respiratory disease studies within the id.DRIVE Study Network (e.g., effectiveness studies, impact studies).

⁽¹⁾ SARS-CoV-2, Influenza A/B, RSV A/B, Adenovirus, Parainfluenza viruses (1-4), hMPV, HRV, HEV, human coronaviruses (229E/NL63/OC43/HKU1), and human bocavirus (1-4).

⁽²⁾ Healthcare utilisation outcomes are defined by outcome (hospitalisation without ICU admission or in-hospital death; ICU admission without in-hospital death; in-hospital death), by the need for respiratory support (none; non-invasive ventilation; mechanical ventilation; ECMO), discharge destination and length of stay.

⁽³⁾ Factors associated with an infection by pathogen of interest versus not being infected by the pathogen of interest among adult patients hospitalised with SARI

10.2 CVE Module

10.2.1 Primary objective

- 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 the selected comparator group.

10.2.2 Secondary objectives

- 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 the selected comparator group:
 - by SARS-CoV-2 genetic variants,
 - within populations of special interest (e.g., specific age groups, specific immunocompromised or chronic conditions, pregnant women),
 - by time since last COVID-19 vaccine dose,
 - by time between COVID-19 vaccine doses,
 - by number or type(s)⁽¹⁾ of the COVID-19 vaccine doses given prior to the last dose.

10.2.3 Exploratory objectives

- 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 the selected comparator group:
 - by severity level⁽²⁾,
 - by calendar time⁽³⁾,
 - by history and calendar time⁽³⁾ of prior SARS-CoV-2 infection
- 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 the selected comparator group.

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

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

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

10.3 RSV VE Module

10.3.1 Primary objective:

- To estimate RSV VE for brand-specific RSV vaccine against hospitalisation due to laboratory-confirmed RSV infection overall or within a specific timeframe from vaccination in adult patients with SARI, eligible to receive the vaccine.

10.3.2 Secondary objectives

- As primary objective, but stratified by/subgroup analyses among:
 - RSV subtype A and B,
 - populations of special interest (e.g., age groups, gender, chronic medical condition risk groups, among the immunocompetent, among those with co-administered vaccines),
 - time since vaccination,
 - history and time since prior RSV infection within the last 12 months,
 - country and study site,
 - SARI severity level.

10.3.3 Exploratory objectives

- Descriptive analysis of vaccinated and unvaccinated cases and controls: demographic, clinical, severity, length of hospital stay, and laboratory characteristics.

11 METHODS

11.1 Study Design

11.1.1 Surveillance Module

This study is an observational multi-country, multi-centre, hospital-based surveillance study of viral respiratory pathogens in adults hospitalised with SARI.

11.1.2 VE Modules

A multi-country, multi-centre, hospital-based study with TNCC design is used for these modules.

11.2 Study Contributors

The participating Study Contributors (study sites) are either individual hospitals or hospital networks. The data collection will be a prospective data collection from primary and secondary data sources. In some sites, data will additionally be retrieved from the existing hospital databases and linked data. Sites can also collect data retrospectively if information on all critical variables (exposure, case/control status, viral pathogens, demographics) can be collected retrospectively.

11.3 Study Population inclusions and exclusion criteria

For all 3 modules:

Adults (18 years and older) presenting at the participating hospitals during the study period who are:

- Hospitalised and meet the SARI case definition.
- Willing and able to provide informed consent, when applicable, obtained from the patient or from the patient's Legally Acceptable Representative(s) (LAR).
- Only for sites in the United Kingdom: participants are excluded if deemed mentally incapacitated to provide informed consent due to a condition other than SARI, as defined by the United Kingdom Mental Capacity Act 2005.

Additional inclusion and exclusion criteria for the VE Modules:

- Willing and able to provide the protocol-required respiratory specimen(s).

Additional inclusion criteria CVE module:

- Ever eligible for COVID-19 vaccination prior to hospital admission.

Additional inclusion criteria RSV module:

- Eligible to receive RSV vaccination following to their residence country/regional immunisation programme prior to hospital admission

Addition exclusion criteria CVE module:

- COVID-19 hospitalisation within three months prior to the current admission. Hospital transfers are not considered as a prior hospitalisation.
- Received last vaccine dose with other than EMA-approved COVID-19 vaccine brand (EMA approval status at time of hospitalisation)

11.4 Study Period

The study provides year-round surveillance, with a study period lasting minimum 12 months with possibility to extend.

11.5 Study Outcomes and Endpoints

11.5.1 Surveillance Module

The outcome of interest for the primary objectives will be **laboratory-confirmed infection** (Section 11.7.4) with one of the viral respiratory pathogens of interest in patients hospitalised with SARI symptoms, and laboratory-confirmed co-infection (Section 11.7.5) for the secondary objectives.

Healthcare utilisation outcomes of interest are:

- **Level of severity** (Section 11.5.5.1)
- **Discharge destination** (Section 11.7.6)
- **Length of stay** (section 11.5.5.3)

Pathogen-specific SARI incidences will be calculated to address the first exploratory objective (Section 11.11.5). The denominator will be based on the sum of the catchment populations covered by the Study Contributors [17].

Feasibility assessments for future respiratory disease impact and effectiveness studies will be made as described in Section 11.11.6.

11.5.2 CVE Module

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

The primary endpoint is hospitalisation due to laboratory-confirmed SARS-CoV-2 infection in adult patients with SARI.

11.5.2.2 Secondary endpoint: SARS-CoV-2 genetic variants

Genomic sequencing is an optional component of the study. Sites opting into this module will perform sequencing using commercially available molecular kits. For prospective data collection, participating sites aim to sequence all SARS-CoV-2-positive cases. For retrospective data, sequencing results will be used if present in medical records.

11.5.3 RSV VE Module

11.5.3.1 *Primary endpoint: laboratory-confirmed RSV*

The primary endpoint is hospitalisation due to laboratory-confirmed RSV infection in adult patients with SARI who were eligible for vaccination in their country.

