MASTER PROTOCOL for Study Contributors

Brand-specific respiratory syncytial virus vaccine effectiveness in Europe

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

id.DRIVE

Version 2.0

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Abbreviations: FISABIO, Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana; P95, P95 Epidemiology & Pharmacovigilance

DOCUMENT HISTORY

Version control table for this Master Protocol

Version	Version date	Reason for new version
1.0	21 March 2024	First version of protocol created
2.0	07 June 2024	In this version modified-SARI definition is updated to include patients hospitalised with suspicion of a respiratory infection.

BACKGROUND OF THIS MASTER PROTOCOL

This Master Protocol describes a European, non-interventional study to estimate the effectiveness of vaccines) against respiratory syncytial virus (RSV). Of interest is the effectiveness against hospitalisation due to severe acute respiratory infection (SARI) caused by RSV. The study is a multi-country, hospital-based study with test-negative case-control (TNCC) design.

This Master Protocol will be used to create Study Requestor (i.e., Pharmaceutical Company Partner)-specific protocols that meet the requirements of the Study Requestors (Pharmaceutical Company Partners). From the Study Requestor-specific protocols, Study Contributor (i.e., study site)-specific protocols will be developed, which detail the data collection and requirements at the specific Study Contributor level. This Master Protocol is set up to harmonise study methods (e.g., study objectives, study participant inclusion/exclusion criteria, case definitions, exposures, outcomes, and data collection) and to mutualise healthcare provider/Study Contributor resources.

This Master Protocol has been developed by the id.DRIVE public-private partnership (https://iddrive.eu). The id.DRIVE partnership intends to conduct studies on infectious diseases, vaccines, related preventive measures and therapeutics (e.g., antivirals and monoclonal antibodies) for infectious diseases. Current id.DRIVE members are FISABIO (Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana, Spain), P95 Epidemiology & Pharmacovigilance (Belgium), AstraZeneca (United Kingdom), GSK (GlaxoSmithKline, Belgium), Janssen (Belgium), Novavax (United States), Pfizer (United States), and Valneva (France).

The outline of this Master Protocol was inspired by the Preparing for RSV Immunisation and Surveillance in Europe (PROMISE) project (https://imi-promise.eu).

1 TITLE PAGE

Abbreviated study title	Brand-specific respiratory syncytial virus vaccine effectiveness in Europe
Full study title	Brand-specific respiratory syncytial virus (RSV) vaccine effectiveness in Europe - A contribution of id.DRIVE, a public-private partnership to facilitate the conduct of observational studies on infectious diseases, vaccines, related preventive measures and therapeutics for infectious diseases in Europe
HMA/EMA catalogue number	EUPAS1000000035
Master Protocol version	2.0
Date of protocol version	07 June 2024
Active substance(s)	Study Requestor RSV vaccine
Study status	Non-interventional
Research question and objectives	*Primary objective:* **Objective 1.** to estimate brand-specific respiratory syncytial virus (RSV) vaccine effectiveness (VE) against hospitalisation due to laboratory-confirmed RSV infection in modified severe acute respiratory infection (modified SARI) older adult patients *Secondary objectives:* **Objective 2.** as objective 1, but stratified by: ▪ RSV subtype A and B infection (objective 2.1) ▪ population of special interest (e.g., age groups, gender) (objective 2.2) ▪ time since vaccination (objective 2.3) ▪ calendar time (objective 2.4) ▪ modified SARI severity level[1] (objective 2.5)
Country(ies) of study	Belgium, Germany, Spain, and Italy. Additional countries may be included in the course of the study.

Abbreviation: HMA/EMA catalogue, Heads of Medicines Agencies/European Medicines Agency catalogue of real-world data studies

[1] SARI severity levels are defined by hospital outcome (intensive care unit [ICU] admission; in-hospital death) and/or respiratory support. As an additional indicator of severity at hospitalisation and throughout hospitalisation, progression risk is defined as proportion of in-hospital deaths and proportion of ICU admissions among all hospitalised SARI patients.

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5 GLOSSARY

Term	Description
Action	means all the activities, including research activities, carried out by the Partners under the Consortium Agreement as described in further detail in the Governance Charter.
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.
Consortium	Means the group of Partners that are parties to the Consortium Agreement. The Consortium has no separate legal personality.
Consortium Agreement	means the agreement and all of its appendices (including the Governance Charter), together with amendments signed by all the authorised representatives of the Partners.
COVIDRIVE	means the public-private partnership for the estimation of brand-specific COVID-19 vaccine effectiveness in Europe organised under the Consortium Agreement.
Data Collection	means a data collection under a single or under multiple protocols (incl. Master Protocol(s)) for the purpose of Primary Data Use.
Governance Charter	means a document, appended to the Consortium Agreement, which provides details on the governance of the Action: objectives, guiding principles, stakeholders, roles and responsibilities, legal and regulatory environment, communication and expected tasks and Deliverables that will guarantee an efficient and fair execution of the Action. The Governance Charter is made available by the Co-Coordinators upon request.
Id.DRIVE	means the public-private partnership for conducting observational studies on infectious diseases, vaccines, related preventive measures and therapeutics for infectious diseases in Europe organised under the Consortium Agreement. For the avoidance of doubt, COVIDRIVE became a part of id.DRIVE as described in further detail in the id.DRIVE 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.
Informed Consent Form	means the document to inform the Study participants of the purpose of the Data Collection, data handling and possible risks and benefits of participating in the Study in lay language and document the voluntary decision of the Study participant to participate in the Study. The Informed Consent Form is adapted to national requirements, translated into the language of the Study participant and approved by the ethics committee of the Study Contributor at which the Study is performed.

Master Protocol	means the protocols agreed by the Partners to harmonise Data Collection and to ensure the potential mutualisation of e.g., Study Contributor resources.
Partner	means a legal entity signatory of the Consortium Agreement. Partners are either Core Platform Partners or Pharmaceutical Company Partners.
Pharmaceutical Company Partner	means a Partner that is a pharmaceutical company.
Primary Data Use	means the use of patient's data for the purpose of a single Study or multiple Studies defined prior to id.DRIVE Data Collection.
Pseudonymised data	means data that is processed in such a manner that the personal data can no longer be attributed to a specific person but still allows for re-identification in combination with additional information, in line with the provisions of the European Union General Data Protection Regulation (the "GDPR").
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.
Secondary Data Use	means the use of patients' data that has already been collected for the purpose of a single Study or multiple Studies as defined after Data Collection.
Study	means a study on infectious diseases, vaccines, related preventive measures and therapeutics for infectious diseases requested by a specific Study Requestor through Primary Data Use or Secondary Data Use to be performed in the framework of the Action.
Study Contributor	or "Study Site" or "Site", means an institution that collects/owns data of interest for Studies and that signs a Study Contributor Agreement with P95 after being selected via a study-specific selection process.
Study Requestor	means the Partner that requests to perform a specific Study.
Study Results Publication	means a scientific publication reporting on the Study including all Study objectives identified in the individual Study protocol(s).
Study Sponsor	means the organisation which takes on the responsibility – on behalf of the Consortium – to initiate, manage and finance the Studies, as well as ensuring the operational/administrative coordination of the network of Study Contributors. The Study Sponsor is P95.
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.