11.5.3.2 *Secondary endpoint: detection of RSV subtypes A and B*

The secondary endpoints in patients hospitalised with SARI symptoms include the detection of RSV subtypes A and B.

Information on the RSV subtypes (A and B) will be collected to the extent possible, preferably on all confirmed RSV cases when sample quality allows.

11.5.4 Case and controls (VE modules)

11.5.4.1 *Cases ('test-positive cases')*

Test positive case : patients who meets the SARI case definition AND tests positive for SARS-CoV-2 or RSV using RT-PCR or similar molecular assays, with specimens collected between 14 days up to 72 hours after hospital admission.

11.5.4.2 *Control ('test-negative control')*

Test negative control : patients who meets the SARI case definition AND have all respiratory samples testing negative for SARS-CoV-2 or RSV, respectively using RT-PCR or similar molecular assays, with specimen(s) collected between 14 days prior to and up to 72 hours after hospital admission.

Alternative control definitions may be explored by means of sensitivity analyses.

11.5.5 Severity levels

11.5.5.1 *SARI severity levels*

The following three mutually exclusive categories will characterise the severity of the hospitalisation:

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

Additional severity levels may be defined by Study team, based on data availability.

11.5.5.2 *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)

Additional respiratory support severity levels may be defined by the Study Team, based on data availability.

11.5.5.3 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.

Hospitalisation that takes place within three months of the discharge from another SARI hospitalisation will be considered as part of the same episode. The length of stays of the admission will be summed.

11.6 Exposure definitions (VE modules)

11.6.1 CVE module

1. Vaccinated with at least one dose: vaccinated with at least one 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 > six months ago: received last COVID-19 vaccine dose > six months prior to symptom onset⁽⁴⁾
7. Vaccinated with seasonal COVID-19 vaccine with the brand of interest⁽¹⁾: received the seasonal COVID-19 vaccine brand of interest within the season of interest⁽⁵⁾ and ≥ 14 days before symptom onset
8. Unvaccinated with seasonal COVID-19 vaccine: did not receive any COVID-19 vaccine within the season of interest⁽⁴⁾⁽⁵⁾
9. Other: additional vaccine exposure 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.

11.6.2 RSV VE module

1. Vaccinated with the RSV vaccine during the study period of interest: 'Vaccinated' study participants were vaccinated with the exposure of interest (e.g., single dose/primary vaccination/at least one dose) of the RSV vaccine during the study period of interest (e.g., ever/the last 12 months), within the appropriate timeframe for the product to be effective (e.g., ≥ 15 days) prior to SARI symptom onset, where day one is the date of vaccination.
2. Unvaccinated during the study period of interest: 'Unvaccinated' study participants did not receive any RSV vaccine (investigational or licensed) during the study period of interest (e.g., never/the last 12 months).
3. Recently vaccinated with the RSV vaccine: 'Recently vaccinated' study participants were vaccinated with the exposure of interest (e.g., single dose/primary vaccination/at least one dose) of the RSV vaccine during the study period of interest (e.g., ever/the last 12 months), within the appropriate timeframe for the product to be ineffective (e.g., < 15 days) prior to SARI symptom onset.
4. Other: Additional vaccine exposure definitions might be developed depending on the real-life use of the RSV vaccines.

11.7 Definitions

11.7.1 Hospitalised patient

Persons 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 (i.e., admission to the referring hospital).

11.7.2 SARI patient

A SARI patient 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].

11.7.3 Extended SARI case definition (VAHNSI only)

Additionally, an extended SARI case definition is uniquely applicable at the Study Contributor VAHNSI. This definition is designed to more accurately capture exacerbations of underlying cardiopulmonary disease (e.g. acute exacerbation of COPD, asthma, or CHF).

In this extended case definition a SARI patient is defined as a **hospitalised person** with a suspicion of a respiratory infection or exacerbation of underlying COPD, asthma, or CHF, with **at least one** of the following symptoms, signs, or confirmed SARI evidence:

- cough (new or worsening)
- fever ($\geq 38\text{ C}^\circ$)
- shortness of breath (new or worsening)
- sudden onset of anosmia, ageusia or dysgeusia
- runny nose (rhinorrhea), nasal congestion, or coryza
- sore throat or hoarseness
- sputum production (new or worsening)
- wheezing (new or worsening)
- chills or rigors
- abnormal auscultatory findings suggestive of pneumonia
- radiographic finding consistent with pneumonia

with **symptom onset within the last 14 days** prior to hospital admission.

11.7.4 Laboratory-confirmed infection

For each studied pathogen, a laboratory-confirmed infection is a RT-PCR or multiplex RT-PCR on a respiratory specimen(s) collected between 14 days prior to and up to 72 hours after hospital admission. If all samples collected in this time frame are negative, the patient is considered as not having any laboratory-confirmed infection.

11.7.5 Laboratory-confirmed co-infection

Laboratory-confirmed co-infection is defined as two or more laboratory-confirmed infections on any respiratory sample taken in the accepted timeframe (collected between 14 days prior to and up to 72 hours after hospital admission).

11.7.6 Discharge destination

Destination at hospital discharge will be specified using the following categories:

- Home
- Home with nursing care
- Transfer to another hospital
- Rehabilitation centre
- Nursing home or other long-term care facility
- Other
- No information

11.7.7 Risk groups

Risk groups will consist of those patients with specific chronic conditions (e.g., immunocompromised), long-term care facility residents, and the elderly. Specific

categorisations of risk groups may be provided in the study module specific Statistical Analysis Plans (SAPs).

11.8 SARI patient identification

Hospitalised SARI patients will be identified based on the defined SARI definition (11.7.2). Depending on the Study Contributor, the SARI patient's point of identification will be different (e.g., during consultation in the emergency department, 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). For every participating study site, the patient flow will be documented in detail.