6 ABBREVIATIONS

BiPAP	Bi-level positive airway pressure
BMI	Body mass index
CCA	Complete case analysis
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
DMP	Data management plan
ECDC	European Centre for Disease Prevention and Control
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
ED	Emergency department
EDC	Electronic data capture
EMA	European Medicines Agency
ESKD	End-stage kidney disease
ESLD	End-stage liver disease
EU	European Union
FDA	United States Food and Drug Administration
FISABIO	Fundación para Fomento de Investigación Sanitaria y Biomédica la Comunidad Valenciana
GAM	Generalised additive model
GDPR	General Data Protection Regulation
GEE	Generalised estimating equations
GEP	Good Epidemiological Practice
GLM	Generalised linear model
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GPP	Good Publication Practice
GSK	GlaxoSmithKline
HIV	Human immunodeficiency virus
HMA	Heads of Medicines Agencies
ICD	International Classification of Diseases
ICF	Informed consent form
ICMJE	International Committee of Medical Journal Editors
ICSR	Individual case safety report
ICU	Intensive care unit
IEC	Independent ethics committee

IEE	Independence estimating equations
IRB	Institutional review board
ISC	Independent Scientific Committee
ISF	Investigator site file
LAR	Legally acceptable representative
MAH	Marketing authorisation holder
MHRA	Medicines and Healthcare products Regulatory Agency
mAb	Monoclonal antibody
NIP	National immunisation programme
OR	Odds ratio
PA	Population-averaged (odds ratio)
POC	Point-of-care
PPP	Public-private partnership
PROMISE	Preparing for RSV Immunisation and Surveillance in Europe
QAAC	Quality Assurance and Audit Committee
RADT	Rapid antigen detection test
RE-MA	Random-effects meta-analysis
RNA	Ribonucleic acid
RR	Relative risk
RSV	Respiratory syncytial virus
RT-PCR	Reverse transcription polymerase chain reaction
rVE	Relative vaccine effectiveness
SAE	Serious adverse event
SAP	Statistical analysis plan
SARI	Severe acute respiratory infection
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SIV	Site initiation visit
SS	Subject-specific (odds ratio)
ST	Study Team
THL	Finnish Institute for Health and Welfare
TMA	transcription-mediated amplification
TNCC	Test-negative case-control
UK	United Kingdom
US	United States
VE	Vaccine effectiveness
WHO	World Health Organisation

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8 ABSTRACT

Background

- Respiratory syncytial virus (RSV) is a common cause of respiratory tract infections. Older adults are at higher risk for hospitalisation and death. RSV vaccines have received European Union (EU) marketing authorisation to prevent RSV-associated lower respiratory tract disease in adults aged 60 years and older.
- Pharmaceutical Company Partners may use the id.DRIVE public-private partnership (PPP) to conduct their future vaccine effectiveness (VE) studies as part of their European regulatory obligations.
- This study protocol details a non-interventional study through the id.DRIVE partnership to estimate the effectiveness of an RSV vaccine against RSV-related modified severe acute respiratory infection (SARI) hospitalisations in older adults.

Research question

The study aims to continuously monitor VE of an RSV vaccine against RSV-related modified SARI hospitalisations in older adults using a network of hospitals across Europe.

Research objectives

Primary objective (objective 1): to estimate brand-specific RSV VE against hospitalisation due to laboratory-confirmed RSV infection in modified SARI older adult patients.

Secondary objective (objective 2): as objective 1, but stratified by:

- RSV subtype A and B infection (objective 2.1)
- population of special interest (e.g., age groups, gender) (objective 2.2)
- time since vaccination (objective 2.3)
- calendar time (objective 2.4)
- modified SARI severity level[2] (objective 2.5)

Study methods

Study design: The study is a multi-country, hospital-based test-negative case-control (TNCC) study.

Study period: The study provides continuous (i.e., year-round) RSV surveillance, with a study period lasting minimum one epidemiological year with a possible extension.

Countries: The study will be conducted in multiple countries in Europe[3].

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

- The patient is ≥60 years old at the time of admission to the hospital.

[2] SARI severity levels are defined by hospital outcome (intensive care unit [ICU] admission; in-hospital death) and/or respiratory support. As an additional indicator of severity at hospitalisation and throughout hospitalisation, progression risk is defined as proportion of in-hospital deaths and proportion of [ICU] admissions among all hospitalised SARI patients.

[3] The list of countries will be extended as the id.DRIVE network grows (e.g., the UK).

- The patient is eligible to receive vaccination against RSV (depending on the vaccination programme in the patient´s country of residence).
- Informed consent is obtained from the patient or from the patient's legally acceptable representative(s) (LAR(s)) prior to enrolment.

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

- The patient is unable or unwilling to provide the protocol required respiratory specimen(s) for any reason.

'Modified SARI patients' will be identified among patients admitted to the hospital with at least one overnight stay. A 'modified SARI patient' is a person hospitalised with a suspicion of a respiratory infection with at least one of the following symptoms:

- cough
- shortness of breath
- fever (≥38 C^{o})

with symptom onset within the last 10 days prior to hospital admission. This SARI definition is modified from the latest European Centre for Disease Prevention and Control (ECDC) SARI case definition[4] to include at minimum a 'suspicion of a respiratory infection'. Also, to be closer to the RSV-specific case definitions [1, 2], time since symptom onset has been reduced and sudden onset of anosmia, ageusia or dysgeusia has been excluded from the symptoms list. Sensitivity analysis will be done applying the WHO-RSV case definition[5] and id. DRIVE case definition[6].

Cases ('test-positive cases'): Study participants who meet the 'modified SARI patient' definition AND have tested positive for at least one RSV RT-PCR or similar molecular assay, with specimens collected within 10 days prior and up to 72 hours after hospital admission. Test-positive cases include laboratory-confirmed coinfections.

Controls ('test-negative controls'): Study participants who meet the 'modified SARI patient' definition AND have all respiratory samples being negative for RSV RT-PCR or similar molecular assays, with specimen(s) collected between 10 days prior to and up to 72 hours after hospital admission. Test-negative controls include study participants negative for other pathogens and study participants positive to other pathogens based on specimen(s) collected between 10 days prior to and up to 72

[4] EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL (2021). *ECDC Technical report: Core protocol for ECDC studies of COVID-19 vaccine effectiveness against hospitalisation with Severe Acute Respiratory Infection laboratory-confirmed with SARS-CoV-2, version 1.0, 2021*. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/Core-protocol-for-ECDC-studies-of-COVID-19-vaccine-effectiveness-against-hospitalisation-with-SARI.pdf. [Accessed: 24-11-2022].

[5] 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]

[6] 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 (≥ 38 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 Severe Acute Respiratory Infection, 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]].

hours after hospital admission.

Exposure (RSV vaccination)

- **Vaccinated with RSV vaccine during the study period of interest'**:
  vaccinated with exposure of interest: e.g. single dose/primary vaccination/at least one dose of the RSV vaccine during the epidemiological year(s) of interest, within the appropriate timeframe for the product to be **effective** prior to modified SARI symptom onset.
- **Unvaccinated with RSV vaccine during the study period of interest'**:
  did not receive any RSV vaccine during the epidemiological year(s) of interest.
- **'Recently vaccinated with RSV vaccine during the current RSV season'**:
  Vaccinated with *exposure of interest: e.g. single dose/primary vaccination/at least one dose* of the RSV vaccine during the epidemiological year(s) of interest, within the appropriate timeframe for the product to be **ineffective** prior to modified SARI symptom onset.
- **'Other'**:
  additional vaccine exposure definitions might be defined depending on the real-life use of the RSV vaccines.

Data sources, data collection

The study uses a combination of primary (e.g., specific laboratory results, vaccine cards) and secondary data sources (e.g., existing hospital databases, vaccine registries and linked data).

After study enrolment, data will be collected directly from the patient or by consulting medical records. Information to be collected at minimum includes date of modified SARI symptom onset, date of hospitalisation, respiratory specimen testing results, and information on the potential confounders and effect modifiers.

Exposure status, RSV vaccine information and date(s) of vaccination(s) will be ascertained by consulting vaccination registries, vaccination cards or medical records (depending on the country and region). Where needed, treating physician or other health care professionals will be contacted to obtain additional information.

Context information on national/regional vaccination recommendations and RSV vaccine label information will be collected from external sources.

Covariates

Variables that are potential confounders and/or effect modifiers will be collected at Study Contributors. These include: age, gender, history of selected morbidities of interest (e.g., asthma, lung disease, cardiovascular disease, and immunocompromising conditions)[7], vaccination against other respiratory pathogens (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], influenza, *Streptococcus pneumoniae*), history of prior RSV infection, prior modified SARI hospitalisation(s), pregnancy (and term), smoking history, history of anti-RSV antibodies received either as prophylaxis

[7] Definitions of the comorbidities of interest will be specified in detail as part of the electronic case report form (eCRF).

or treatment for the current or previous modified SARI episodes, body mass index (BMI), and long-term care facility residence.

RSV testing

Reverse transcription polymerase chain reaction (RT-PCR) or another ribonucleic acid (RNA) amplification system with at least the same sensitivity as RT-PCR (e.g., transcription-mediated amplification [TMA]) will be required to confirm an RSV infection. RT-PCR assays must be used for the detection of at least RSV, SARS-CoV-2, and influenza. Information on the RSV subtypes will be collected to the extent possible, preferably on all confirmed RSV cases when sample quality allows.

Respiratory sampling should preferably be done in both the nasopharynx and oropharynx, using a stiff oropharynx swab or a flexible nasopharynx swab. Additional respiratory specimens are accepted (e.g., saliva/saline mouth wash, sputum, bronchoalveolar lavage, or aspirates), when collected as part of patient diagnostic work-up.

It is recommended that specimens are collected *within 10 days prior to and up to 72 hours after hospital admission* for analysis of the primary objective. All test-negative tests will be re-tested at hospital admission.

Sample size

The sample size requirements strongly depend on RSV circulation, the case-control ratio, overall vaccination coverage and share of the different RSV vaccine brands. Due to the nature of the TNCC design, all cases and controls are recruited and data on them are collected. This is a key aspect of the TNCC and additionally crucial for surveillance use-cases. If balancing of case-control ratios is desired, this can be handled at the analysis stage for brand-specific analyses (for example by matching). As such, the sample size requirements will be different for the different vaccine brands. Sample size requirements will be calculated for each Study Requestor-specific protocol (for both interim and final analysis when applicable.) In case the parameter settings used for these sample size calculations are very different from what is observed in the study, the sample size calculations will be updated accordingly.

To account for potential loss of precision due to covariate adjustment in regression models, the required sample size estimate will be inflated by a factor fixed in advance. Commonly, a value of 20% is used, although other values – e.g., 50% or 100% (i.e., double) – can also be used, albeit with an associated impact on data collection costs. For example, if the uninflated sample size is estimated to be 1,000 SARI patients, the required sample size will be reported as 1,200 SARI patients, assuming an inflation factor of 20%.

Statistical analysis

Descriptive analyses will be performed to describe the study population, the evolution of the RSV dynamics and the RSV vaccination coverage for the brands of interest.

VE is defined as (1 – OR) x 100%, where *OR* denotes the (exposure) odds ratio, comparing the confounder-adjusted odds of vaccination among RSV-positive study participants to the odds of vaccination among RSV-negative study participants.

VE estimates will be adjusted for calendar time at minimum, and additionally the following confounders – age, sex, and comorbidities (e.g. number of chronic conditions). Adjustments are usually achieved through inclusion of the relevant terms in the logistic regression models, with (penalised) spline terms for calendar time and age. However, other methods may be considered as well.

Clusters will be defined at the hospital network (Study Contributor) level. If some networks have hospitals that 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.

An important choice is whether the exposure odds ratios are desired to have a subject-specific (SS) or population-averaged (PA) interpretation. The SS OR compares odds of vaccination among the RSV-positive cases to the odds of vaccination among the RSV-negative controls from the same Study Contributor (conditional on other covariates) and necessitates the inclusion of a fixed-effect of a random-effect term for Study Contributor or via a meta-analysis. The PA OR compares the odds of vaccination among the RSV-positive cases across the Study Contributors to the odds of vaccination among RSV-negative controls across the Study Contributors (conditional on other covariates) and is commonly obtained from a generalised estimating equation (GEE) model. Care should be taken with regards to method selection (estimators for point-estimates and standard errors) to avoid biased VE estimates when the clustering variable is a potential confounder.

Sensitivity analyses will be conducted as appropriate. A complete and detailed statistical analysis plan (SAP) will be developed prior to the conduct of the analysis.

Reporting

Progress reports will be prepared every two months. Interim analyses will be planned as appropriate. A final study report will be written. Interim reports and the final report will be submitted to the European Medicines Agency (EMA) and other competent regulatory bodies (e.g., Medicines and Healthcare products Regulatory Agency (MHRA), U.S. Food and Drug Administration (FDA) by the marketing authorisation holder (MAH) to meet regulatory requirements.

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 describes all functions, processes, responsibilities and specifications for data collection, cleaning, and validation.

An expert consensus group to classify exposure groups will consist of members of the Study Teams. In case of disagreement, the Independent Scientific Committee (ISC) of id.DRIVE will be consulted.

Ethical considerations

Study Contributor-specific protocols (developed by the Study Contributors themselves, based on this Study Requestor-specific protocol) will be submitted to relevant independent ethics committee(s) (IECs) following local regulations. Informed consent will be obtained from participants/guardians as specified by the national/regional IEC.

Study limitations

Study limitations include:

- Time-varying confounders and effect modifiers: these include seasonality, RSV subtypes, levels of vaccine-induced and natural immunity in the population, and timing of RSV vaccination programmes. Their complex interplay makes it challenging to disentangle waning of vaccine-induced immunity, differences in VE against different RSV subtypes, and infection-acquired immunity.
- Misclassification of disease status: RSV RT-PCR assays have a high specificity and sensitivity, but a single respiratory swab may miss 50% of RSV infections among older adults. RT-PCR sensitivity is influenced by several factors, including operator sampling technique, type of specimen, number of specimens, and timing of sampling. To explore any potential bias due to disease misclassification, sensitivity analyses regarding time between symptom onset and swabbing are performed.
- Prior infection: Infection-acquired immunity is an effect modifier of VE. Although information on past RSV infection is collected in this study, prior infection may be undocumented (e.g., asymptomatic disease).
- Unaccounted for 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 generic Master Protocol on which this Study Requestor-specific protocol is based (MASTER PROTOCOL Brand-specific respiratory syncytial virus vaccine effectiveness in Europe version 2.0), and its significant amendments, will be listed in the Heads of Medicines Agencies/European Medicines Agency (HMA/EMA) catalogue of real-world data studies. Study reports, each for a specific vaccine brand, will likewise be listed in the HMA/EMA catalogue and will be submitted to peer-reviewed open-source international journal(s).