11.9 Pathogens of interest and laboratory testing

11.9.1 Pathogens of interest

The pathogens of interest are as follows:

- SARS-CoV-2
- Influenza:
 - o Influenza A:
 - A-H1
 - A-H3
 - o Influenza B
- RSV:
 - o RSV A
 - o RSV B
- Parainfluenza:
 - o Type 1
 - o Type 2
 - o Type 3
 - o Type 4
- hMPV
- HRV
- HEV
- Adenovirus
- Human coronavirus:
 - o Type 229E
 - o Type NL63
 - o Type OC43
 - o Type HKU1
- Human bocavirus:
 - o Unspecifiedor if available:
 - o Type 1
 - o Type 2
 - o Type 3
 - o Type 4

Additional pathogens may be added to the study depending on epidemiological trends (e.g., inclusion of an emerging pathogen).

11.9.2 Laboratory testing

To the extent possible, clinical specimens will be collected from the patients eligible for the study as part of routine clinical sampling for diagnostic work-up. However, depending on local practice, additional sampling for the purpose of the study may be required. Samples collected between 14 days prior to and up to 72 hours after admission are accepted. Nasopharyngeal or oropharyngeal swabs are recommended. Additional respiratory specimens are accepted (e.g., nasal swabs, oropharyngeal swab, saliva, mouth wash, bronchoalveolar lavage, aspirates). Sample type will be recorded.

All patients tested negative for RSV prior to hospitalisation will be re-tested at hospital admission.

The respiratory samples will be tested within the local laboratory infrastructures of the participating Study Contributors, for at least SARS-CoV-2, influenza A/B and RSV A/B. In addition, some study contributors will additionally test for other viral respiratory pathogens such as adenovirus, parainfluenza 1-4, hMPV, HRV, human enterovirus (HEV), human bocavirus 1-4, and human coronaviruses (229E/NL63/OC43/HKU1). The testing will be performed by using validated RT-PCR, or another RNA amplification system with at least the same sensitivity as RT-PCR (e.g., TMA).

Further subtyping will be performed on specimens that test-positive for:

- RSV:
 - Subtype A and B
- Influenza:
 - Type A and B
 - Subtypes A H1, Influenza A H3

11.10 Study variables

Information will be collected on patient demographics (e.g. age and gender), risk factors (selected chronic conditions, such as chronic pulmonary disease, cardiovascular disease and immunodeficiency disorders, as well as for example BMI), previous respiratory infections, vaccination history for respiratory illnesses. In addition, health care resource use indicators associated with the current hospitalization will be collected such as respiratory support, ICU stay. The complete dataset can be found in the id.DRIVE Common dataset case report form.

11.11 Statistical Methods

A SAP will be developed prior to the conduct of the analysis. The SAP specifies all statistical analyses, including sensitivity analyses, to be conducted and will include table shells and mock figures. There will be one common SAP for the Surveillance module and study-requestor specific SAPs for the VE modules.

11.11.1 Surveillance Module

11.11.1.1 Sample Size Considerations

The primary objective of this surveillance study is to determine the proportion of relevant pathogens among the admitted SARI patients. Table 1 below demonstrates the anticipated precision (by Clopper-Pearson Binomial Exact 95% confidence interval [18]) corresponding to the expected proportion of each primary pathogen of interest. The precision (margin of error) was calculated as the half-width of the interval:

$$\text{Margin of error} = \frac{Upper_{CI} - Lower_{CI}}{2}$$

where $Upper_{CI}$ and $Lower_{CI}$ denote the upper value and lower bounds of the 95% CI. To address potential variability in annual recruitment, precision estimates were calculated under multiple scenarios, with projected estimated enrolment ranging from 4,000 to 10,000 patients in increments of 1,000. Based on data from the id.DRIVE platform for the 2024-2025 season, the estimated prevalences of COVID-19, RSV, and influenza were 9%, 5%, and 12%, respectively [19]. Accordingly, precision calculations were performed assuming prevalence ranges of 6-11% for COVID-19, 4-8% for RSV, and 10-15% for influenza.

Table 1. Anticipated precision regarding the prevalence corresponding to the expected proportion of the pathogens of interest with various (anticipated) numbers of admitted SARI patients.

Number of admitted SARI patients	Pathogen of interest	Minimum expectation		Maximum expectation	
		Prevalence case among admitted SARI patients (%)	Precision (%)	Prevalence case among admitted SARI patients (%)	Precision (%)
3,000	COVID	6	0.867	11	1.136
	RSV	4	0.718	8	0.988
	Influenza	10	1.090	15	1.294
4,000	COVID	6	0.749	11	0.982
	RSV	4	0.620	8	0.853
	Influenza	10	0.942	15	1.119
5,000	COVID	6	0.668	11	0.877
	RSV	4	0.553	8	0.762
	Influenza	10	0.842	15	1.000
6,000	COVID	6	0.609	11	0.800
	RSV	4	0.504	8	0.695
	Influenza	10	0.767	15	0.912
7,000	COVID	6	0.564	11	0.740
	RSV	4	0.466	8	0.643
	Influenza	10	0.710	15	0.844
8,000	COVID	6	0.527	11	0.692
	RSV	4	0.436	8	0.601
	Influenza	10	0.664	15	0.789
9,000	COVID	6	0.496	11	0.652
	RSV	4	0.411	8	0.566
	Influenza	10	0.625	15	0.743
10,000	COVID	6	0.471	11	0.618
	RSV	4	0.389	8	0.537
	Influenza	10	0.593	15	0.705

The precisions provided by these scenarios are within an acceptable range [20]. Note that the margin of error will increase if the number of recruited patients decreases. Further sample size justifications for a specific data collection season, as well as for other study objectives, will be detailed in the surveillance SAP.

11.11.1.2 Total SARI and pathogen-specific SARI numbers

The total number and proportion of positive laboratory samples for each respiratory pathogen of interest (see section 11.9.1) and co-infections (see section 11.7.5) will be provided. Counts and proportions (% along with 95% exact binomial confidence intervals) will be calculated by calendar time, by Study Contributor, by country, and by age and risk groups of interest. Co-infections (%) will be described, by number of pathogens, by combination of pathogen type, by healthcare utilisation outcomes, by

age groups, and by presence of chronic conditions. Visualisations of these counts and percentages over time will be provided.

11.11.1.3 *Demographic and clinical characteristics of SARI*

Demographic and clinical characteristics of the SARI patients will be provided, overall and by SARI-causing pathogen (type and/or subtype), including age groups, gender, symptoms, presence of chronic conditions, BMI, vaccination status, having had preventive monoclonal antibodies, pregnancy, use of antiviral or virus-specific monoclonal antibody therapy, long-term care facility residence, and healthcare utilisation outcomes. Overall clinical characteristics will also be provided, stratified by calendar month of disease-onset.

11.11.1.4 *Healthcare utilisation outcomes*

Logistic regression will be used to explore risk factors of pathogen-specific SARI hospitalisation and the presence of co-infections (by number of co-infections and involved pathogens, when feasible), while ordinal logistic regression will be used for healthcare utilisation outcomes (as defined in Section 11.11.1.4). Potential risk factors include age, gender, and chronic conditions.

11.11.1.5 *Incidence rates*

As part of the exploratory objectives, pathogen-specific SARI incidence rates (per 100,000 person-years) will be calculated and monitored over time to identify trends using the following formula [21]:

$$\text{Incidence rate} = \frac{\text{Number of events in specified period}}{\text{Average number of persons at risk during the same specified period}}$$

The number of events in a specific period will be calculated by multiplying the percentage of SARI patients testing positive for a specific pathogen within the selected time period with the total number of SARI patients (included in the surveillance study module and missed SARI patients identified by screening logs). Alternatively, the untested SARI events may be accounted for by multiple imputation of expected testing results (e.g., for RSV [6, 7]).

Incidence estimates will not be calculated unless denominator populations can be identified and there is an accurate process for identifying hospitalised SARI patients missed by the surveillance study module. Study Contributor-specific denominator data will be based on the reported catchment population of each hospital, expected to reflect the average number of persons at risk during that same time period. When exact hospital catchment populations are unknown, other sources of information will be pursued (e.g. administrative boundaries and hospital bed capacity). To derive age-specific denominator populations for each site, regional age-distribution data will be used where available. If regional data are unavailable, national age-distribution data will be applied. These age-specific distributions will be used to model the demographic

structure of each site's catchment population. Finally, these outputs will be used to calculate age-specific incidence rates of SARI hospitalisation by attributable pathogen.

11.11.1.6 Feasibility assessments

To assess the feasibility of the id.DRIVE Study Network to be leveraged for future effectiveness or impact studies, e.g., for new RSV, COVID-19 or influenza vaccines, detailed data on vaccination against respiratory pathogens will be collected. The data will be reviewed for quality, including data source for ascertainment (e.g., medical records, registries) and completeness of the data (e.g., product brand/product, date of vaccinations) by Study Contributor. Product-specific coverages, in addition to total SARI and pathogen-specific case numbers, will allow for sample-size target estimations for future studies.

11.11.2 VE Modules

11.11.2.1 Sample Size Considerations

The technical considerations for the calculation of the targeted samples sizes will be detailed in Study Requestor specific-SAP. The sample size requirements strongly depend on the objectives (primary vaccination, booster vaccination, seasonal vaccination), case-control ratio, overall vaccination coverage, share of the different vaccine brands, as well as the anticipated VE. As such, the sample size requirements and assumptions will be different for each vaccine brands.

In case the parameter settings used for these sample size calculations are very different from what is observed in the study, the sample size calculations will be updated accordingly with the observed outputs.

11.11.2.2 Time to number of cases

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

11.11.3 Data analysis

11.11.3.1 Context information

Context information will be provided by describing the circulating pathogen of interest (e.g. SARS-CoV-2 variants or RSV subtypes) during the study period in the countries (or regions) where the Study Contributors are located. National (or regional) vaccination recommendations over time will be described (including licensed age groups, contraindications, number of doses and timing between doses). The external data sources used to describe the distribution of pathogens of interest (e.g. SARS-CoV-2 or RSV), vaccination coverage, and vaccination recommendations will be specified in the Study-specific SAP.

11.11.3.2 Descriptive analysis of demographics and baseline characteristics

For every brand of interest, visualisations and tabular summary based on the final brand-specific analytical dataset will be produced, including:

- Figure and/or Table representing the number of test-negative controls and test-positive cases (possibly by variants or subtypes) over time
- Figure and/or Table representing the distribution of relevant covariates among test-positive cases and test-negative controls,
- Table describing the characteristics of test-positive cases and test-negative controls as predefined in the Study-specific SAP.

11.11.3.3 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 missingness is independent of the test status of pathogen of interest during the SARI episode (missing completely at random assumption). Provided the described mechanism for missingness is correct, a complete case analysis (CCA) will not yield biased results. Accordingly, the primary analysis will use the CCA approach, excluding observations with missing data on the outcome, the exposure of interest or any covariates included in the final logistic regression model. If more than 10% of SARI patients have missing covariate information, CCA may become inefficient, and alternative methods -such as multiple imputation or augmented CCA - will be explored.

11.11.3.4 Vaccine effectiveness

VE estimates will be adjusted for symptom-onset date at minimum to address time-varying confounding. The confounder-adjusted VE estimates will also include adjustment for other potential confounders, including age, gender, and comorbidities (for example: number of chronic conditions).

The VE against laboratory-confirmed [*pathogen of interest (e.g. SARS-CoV-2/RSV)*] 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 test-positive cases to the odds of vaccination among test-negative controls.

Adjustments will be implemented by including the relevant terms in the logistic regression models. Calendar time and age will be modelled using (penalised) cubic splines to allow for flexible adjustment. Alternative specifications (e.g., natural splines, B-splines) may be considered. Additional covariates may be evaluated for inclusion into the models; if applicable, the selection of relevant covariates and the model building procedures will be detailed in the Study Requestor-specific SAP.