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

Funding

The generic Master Protocol (MASTER PROTOCOL Brand-specific respiratory syncytial virus vaccine effectiveness in Europe version 2.0), the basis for this Study Requestor-specific protocol, has been developed by the id.DRIVE PPP, which has received funds from AstraZeneca, GSK, Janssen, Novavax, Pfizer, and Valneva, leveraging public health capacity from Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana (FISABIO) and existing infrastructure at P95. Other partners (vaccine companies or other institutes) might join id.DRIVE at later stages.

The execution of the study will be funded by pharmaceutical companies which may join progressively. This specific funding will be transparently acknowledged in all communications.

Id.DRIVE public-private partnership

id.DRIVE is an open PPP. Current members are FISABIO (Spain), P95 Epidemiology & Pharmacovigilance (Belgium), AstraZeneca (United Kingdom), GSK (Belgium), Janssen (Belgium),

Novavax (US), Valneva (Austria) and Pfizer (US). Past members are the Finnish Institute for Health and Welfare (THL, Finland), CureVac (Germany), Moderna (United States), Sanofi (France) and Bavarian Nordic (Denmark). Id.DRIVE aims to facilitate the conduct of observational studies on infectious diseases, vaccines, related preventive measures and therapeutics for infectious diseases in Europe.

Study status

Non-interventional

Study sponsor

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9 RATIONALE AND BACKGROUND

Respiratory syncytial virus (RSV) is a common pathogen causing respiratory tract infections [3], and its burden is increasingly recognised among older adults. In high-income countries, RSV-related annual hospitalisations were estimated to be 787,000 in 2021 [4], with an annual hospitalisation rate of 145 per 100,000 for RSV-associated acute respiratory infections in adults ≥60 years of age [5]. In older adults, RSV case fatality proportion was estimated to be 8% [6], with both hospitalisation and mortality rates found to be comparable to influenza [7]. Adults with underlying medical conditions [8, 9] and frailty [10, 11] are at higher risk for hospitalisation and death, potentially due to exacerbation of existing chronic conditions, such as chronic obstructive pulmonary disease and congestive heart failure.

RSV has two main subtypes: A and B, with either of them predominating in a given season, although they may circulate simultaneously in the population [12]. In temperate climates, RSV typically follows a distinct seasonal pattern, with a peak between December and February. Reverse transcriptase-polymerase chain reaction (RT-PCR) and (PCR-based) point-of-care (POC) tests are the gold-standard for the diagnosis of RSV infections. Rapid antigen detection tests (RADT) are also used for the RSV diagnosis, as they require less time and resources, but have a lower sensitivity [13]. Clinical severity is strongly associated with viral load, which declines seven days after inoculation [14].

The development of safe and efficacious vaccination products is essential in addressing the public health impact of RSV-associated illness. Two protein-based vaccines have been approved for use in adults 60 years and older. As of 20 November 2023, the following RSV vaccines are authorised for use in the EU: Arexvy® (GSK) and Abrysvo® (Pfizer).

Although the efficacy of RSV vaccines has been investigated thoroughly during clinical trials, continuous evaluation of product-specific vaccine effectiveness (VE) under real-world conditions once used as part of the national immunisation programmes (NIPs) remains crucial. Real-world studies allow for the evaluation of more rare outcomes such as hospitalisation. Additionally, duration of vaccine-induced protection, differential VE based on RSV subtypes, and VE in risk groups such as immunocompromised or patients with chronic conditions can be assessed.

Id.DRIVE, a not-for-profit public-private partnership (PPP) launched in January 2024, is leveraging COVIDRIVE, a PPP that addressed the joint need to monitor coronavirus disease 2019 (COVID-19) vaccination programmes for public health institutes and assess brand-specific COVID-19 vaccine effectiveness for vaccine companies as part of their regulatory obligations. Id.DRIVE will facilitate the conduct of studies on infectious diseases' burden, -vaccines, -preventive measures, and -therapeutics (e.g. antivirals, monoclonal antibodies) in the European region. Current id.DRIVE members are FISABIO (Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana, Spain), P95 epidemiology & Pharmacovigilance (Belgium), AstraZeneca (UK), GSK (GlaxoSmithKline, Belgium), Janssen (Belgium), Novavax (US), Pfizer (US), and Valneva (France). The Pharmaceutical Company Partner will use this partnership to conduct its future RSV VE studies as part of its European regulatory obligations.

This Study Requestor-specific protocol describes a non-interventional study to estimate the effectiveness of RSV vaccines against RSV-related hospitalisations through the id.DRIVE partnership.

This study is a multi-centre, hospital-based, case-control study with test-negative controls (test-negative case-control [TNCC] design). The hospital-based TNCC design is efficient for studying rare outcomes, allows potentially for patient-reported or healthcare provider-reported data collection, and can minimise disease misclassification and confounding by healthcare-seeking behaviour. Data will be collected through a wide network of hospitals located in several European countries.

The outline of this Study Requestor-specific protocol was inspired by the Preparing for RSV Immunisation and Surveillance in Europe (PROMISE) project (https://imi-promise.eu) and the COVIDRIVE project (https://iddrive.eu/).

10 RESEARCH QUESTION AND OBJECTIVES

10.1 Research question

The study aims to continuously monitor VE of an RSV vaccine of interest against RSV-related modified SARI hospitalisations at the vaccine brand/product-specific level using a network of hospitals across Europe.

10.2 Research objectives

10.2.1 Primary objective

Objective 1: to estimate brand-specific RSV VE against hospitalisation due to laboratory-confirmed RSV infection in severe acute respiratory infection (modified SARI) older adult patients.

10.2.2 Secondary objectives

Objective 2: as objective 1, but stratified by:

- RSV subtype A and B infection (objective 2.1)
- population of special interest (e.g., age groups, gender)[8] (objective 2.2)
- time since vaccination (objective 2.3)
- calendar time (objective 2.4)
- modified severity level[9] (objective 2.5)

[8] For example, specific age groups, specific immunocompromised or chronic conditions

[9] Severity levels are defined by hospital outcome (intensive care unit [ICU] admission; in-hospital death) and/or respiratory support. As an additional indicator of severity at hospitalisation and throughout hospitalisation, progression risk is defined as proportion of in-hospital deaths and proportion of [ICU] admissions among all hospitalised SARI patients.

11 RESEARCH METHODS

11.1 Study design

This study is a multi-country[10], multi-centre, hospital-based case-control study with TNCC design.

A combination of primary and secondary data collection will be used to obtain the relevant data. The Schedule of Activities (Figure 1) shows the primary data collected from subjects during the study period.