Heterogeneity between countries and Study Contributors may exist due to differences in recruitment, local differences in the intensity of the epidemic and healthcare practices. Potential intra-cluster between subjects from the same study site is expected and will be accounted for by using GEE, or random effects meta-analysis models (RE-MA) when individual data from some Study Contributors cannot be obtained to perform the GEE analysis due to certain data restriction conditions. If some Study Contributors are networks that have hospitals which are very different (e.g. geographically separated), then clustering could be defined at the hospital level for these networks. However, similarities between these hospitals may remain due to being part of the same hospital network, in which cases these would not be treated as being independent of each other

Heterogeneity across study sites may also be addressed using Generalised Additive Models (GAM), which provide subject-specific (SS) estimates, in contrast to GEEs that yield population-averaged (PA) estimates [22]. The OR derived from a GAM compares the odds of vaccination among test-positive cases to test-negative controls within the same Study Contributor, conditional on covariates. This approach requires inclusion of either fixed or random effects for Study Contributors within a multivariable model. In contrast, GEE produces an OR comparing vaccination odds across all sites. While GEE is generally more efficient than GAM, it does not allow direct estimation of site-specific VE. As an alternative, Study Contributor-specific VE estimates under GEE can be obtained by conducting separate analyses using patient-level data from each Study Contributor, where the GEE model simplifies to a multivariable logistic regression. When a study opts to use GAM models, incorporating a fixed-effect term for study site within a multivariable logistic regression framework is recommended due to its simplicity of implementation and the fact that no additional adjustments to standard errors are required.

Finally, the RE-MA approach should be considered only when aggregated data are available for some or all Study Contributors. This method offers the advantage of easily incorporating estimates from Study Contributors that are unable to share patient-level data. In addition, RE-MA provides direct estimates of site-specific VE and is generally regarded as intuitive, facilitating communication among researchers [22]. However, its main limitations include reduced statistical power and potential convergence issues, particularly when the outcome of interest is rare or when some Study Contributors have relatively small sample sizes [23]. When most, if not all study sites can share individual patient data, GEE is generally preferred.

11.11.3.5 Matching

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

11.11.3.6 Absolute and relative VE

When the comparator group consists of unvaccinated subjects, the term absolute VE 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 VE 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 vaccine within the season of interest.

Exposure definitions for these comparator groups are defined in section 11.6. A rationale for the selection of the appropriate comparator group(s) will be given and each time, the interpretation of the VE results will be done in the light of the comparator group used to calculate the VE estimates.

11.11.3.7 Sensitivity analyses

Multiple sensitivity analyses will be conducted, with specifications tailored to the respective modules. Each module will include its own set of sensitivity analyses to assess the robustness of findings under alternative assumptions and/or modelling strategies. All sensitivity analyses will be pre-specified in the Study Requestor-specific SAP.

11.11.3.7.1 CVE Module

Various sensitivity analyses will be conducted to support the findings in the main analyses. These may include:

- Evaluating the impact of the time interval between symptom onset date and swab collection;
- Exploring alternative endpoint definitions (e.g. excluding subjects with vaccine-preventable viruses from the test-negative control group);
- Assessing potential confounding due to correlations in vaccination behaviour for other vaccine-preventable pathogens (by additionally adjusting for vaccination status against these pathogens in logistic regression models);
- Examining different SARI case definitions;
- Excluding subjects who received monoclonal antibodies and/or other anti-SARS-CoV-2 products for treatment or pre-/post-exposure prophylaxis prior to hospitalisation, if such use is substantial in the population.

11.11.3.7.2 RSV VE Module

Multiple sensitivity analyses will be conducted to evaluate the robustness of the findings. These may include:

- Assessing the impact of different SARI case definitions (id.DRIVE case definition³, WHO-RSV case definition⁴);
- Assessing the impact of different control definitions (e.g. triple negative);
- Evaluating the effect of alternative sample types of RSV detection;
- Examining the influence of varying time intervals between hospitalisation and swab collection to assess potential nosocomial infections;
- Investigating the impact of including participants co-enrolled in interventional trials;
- Restricting analyses to patients hospitalised primarily for respiratory infection;
- Restricting analyses to patients who were long-term care facility residents prior to hospitalisation as a proxy for frailty;
- Excluding outlying or influential Study Contributors;
- Excluding patients who received monoclonal antibodies or other RSV products for treatment or pre-/post-exposure prophylaxis prior to hospitalisation, if such use is substantial;
- Exploring unmeasured confounding or biases using negative control methods, including negative control.

11.12 Data Management

Data collection, statistical analysis, and preparation of the study report are activities firewalled from the Study Requestor(s) to avoid perception of undue influence on the study report and result interpretation.

All data are collected from pre-existing medical files (registries and/or patient files), and are therefore considered as a secondary data collection, except for laboratory results that will be collected specifically for the purpose of the study and are considered as a primary data collection (Section 11.9 and Section 11.10).

11.12.1 Data management at Study Contributor level

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

³ An id.DRIVE definition of SARI (defined as requiring hospitalisation with a suspicion of a respiratory infection with symptom onset within the last 14 days prior to hospital admission, having at least one of the following symptoms: cough, shortness of breath, fever ($\geq 38\text{ }^{\circ}\text{C}$) or sudden onset of anosmia, ageusia or dysgeusia) will be used in sensitivity analyses. This SARI definition is modified from the latest ECDC case definition (specifying “suspicion of respiratory infection”). EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL (2023). Core protocol for ECDC studies of COVID-19 vaccine effectiveness against hospitalisation with SARI, laboratory-confirmed with SARS-CoV-2 or with seasonal influenza - Version 2.0. Available from: <https://www.ecdc.europa.eu/en/publications-data/core-protocol-ecdc-studies-covid-19-vaccine-effectiveness-against-0> [Accessed: 17-08-2023]].

⁴ A World Health Organisation (WHO)-expanded definition of RSV-SARI (severe disease – defined as requiring hospitalisation AND acute – defined as onset within the last 10 days AND respiratory infection – defined as having at least one of the following: shortness of breath or cough) will be used in sensitivity analyses. [Source: <https://www.who.int/teams/global-influenza-programme/global-respiratory-syncytial-virus-surveillance/case-definitions>]

11.12.2 Data flow

1. The Study Contributor collects the data and enters/uploads it in the electronic data capture (EDC) system.
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 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 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.

11.13 Quality Management

11.13.1 Independent Scientific Committee

The ISC is composed of independent external experts (from organisations or institutions which are not partners of id.DRIVE) with expertise/experience relevant for study modules.

The roles and responsibilities of the ISC are the following:

- reviews and makes recommendations for protocols;
- reviews and makes recommendations for study reports and publications.

11.13.2 Quality Assurance and Audit Committee

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

11.13.3 Monitoring

Monitoring activities include:

- During the site initiation visit, the processes for study conduct are assessed with the Study Contributor.
- 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 patients enrolled), to ensure regular data input to the id.DRIVE EDC system, and to discuss potential protocol deviations or other issues related to the study conduct.
- Sites will be asked to keep high-level screening logs (including number of SARI patients missed or not consented for the study with age group), as they may affect interpretation of trend data.
- 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 independent ethics committee (IEC), auditors and representatives from regulatory authorities direct access to all study-related documents. Efforts will be made to maintain participant confidentiality at all times.

11.13.4 Data quality checks at central level

Programmed checks are run on EDC system-extracted data and the identified data issues are manually queried in EDC system every two weeks. After the Study Contributor responds to the queries by updating or confirming the data entered in EDC system, P95 closes the queries. Per agreement, the identified data issues are also sent to the corresponding Study Contributors. All the queries should be closed before database lock. In addition, whenever possible our data is monitored against external references on for example vaccination coverage.

11.14 Limitations of the Research Methods

11.14.1 Surveillance study

The following challenges and limitations for the real-world evaluation of SARI-causing viral pathogens have been identified at the time of writing this protocol.

With sentinel surveillance, generalisability may be limited as social and demographic factors are not uniform across a country and therefore the catchment population of a sentinel network may not be comparable with the remaining population of a country. Under-detection of pathogens of interest may occur. RT-PCR sensitivity is influenced by several factors, including specimen type, timing of collection, assay performance and quality of sampling technique. Sensitivity also differs by pathogen, with larger under-detection rates for certain viruses, such as RSV [24]. To reduce under-detection, sites use high sensitivity assays, collect specimens within 72 hours of hospital admission and record factors known to affect RT-PCR sensitivity [11]. As part of the standard of care at sites, study staff are also trained in procedures for collecting and handling respiratory specimens for the diagnosis of viral respiratory pathogens.

With RT-PCR, a positive result is highly specific for the presence of the viral pathogen nucleic acid of interest. False positives only occur in the rare event of laboratory contamination. However, RT-PCR does not differentiate between viable and nonviable virus, and a positive result may indicate an older infection, non-causal to the current SARI episode. This would be more frequent with prolonged viral shedding, such as COVID-19 [25]. Notably, as only results of specimens sampled within 72h after admission are included, inclusion of hospital-acquired infections will be avoided.

The use of different RT-PCR or multiplex assays across Study Contributors may impact the comparability across sites or with other surveillance systems. However, the laboratory tests used by the Study Contributors are those used for the diagnostic work-up of patients admitted and are either commercial assays with known high sensitivity, specificity and/or concordance [26] or in-house developed assays that have undergone quality and/or validation processes.

Depending on each Study Contributor, the proportion of hospitalised SARI cases captured and included in the surveillance study module will vary. The feasibility of generating pathogen-specific incidence estimates will be evaluated for each site, and incidence will be reported only when considered valid. Proxy denominator populations may limit level of detail available, such as the ability to calculate incidence by specific chronic conditions. However, even when incidence cannot be determined, the surveillance data will still provide important information, including the proportional contribution of chronic conditions among patients with a given pathogen and comparisons of these proportions across pathogens.

Several different SARI definitions (WHO SARI definition, ECDC SARI definition) are currently in use in epidemiological studies and surveillance systems of respiratory pathogens, each with different levels of sensitivity that limit comparability of findings. For this study we apply an (extended) ECDC SARI case definition. However, because SARI symptom type and date of symptom-onset are also collected, sensitivity analyses will be performed using alternative SARI case definitions (WHO SARI definition, modified ECDC SARI definitions)

11.14.2 CVE Module

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 [27]. 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 [28]. 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 [29], 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 [30, 31], 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 [32-35]. 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 [36]. 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 [34]. 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 [37]. 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 [38, 39]. 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 [40]. 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 [41]. 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 in all sites. 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, obtaining sufficient samples to obtain accurate estimates for primary and secondary objectives may be a challenge.

11.14.3 RSV VE Module

Due to high demand, cost-effectiveness, limited vaccine supplies and guidance from expert committees, Western countries often prioritise high-risk groups such as the elderly, residents in care facilities, and those with specific chronic conditions. This prioritisation creates potential confounding factors in studies on VE.

Untangling waning of vaccine-induced immunity, varying VE against different RSV subtypes, and infection-acquired immunity is challenging due to the complex interaction of these factors.

Infection-acquired immunity protects against re-infection but may wane and act as an effect modifier of VE. Hybrid immunity, combining infection-acquired and vaccine-induced immunity, is suggested for optimal protection against severe disease. However, identifying past RSV infection poses challenges due to potential underreporting or misclassification, especially with clinical-based diagnoses and the absence of serological results. This prior infection status could also introduce confounding, influencing vaccination decisions.

The TNCC study design minimises unmeasured confounding tied to general health care-seeking behaviour. However, specific health practices may still confound results. Vaccination uptake may be higher among individuals strongly adhering to preventive practices such as social distancing, reducing natural infection risk. Conversely, being vaccinated may lead to a false sense of security, relaxing precautions and increasing exposure risk. Additionally, those likely to get vaccinated against RSV may also favour influenza, SARS-CoV-2, and/or pneumococcal vaccinations, potentially biasing results. Sensitivity analyses redefining control groups will explore this bias. In this study, exposure ascertainment is based on multiple sources including vaccine registries, vaccination cards and medical records. Although vaccination status captured in medical records is neither validated against primary records nor validated verbally with the patient, misclassification is likely to be limited: complete exposure data is required for a participant to be retained in the id.DRIVE study (mandatory variables included date of administration, dose number and vaccine brand).