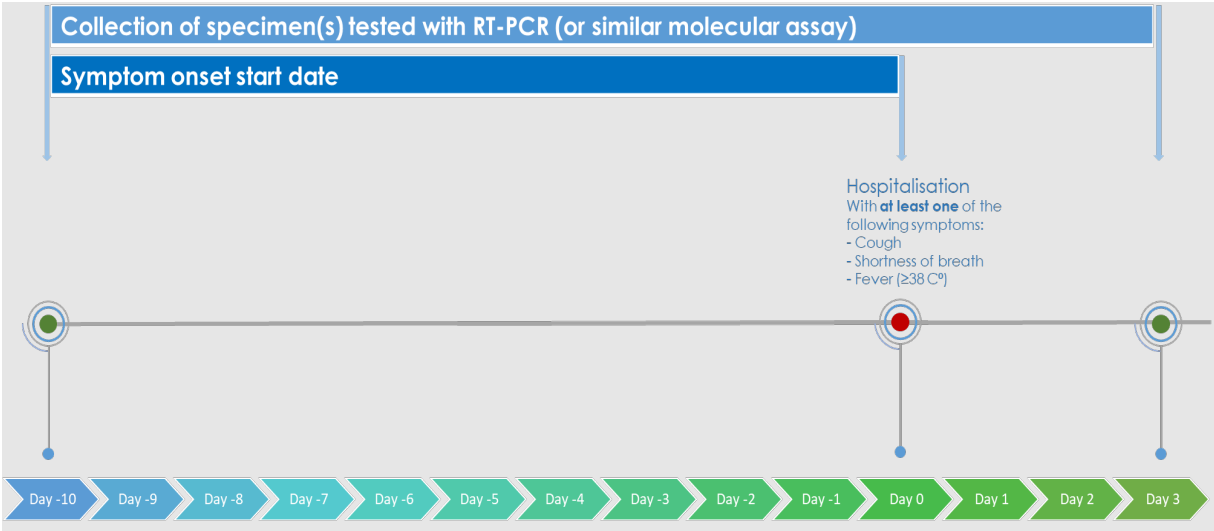

Figure 1. Schedule of activities for the primary data collection during the study period.

11.2 Study Contributors

In this study, the term 'Study Contributor' is used in lieu of 'study site'.

The participating Study Contributors are either individual hospitals or hospital networks. The data collection will be a prospective data collection from primary data sources (e.g., specific laboratory results) and secondary data sources (e.g., existing hospital databases, vaccine registries and linked data). Retrospective data collection will be considered to allow capture of whole epidemiological year data in Study Contributors with late set-up.

[10] The list of countries will be extended as the id.DRIVE network grows.

11.3 Study population

11.3.1 Patient identification

Systematic screening of individuals presenting with respiratory symptoms at participating hospitals during the study period is organised. The study population consists of hospitalised[11] modified SARI patients. Those who fulfil all the inclusion criteria but not the exclusion criterion will be proposed to be part of the study. A modified SARI patient is a person hospitalised with a suspicion of a respiratory infection with at least one of the following symptoms:

- cough
- shortness of breath
- fever (≥38 C°)

with symptom onset within the last 10 days prior to hospital admission. This SARI definition is modified from the latest European Centre for Disease Prevention and Control (ECDC) case definition [15] Sensitivity analysis will be done applying the WHO-RSV case definition[12] and id.DRIVE case definition[13].

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

11.3.2 Inclusion criteria

Individuals (patients) *must fulfil all* of the following inclusion criteria to be included in the study as study participants:

- The patient is ≥60 years old at the time of admission to the hospital.
- The patient is eligible to receive vaccination against RSV (depending on the vaccination programme in the patient´s country of residence).
- Informed consent is obtained from the patient or from the patient's legally acceptable representative(s) (LAR(s)) prior to enrolment.

[11] The patient is hospitalised for minimum one whole night ("one overnight stay").

[12] 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]

[13] 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 (≥ 38 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 Severe Acute Respiratory Infection, 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]].

11.3.3 Exclusion criteria

Individuals (patients) *must not fulfil any* of the following exclusion criteria to be included in the study as study participants:

- The patient is unable or unwilling to provide the protocol required respiratory specimen(s) for any reason.

11.4 Study period

The study provides continuous (i.e., year-round) RSV surveillance, with a study period lasting minimum one epidemiological year with a possible extension.

11.5 Study outcomes

11.5.1 Primary outcome: laboratory-confirmed RSV

The outcome of interest for the primary analysis will be RSV detection in patients hospitalised with symptoms consistent with the modified ECDC SARI definition.

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. Respiratory sampling should preferably be done in both the nasopharynx and oropharynx, using a stiff oropharynx swab or a flexible nasopharynx swab. Additional respiratory specimens are accepted (e.g., saliva/saline mouth wash, sputum, bronchoalveolar lavage, or aspirates), when collected as part of patient diagnostic work-up.

RSV infection must be laboratory-confirmed by RT-PCR or another RNA amplification system with at least the same sensitivity as RT-PCR (e.g., transcription-mediated amplification [TMA]). RT-PCR assays must be used for the detection of at least RSV, SARS-CoV-2, and influenza.

Only Study Contributors where laboratory confirmation is performed by RT-PCR or another RNA amplification system with similar sensitivity (e.g., transcription-mediated amplification [TMA]) are eligible to participate in the study.

11.5.2 Secondary outcomes

The secondary outcomes in patients hospitalised with modified SARI symptoms include:

- detection of RSV subtypes A and B
- modified SARI severity level of study participants (both cases and controls), including respiratory support severity level

11.5.2.1 RSV subtypes

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.

11.5.2.2 Modified SARI severity level and respiratory support severity level

Severity will be assessed in two ways, first by intensive care unit (ICU) admission and in-hospital death outcomes, and through outcomes related to respiratory support.

ICU and in-hospital mortality:

The following three mutually exclusive categories will characterise the worst level of severity of hospitalisation due to SARI:

1. Hospital admission without ICU admission and without in-hospital death;
2. ICU admission without in-hospital death;
3. In-hospital death
    a. during ICU stay
    b. outside of ICU stay

As an additional indicator of severity at hospitalisation and throughout hospitalisation, progression risk is defined as proportion of in-hospital deaths and proportion of ICU admissions among all hospitalised SARI patients.

The following categories will complement the characterisation of the severity of hospitalisation due to SARI. For each patient, the highest level of respiratory support ever received during the hospital stay will be reported.

1. No respiratory support;
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).

11.6 Definitions

11.6.1 'Hospitalised patient'

A 'hospitalised patient' is defined as a person admitted to the hospital with overnight stay[14]. In case of referral to another hospital, the date of hospital admission is defined as the date of first admission.

[14] The patient is hospitalised for minimum one whole night ("one overnight stay").

11.6.2 'Modified SARI patient'

A 'modified SARI patient' is defined as a person hospitalised with a suspicion of a respiratory infection with at least one of the following symptoms:

- cough
- shortness of breath
- fever (≥38 C°)

with symptom onset within the last 10 days prior to the current hospital admission. This SARI definition is modified from the latest ECDC case definition [15]. Sensitivity analysis will be done applying the WHO-RSV case definition[15] and id. DRIVE case definition[16].

Additionally, the International Classification of Diseases (ICD)-10 codes and corresponding definitions listed below could be used as a guideline to identify potential modified SARI patients (i.e., for screening), if deemed appropriate at specific Study Contributors:

- J00-J06: Acute upper respiratory infections
- J21.0, J21.8, J21.9: Bronchiolitis
- J12-J18: Pneumonia
- J20-J22: Other acute lower respiratory infections
- J40-J47: Chronic lower respiratory diseases

11.6.3 'Study participant'

A 'study participant' is defined as a patient who meets the 'hospitalised patient' AND 'modified SARI patient' definitions, AND fulfils all the inclusion criteria but none of the exclusion criteria.

11.6.4 'Case' ('test-positive case')

'Cases' are study participants who meet the 'modified SARI patient' definition AND have tested positive for at least one RSV RT-PCR or similar molecular assays, with specimens collected within 10 days prior and up to 72 hours after hospital admission. Test-positive cases include laboratory-confirmed coinfections.

[15] 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]

[16] 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 (≥ 38 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 Severe Acute Respiratory Infection, 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]].

11.6.5 'Control' ('test-negative control')

'Controls' are study participants who meet the 'modified SARI patient' definition AND have all respiratory samples being negative for RSV RT-PCR or similar molecular assays, with specimen(s) collected between 10 days prior to and up to 72 hours after hospital admission. Test-negative controls include study participants negative for other pathogens and study participants positive to other pathogens based on specimen(s) collected between 10 days prior to and up to 72 hours after hospital admission.

11.7 Identification of modified SARI patients

Modified SARI patients will be identified based on the 'modified SARI definition' (section 13.6.2) either prospectively (e.g., during consultation in the emergency department (ED) or at admission to an infectious disease or internal medicine hospital ward) or retrospectively by hospital database search or from respiratory samples sent to the virology laboratory.

11.8 Exposure

11.8.1 Exposure definitions

11.8.1.1 'Vaccinated with [RSV vaccine name] during the study period of interest'

'Vaccinated' study participants were vaccinated with exposure of interest: e.g. single dose/primary vaccination/at least one dose of RSV vaccine of interest during the epidemiological year(s) of interest, within the appropriate timeframe for the product to be **effective** prior to modified SARI symptom onset.

11.8.1.2 'Unvaccinated with [RSV vaccine name] during the study period of interest'

'Unvaccinated' study participants did not receive any exposure of interest: e.g. single dose/primary vaccination/at least one dose of RSV vaccine of interest during the epidemiological year(s) of interest.

11.8.1.3 'Recently vaccinated with [RSV vaccine name] during the current RSV season'

'Recently vaccinated' study participants were vaccinated with exposure of interest: e.g. single dose/primary vaccination/at least one dose of RSV vaccine of interest during the epidemiological year(s) of interest, within the appropriate timeframe for the product to be **ineffective** prior to modified SARI symptom onset.

11.8.1.4 'Other'

Additional vaccine exposure definitions might be defined depending on the real-life use of the RSV vaccines.

11.8.2 Exposure ascertainment

Information on all prior RSV vaccine doses will be collected. Vaccination status, vaccination date, vaccine dose and vaccine name and brand information are required. Depending on the Study Contributor, the source for exposure ascertainment will be different and may include vaccination registries, medical records, or vaccination cards. Information on the source documentation of the exposure ascertainment will be collected.

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

11.9 Covariates

The complete dataset can be found in the id.DRIVE common dataset case report form (eCRF) and is summarised in Table 1. All covariates are being collected for both prospective and retrospective subjects, if available.

Table 1. Study covariates and health care use

Covariate[17]	Description
Age at hospital admission	Years, calculated based on date of birth and date of admission
Gender assigned at birth	Male, female
Chronic conditions*	
Asthma	Binary If yes, subcategory 'Mild intermittent', 'Mild persistent', 'Moderate persistent', 'Severe persistent', 'No information'
Lung disease	Binary If yes, subcategory 'COPD' and stage (GOLD I – IV, No information)
Cardiovascular disease	Binary If yes, subcategory 'Congestive heart failure'
Hypertension	Binary
Chronic liver disease	Binary If yes, subcategory 'End-stage liver disease (ESLD)': 'No', 'Yes', 'No information'
Chronic renal disease	Binary If yes, subcategory 'End-stage kidney disease (ESKD)': 'No', 'Yes but without dialysis', 'Yes and on dialysis', 'No information'
Diabetes type I	Binary
Diabetes type II	Binary
Obesity	Binary
Cancer	Binary If yes, specification of subcategories: 'Solid tumour', 'Haematological cancer', 'No information'. If solid tumour or haematological cancer is yes, further specification of cancer type to be selected from list.

[17] Some covariates might not be collected across all Study Contributors. This will be specified in the Study Requestor-specific protocol and SAP after completion of feasibility assessments.

Covariate[17]	Description
Immunodeficiency (or organ transplant)	Binary If yes, specification of subcategories: 'Solid organ or islets transplant', 'Hematopoietic stem cell transplantation', 'Primary immunodeficiency', 'Advanced or untreated human immunodeficiency virus (HIV) infection', 'Iatrogenic immunodeficiency', 'Other'. If solid organ or islets transplant is yes, specification of subcategories: 'Kidney', 'Liver', 'Intestines', 'Heart', 'Lung', 'Pancreas', 'Other', 'No information'
Neurological disorders	Binary
Receiving chronic oxygen supplemental therapy	Binary (defined as oxygen used for at least 15 h per day in chronically hypoxaemic patients)
Body mass index (BMI)	Continuous
Smoking history	Never smoker, ex-smoker, occasional smoker, daily smoker, no information
Vaccination history RSV	Binary If yes, was it investigational RSV vaccine, brand, date, and source of information
Vaccination history COVID-19	Binary If yes, brand, date, and source of information
Vaccination history influenza	Binary, within 12 months prior to the modified SARI hospital admission If yes, brand, date, and source of information
Vaccination history pneumococcus	Binary, at least one vaccination in the past If yes, brand, date, and source of information
Long-term care facility residence	Binary, if no, specification of residential situation before hospitalisation: 'Home', 'Home with nursing care', 'Transfer from another hospital', 'Rehabilitation centre', 'Nursing home', 'Other', 'No information'
History of RSV in the current season before symptom onset leading to this hospitalisation	Binary If yes, date.
Prior modified SARI hospitalisation episode in previous 12 months	Binary, If yes, time since most recent prior modified SARI hospitalisation
Month and year of prior SARI episode	Month and year
Respiratory support	'None', 'Oxygen therapy', 'Non-invasive ventilation', 'Invasive mechanical ventilation', 'Extracorporeal membrane oxygenation (ECMO)', 'No information'
ICU admission	Binary, date of admission, date of discharge
In-hospital death	Binary, date of hospital discharge or in-hospital death
Post-discharge destination	'Home', 'Home with nursing care', 'Transfer to another hospital', 'Rehabilitation centre', 'Nursing home or other long-term care facility', 'Other', 'No information'
Length of hospital stay	Days, continuous
Treatments received during hospital stay for the management of modified SARI episode	'Antibiotics', 'Antiviral drug(s)', 'Corticosteroid(s)', 'Immune modulator(s)', 'Anti-RSV antibodies', 'Other monoclonal antibodies', 'None of the above'. Brand name, if anti-RSV antibodies received during hospital stay