In some countries (e.g., 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 those countries.

The PROMISE initiative (Preparing for RSV Immunisation and Surveillance in Europe) generic RSV VE protocol recommends the exclusion of persons with a contraindication to the RSV vaccine being studied in order to only capture the eligible population. Such patients are not excluded from the present study as vaccine contraindications cannot be collected. However, numbers are expected to be small.

RT-PCR has a high specificity and sensitivity if sufficient viral load is present in the sample, however, a single respiratory swab may miss around a half of RSV infections among older adults [42]. Diagnostic inaccuracies pose potential bias, influenced by factors like sampling technique, specimen type, number of specimens [43, 42], and timing with respect to symptom onset. In RSV RT-PCR, declining sensitivity over time may yield more false negatives, potentially underestimating VE as false-negative RSV infection cases would be included in the control group. Sensitivity analyses, such as varying the amount of time allowed between symptom onset and sampling, as well as addition of pre-admission RADT, will explore potential misclassification bias. Study staff follow guidance for proper specimen collection, ensuring a robust testing procedure.

Unaccounted potential confounders in this study, such as ethnicity and socio-economic status, could lead to biased VE estimates when certain groups are less likely to be vaccinated. TNCC studies, limited to those accessing healthcare or hospitalised, may not generalise to disadvantaged groups with poor access or nursing home residents, affecting result applicability to the general population.

Estimating sample sizes for brand-specific VE is challenging due to unpredictable and evolving attack rates and vaccination coverage. This challenge is exacerbated by the increasing fragmentation of the vaccine market with more available RSV vaccination products. Despite our study's extensive hospital network, obtaining sufficient samples for accurate estimates of primary and secondary objectives may be challenging.

RSV monoclonal antibodies or other RSV vaccines or therapies may be used in the population. These products may prevent infection or its severity preventing hospitalisation, and lead to disease misclassification due to its effects on sampling and testing. To explore any potential bias due to disease misclassification, sensitivity analyses regarding use of prophylaxis prior to hospitalisation can be conducted.

Time-varying confounders and effect modifiers, including seasonality, RSV subtypes, levels of vaccine-induced and natural immunity in the population, and timing of RSV vaccination programmes and their complex interplay makes it challenging to disentangle waning of vaccine-induced immunity, differences in VE against different RSV subtypes, and infection-acquired immunity. We will do stratified analysis for RSV subgroups, and control for seasonality in the analysis to mitigate this limitation.

As a multi-centre study with numerous hospital sites across countries, heterogeneity of the study population could be of concern. Indeed, inter- and intra-country differences

may exist with regards to vaccine recommendations, vaccine roll-out, RSV epidemiology, population characteristics, and healthcare systems. These differences may lead to clustering at country or Study Contributor level. However, several steps are taken to reduce or take into account these potential sources of bias. Firstly, a single common eCRF is used across all Study Contributors with clear instructions to limit variation in interpretation and data collection. Second, the GEE model accounts for potential intra-cluster correlation among subjects from the same Study Contributor. When matching is applied, cases will be matched to up to four controls by Study Contributor and hospital admission data. Finally, in a sensitivity analysis, influential or outlying sites will be excluded in a leave-one-out procedure to re-estimate VE, as detailed in SAP.

Co-vaccination with RSV, influenza, COVID-19: COVID-19 and influenza VE test-negative studies with influenza and SARS-CoV-2 acute respiratory infection (ARI) controls, respectively, underestimate VE if vaccine-preventable disease-related events are included in the control group [44]. Although this study explores excluding the controls who tested positive for influenza and SARS-CoV-2 via means of sensitivity analysis, to minimise the potential bias of correlated vaccine exposures for respiratory vaccine-preventable diseases, these principles may be generalised to other vaccine-preventable ARI (e.g. pneumococcal disease) aetiologies that we are not able to capture in the study multiplex assay. We may be able to include pneumococcal vaccination in our models to test any effect of this variable on our VE estimate.

12 ETHICAL CONSIDERATIONS

12.1 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) [45], Good Epidemiological Practice (GEP) [46], 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. There is no direct benefit to the participants. Nevertheless, there are important potential societal benefits derived from this study. Insight in SARI pathogen distribution and clinical presentation are key to identify vaccine targets, marketing authorisation, and vaccination policies. Close monitoring of the effectiveness of vaccination products is essential to guide decision-making regarding vaccination products marketing approval, optimisation of vaccination programmes and future vaccine development.

12.2 Informed consent

Written informed consent will be obtained from all participants/guardians as specified by the national/regional IEC, if applicable⁵. The following information should be specified in the informed consent form (ICF) which will be translated in local language: who is responsible for the study, aim of the study, risk of study procedures 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). If informed consent will not be required, the reason will be stated.

12.3 Ethics approval

The protocol will be submitted to relevant 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 10 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.

12.4 Independent Ethics Committee/Institutional Review Board

Consistent with local regulations and prior to enrolment of participants at a given Study Contributor site, the study protocol together with its associated documents (e.g., ICF) will be submitted by the Study Contributor to the responsible institutional review

⁵ Waiver of consent or non-opposition letter may be granted by IEC for observational studies.

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.

12.5 Participants' 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).

12.6 Protocol amendments

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.

12.7 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-Coordination upon written request.

13 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, EDC, data management and analysis.

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.

13.1 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.

13.2 Data capture

The data will be collected using an EDC system as described in the DMP.

13.3 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.

13.4 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.

13.5 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.

14 REPORTING AND DISSEMINATION OF STUDY RESULTS

14.1 Registration of Study Protocol

The study protocol will be included in the European Medicines Agency-Heads of Medicines Agencies (HMA-EMA) catalogue of real world data studies. This protocol will act as common protocol for all Study Requestors.