Covariate[17]	Description
Treatments received prior to hospital admission for the management of current modified SARI episode	'Antibiotics', 'Antiviral drug(s)', 'Corticosteroid(s)', 'Anti-RSV antibodies', 'Other monoclonal antibodies', 'None of the above'. Brand name, if anti-RSV (or other monoclonal) antibodies received during hospital stay
Medicinal product for the prevention of RSV infection within 12 months prior to current hospitalisation	Binary If yes, type ('Antiviral drug', 'Anti-RSV-antibodies', 'Other'), brand and date (month/year) if anti-RSV-monoclonal antibody
Laboratory results (RSV)	Type of specimen(s), date(s), RSV subtype(s)
Laboratory results (SARS-CoV-2)	Type of specimen(s), date(s), genetic variant(s)
Laboratory results (Influenza)	Type of specimen(s), date(s), subtype(s)
Laboratory results (other pathogens)	Type of specimen(s), date(s), identified pathogen(s), subtype(s) and genotype(s) [if applicable]

** Definitions for each chronic condition are specified in the id.DRIVE Common dataset case report form.*
Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; ESLD, end-stage liver disease; ESKD, end-stage kidney disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICU, intensive care unit; RSV, respiratory syncytial virus; SARI, severe acute respiratory infection; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

11.10 Sample size considerations

The technical considerations for the calculation of the targeted samples sizes are detailed in Annex 1. The sample size requirements strongly depend on the objectives (primary vaccination, seasonal vaccination), on case-control ratio, overall vaccination coverage and share of the different vaccine brands. Due to the nature of the TNCC design, all cases and controls are recruited and data on them are collected. This is a key aspect of the TNCC design and additionally crucial for surveillance use-cases. If balancing of case-control ratios is desired, these can be handled at the analysis stage for brand-specific analyses. As such, the sample size requirements and assumptions will be different for each vaccine brand and defined by the Study Team. Sample size requirements will be calculated for each Study Requestor-specific protocol (for both interim and final analysis when applicable). In case the parameter settings used for these sample size calculations are very different from what is observed in the study, the sample size calculations will be updated accordingly with the progress reports.

11.11 Data management

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

11.11.1 Data management at Study Contributor level

Each Study Contributor is responsible for the data collection and data management of their participant-level study data. Depending on the Study Contributor, the data collection and source

documentation will be different. A Source Data Location Form for variables is collected during a site initiation visit (SIV).

11.11.2 Data flow

1. The Study Contributor collects the data and enters/uploads it in the Castor® 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 a 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.

11.12 Data analysis

An 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 tables shells and mock figures.

11.12.1 Context information

Context information will be provided in study reports by describing the circulating RSV subtypes during the study period in the countries (or regions) where the Study Contributors are located. National (or regional) RSV 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 RSV viral distribution, vaccination coverage, and vaccination recommendations will be specified in the SAP.

11.12.2 Attrition diagram

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

11.12.3 Descriptive analysis of demographics and baseline characteristics

Visualisations based on the final vaccine brand/product-specific data for analysis will be created including:

- number of test-negative controls and test-positive cases (possibly by RSV subtypes) over time
- distribution of covariates among controls and cases

A tabular summary based on the final brand/product-specific data for analysis will be created, describing the characteristics of cases and controls as predefined in the SAP.

11.12.4 Statistical analyses

VE is defined as (1 – OR) x 100%, where *OR* denotes the (exposure) odds ratio, comparing the confounder-adjusted odds of vaccination among RSV-positive study participants to the odds of vaccination among RSV-negative study participants.

VE estimates will be adjusted for calendar time at minimum, and additionally the following confounders – age, sex, and comorbidities (e.g. number of chronic conditions). Adjustments are usually achieved through inclusion of the relevant terms in the logistic regression models, with (penalised) spline terms for calendar time and age. However, other methods may be considered as well.

Clusters will be defined at the hospital network (Study Contributor) level. If some networks have hospitals that 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.

An important choice is whether the exposure odds ratios are desired to have a subject-specific (SS) or population-averaged (PA) interpretation [16]. The SS OR compares odds of vaccination among the RSV-positive cases to the odds of vaccination among the RSV-negative controls from the same Study Contributor (conditional on other covariates) and necessitates the inclusion of a fixed-effect or a random-effect term for Study Contributor in a multivariable model, or via a meta-analysis. The PA OR compares the odds of vaccination among the RSV-positive cases across the Study Contributors to the odds of vaccination among RSV-negative controls across the Study Contributors (conditional on other covariates) and is commonly obtained from a GEE model. Care should be taken with regards to method selection (estimators for point-estimates and standard errors) to avoid biased VE estimates when the clustering variable is a potential confounder or when the cluster size is informative. For population-averaged estimates, GEE with a working independence correlation structure (IEE, or independence estimating equations) and cluster robust standard errors (Liang-Zeger) should be used. For subject-specific estimates, using a fixed-effect term for Study Contributor in a multivariable logistic regression model (GAM) is recommended due to its ease of implementation; no further adjustments to the standard errors are required.

If effect modification / treatment effect heterogeneity by Study Contributor is of interest, a stratified analysis by Study Contributor can be carried out. Alternately, Study Contributor-specific VE estimates can be obtained by adding interaction terms between Study Contributor and exposure in the models.

11.12.4.1 Missing values

Data on exposure and especially the potential confounders may be missing for a proportion of the study participants. These data are often collected from existing medical records, vaccine registries, etc. which existed before the modified SARI episode, and it seems reasonable to assume that whether the data is missing is independent of the RSV status during the modified SARI episode. Assuming that the described missing data mechanism holds, performing a complete case analysis (CCA) will not lead to biased results. The primary analysis will therefore be a CCA, dropping records with missing information for the outcome, exposure of interest or the covariates. In case >10% of the cases and controls have missing covariate information, CCA is likely to be inefficient and alternatives such as multiple imputation and augmented CCA will be explored. A sensitivity analysis will be carried out comparing results from CCA (where records with missing data are dropped) and full set analysis (with imputed data).

11.12.4.2 Sensitivity analyses

Multiple sensitivity analyses will be performed. Alternative statistical models may be used that differ from models used for the primary and secondary objectives. Additional sensitivity analyses that can be conducted include:

- exploring the effect of time between symptom onset date and swab date,
- exploring the effect of time between symptom onset date and hospitalisation,
- exploring the effect of time between hospital admission and swab date,
- exploring the effects of different modified SARI definitions (id.DRIVE case definition[18], World Health Organisation [WHO]-RSV case definition[19]),
- exclusion of patients who have received monoclonal antibodies and other RSV products for either treatment or pre- or post-exposure prophylaxis prior to hospitalisation if there is significant use thereof in the population,
- exploring unmeasured confounding or biases through negative control methods: negative control exposure and/or negative control outcomes (e.g., exclusion of test-negative controls that tested positive with RADT in the 10 days prior to hospital admission),

[18] 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 (≥ 38 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 Severe Acute Respiratory Infection, 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]].

[19] 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]

- the effect of redefining the positive case group, by including only RSV tested-positive cases without a coinfection, and
- the effect of patients having ≥2 laboratory-confirmed RSV infections in the current season.

All sensitivity analyses will be pre-specified in the SAP.