14.2 Management and reporting of adverse events/adverse reactions

This is an observational epidemiological study for the surveillance of SARI-causing viral respiratory pathogens and for assessing the effectiveness of recommended or routine pathogen-specific 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 become aware, will be reported to the Study Requestor. The individual case safety report form for reporting SAEs is provided in the Investigator Site Files.

14.3 Reports

Study progress is tracked through a centralized dashboard, enabling real-time monitoring of milestones and key indicators. Progress reports can be developed regularly to provide structured updates, while comprehensive study reports may be prepared upon request from study sponsors or requestors.

14.4 Publications

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 pseudonymised patient-level data collected in the scope of the id.DRIVE Study following the id.DRIVE Governance Charter.

15 SOURCES OF FUNDING

The id.DRIVE consortium is a not-for-profit open public-private partnership. The id.DRIVE Study Network has been funded by the current and previous Pharmaceutical Company Partners of the id.DRIVE consortium: FISABIO (Spain), P95 (Belgium), AstraZeneca (United Kingdom), Novavax (United States) and Pfizer (United States), Bavarian Nordic (Denmark), Johnson & Johnson (formerly Janssen) (Belgium), GSK (United Kingdom), Moderna (United States), Sanofi (France), Valneva (Austria), THL (Finland) and CureVac (Germany). Other partners (pharmaceutical company partners or other institutions) may join the id.DRIVE partnership as per governance and participate in the study's funding. All funding will be transparently acknowledged in study communications. The execution of brand-specific study(ies) will be further funded by the Partner requesting the specific study.

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17 ANNEX 1: PATIENTS LACKING CAPACITY

This annex is only applicable for sites in the United Kingdom. According to the United Kingdom 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 deciding one way or another,
 - a) 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 ICU), can still be included in the study.

18 ANNEX 2: VERSION HISTORY OF CVE AND RSV VE PROTOCOLS

18.1 CVE study

Version	Version date	Reason for new version
3.1	2 June 2021	First version Registered in the EU PAS register on 02 August 2021 (EUPAS42328)
3.3	23 December 2021	Amendments: • Removing 'other hospital controls' • use the ECDC possible case definition for SARI instead of the stricter WHO case definition • restructuring the order and organisation of the secondary and exploratory objectives without changing the content • adding variables: - use of anti-SARS-CoV-2 antibody products or similar for pre-exposure prophylaxis, post-exposure prophylaxis and post symptom-onset but prior hospitalisation - full COVID-19 vaccination history including additional doses - symptoms related to the SARI case definition • in addition to RT-PCR, also allowing confirmation of COVID-19 using RNA amplification systems with at least the same sensitivity as RT-PCR (e.g. TMA) • improving sample size section • improving Annex 1 (Vaccine-Associated Enhanced Disease)
4.0	10 October 2022	Amendments: • Addition of comparator groups to objectives • Adding additional dose VE 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 ICF) • Update Annex 6 (sample size calculations)
5.0	18 September 2023	• Addition of glossary • Adaptation of objectives, data analysis and sample-size sections to allow for the addition of estimation of seasonal brand-specific COVID-19

Version	Version date	Reason for new version
		vaccine effectiveness against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients as a primary objective. • Addition of relevant covariates and exposure definitions. • Actualisation of sections “Rationale & Background” and “Limitations of the research methods” to current COVID-19 knowledge. • Update of Data management section. • Update of Quality management section. • Update of section Outcomes-laboratory-confirmed SARS-CoV-2. • Removal of section “unfavourable COVID-19 positivity rates among SARI” : The described approaches were initially defined at the launch of the study, but in practise were not implementable. In place, case-control ratios are identified in risk based monitoring plan (v4.0, 19 Apr 2023) as one of the risks for central monitoring and monitored monthly for each Study Contributor. Sites are consulted if unfavourable case-control ratios are detected, to understand if these ratios are related to screening issues that need addressing or simply reflect hospitalisation trends • Addition of respiratory support in hospital severity level • Removal of precautionary health behaviour survey and associated Annex; no longer warranted based on the evolution of the pandemic • Removal of Vaccine-Associated Enhanced Disease objective and associated annex; i) data collection is challenging, ii) available data do not allow to draw any conclusions with regard to the given objective, iii) no longer warranted based on progress in COVID-19 scientific knowledge • Removal of Annex 4 (study common dataset) and Annex 5 (adult informed consent), now stand-alone documents for the COVIDRIVE study

Version	Version date	Reason for new version
6.0	21 March 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 - Update of Annex 1 : Sample size calculations, technical specifications - Addition of Individual Case Safety Report form for reporting 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	21 February 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 (United Kingdom Mental Capacity Act 2025)

18.2RSV VE study

Version	Version date	Reason for new version
1.0	21 March 2024	First version of protocol
2.0	7 June 2024	In this version modified-SARI definition is updated to include patients hospitalised with suspicion of a respiratory infection.

Version	Version date	Reason for new version
3.0	21 February 2025	Amendments: • change study status wording from “non-interventional study” to “observational study” • update of the list of current id.DRIVE Partners • primary and secondary objectives text clarified • exploratory objective added • sensitivity analysis details added • clarification to specimen collection and laboratory testing • overall reorganization of sections to improve readability • update of the section “Research methods” and section “Limitations of the research methods” to provide more details on the study • added Table 1. “Participating Study Contributors”; Table 2. “Overview of the assays performed at each Study Contributor” and Table 4. “Data sources per Study Contributor for exposures, outcomes (i.e., endpoints) and covariates” • update of Table 3 “Study covariates and health care use” to align with eCRF • frailty as additional covariate at the Henri Mondor Study Contributor added to section “Covariates” • added section “Data sources” • only for sites in the United Kingdom: addition of an exclusion criteria for patients who are deemed mentally incapacitated to provide informed consent (United Kingdom Mental Capacity Act 2025)