12 QUALITY MANAGEMENT

12.1 Independent Scientific Committee

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

The roles and responsibilities of the ISC are the following:

- reviews and makes recommendations for study documents (protocols and SAPs),
- reviews and makes recommendations for study reports, and
- reviews and formulates recommendations for the master scientific documents, which are co-developed by the id.DRIVE partners to harmonise study methodology (e.g., protocols and analyses to assess severe RSV, long-term effectiveness, RSV infection, or transmission).

12.2 Quality Assurance and Audit Committee

The Quality Assurance and Audit Committee (QAAC) of id.DRIVE composed of one quality assurance expert of each Pharmaceutical Company Partner and one quality assurance expert of the Co-Coordinators. The QAAC's mission is to provide, at the partnership level, guidance on implementation, conduct, monitoring and quality assurance of the Studies, as well as to ensure that data quality is in line with the Study request and to, when necessary and to the extent possible, identify areas for improvement.

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

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

12.3 Monitoring

Monitoring activities include:

- Before study start, the Study Contributor will be asked to complete a quality management questionnaire to inform the Study Team on all aspects of the study conduct.
- Before study start, an SIV will be organised by the Study Team.
- During study conduct, regular Study Contributor contacts will be organised to monitor study progress (number of cases and controls enrolled), to ensure regular data input to the id.DRIVE

EDC system and to discuss potential protocol deviations or other issues related to the study conduct.

- Study Contributors will be asked to keep high-level Screening Logs (including number of modified SARI patients missed or not consented for the study with age group and gender), 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 IEC, auditors and representatives from regulatory authorities direct access to all study-related documents. Participant confidentiality will be protected at all times.

12.4 Data quality checks at central level

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

13 LIMITATIONS OF THE RESEARCH METHODS

- Due to high demand and limited vaccine supplies, European 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 [24]. 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 was likely limited: complete exposure data was required for a participant to be retained in the id.DRIVE study (mandatory variables included date of administration, dose number and vaccine brand).
- 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.
- The PROMISE 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.
- Despite RT-PCR's high specificity and sensitivity, diagnostic inaccuracies pose potential bias, influenced by factors like sampling technique, specimen type, number of specimens [17, 18], and timing. In RSV RT-PCR, declining sensitivity over time may yield more false negatives among vaccinated, overestimating VE. Sensitivity analyses, such as varying time between symptom onset and sampling, as well as addition of pre-admission rapid antigen testing, 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 overestimated VE 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.
- This study does not measure frailty, an important potential effect modifier of VE. Frailty has been shown to affect immune responses in older adults to vaccines for infections such as influenza, shingles and pneumococcus [19]. Frailty, impacting immune responses in older adults, lacks a consensus definition and measurement method. Given the study's focus on the general population and frailty's complexity, we collect information on related variables like age, body mass index (BMI), long-term care residence, and chronic conditions instead of directly measuring frailty.
- Last, 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 European hospital network, obtaining sufficient samples for accurate estimates of primary and secondary objectives may be challenging.

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

14.1 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) [20], Good Epidemiological Practice (GEP) [21], the ethical principles that have their origins in the Declaration of Helsinki, and any applicable national laws, regulations and guidelines.

This is an observational study. Therefore, there is no direct benefit to the participants. Nevertheless, there are important potential societal benefits derived from this VE study. Close monitoring of the effectiveness of RSV vaccination products is essential to guide decision-making regarding vaccination products marketing approval, optimisation of vaccination programmes and future RSV vaccine development.

14.2 Ethics approval

The Study Contributor-specific protocols 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 programme 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.

14.3 Informed consent

Written informed consent will be obtained from all participants/guardians as specified by the national/regional IEC, if applicable. The following information should be specified in the informed consent form (ICF) 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.

14.4 Independent ethics committee/Institutional review board

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

Before implementation of any substantial changes to the protocol, protocol amendments will also be submitted to the relevant IRB/IEC in a manner consistent with local regulations. It is the responsibility of the Study Contributor (local) 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 (local) investigator will be responsible for informing the IRB/IEC of the early termination.

14.5 Participant's confidentiality

Data will be pseudonymised at the Study Contributor level prior to data transfer to P95 Epidemiology & Pharmacovigilance. 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 (GDPR).

14.6 Changes to the protocol

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

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

14.7 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 data use, id.DRIVE governance principles will be respected as detailed in the id.DRIVE Governance Charter. The Governance Charter can be made available by the Co-Coordinators upon written request.

15 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 study sites (Study Contributors), 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.

15.1 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.

15.2 Data capture

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

15.3 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 predefined and described as appropriate.

15.4 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.

15.5 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.

16 REPORTING AND DISSEMINATION OF RESULTS

16.1 Study protocol

The study protocol and final study report will be included in the HMA/EMA catalogue of real-world data studies.

16.2 Management and reporting of adverse events/adverse reactions

This is a non-interventional epidemiological study for assessing the effectiveness of recommended or routine RSV 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 (ICSR) form for reporting SAEs is provided in the Investigator Site Files (ISFs).

16.3 Progress, interim and final reports

Progress reports will be provided to the Study Requestors every two months since enrolment of the first study participant. Progress reports will provide an overview of the number of cases, number of controls, number of study participants immunised with any RSV vaccination product brand and number of study participants immunised with the RSV vaccination product brand of interest.

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

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

16.4 Publication

Scientific publication(s) of the study results will be prepared. Co-authorship will be defined following the International Committee of Medical Journal Editors (ICMJE) criteria and the Good Publication Practice (GPP). All publications will be open-access.

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

17 FUNDING

id.DRIVE is a public-private partnership funded by the Pharmaceutical Company Partners and leveraging health capacities from public partners and sites. This generic Master Protocol has been developed by the id.DRIVE partnership, which has received funds from AstraZeneca, Bavarian Nordic, CureVac, GlaxoSmithKline (GSK), Janssen, Moderna, Novavax, Pfizer, Sanofi, and Valneva, leveraging public health capacity from Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana (FISABIO) and the Finnish institute for Health and Welfare (THL) and existing infrastructure at P95. Other Partners (Pharmaceutical Companies or other Institutions) may join the id.DRIVE partnership at later stages. Cost sharing principles are defined in the id.DRIVE Consortium governance charter. The execution of the brand-specific study will be further funded by [Study Requestor] requesting the specific study.

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ANNEX 1: SAMPLE SIZE CALCULATIONS, TECHNICAL SPECIFICATIONS

Sample size calculation

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

Analytical approach: power and minimal detectable VE

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

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

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

and

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

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

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

where z_α and z_β are critical values for the standard normal distribution[20].

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

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

[20] WOODWARD, M. (2013). *Epidemiology: Study Design and Data Analysis, 3rd Ed.*, Chapman and Hall/CRC.

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

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

where

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

for 'cases to controls' ratio *r*, coverage γ, total number of subjects N, and where z_α and z_β are the standard normal z-scores for the type I and type II error rates[20].

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

Simulation-based approach

Data generation workflow

Notation

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

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

General set-up

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

Simulating data at the Study Contributor level

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

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

Simulating Study Contributor-specific VE

Effect of primary series vaccination

To incorporate the expected between-Study Contributor heterogeneity, for each Study Contributor, a Study Contributor-specific odds ratio ($OR_{x,site}$) was generated from a log-normal distribution with a median of $1 - \frac{VE_{x,overall}}{100}$ and variance on the log scale of 0.05. The value of the variance parameter on the log scale was selected to be 0.05 as it introduced an amount of between-Study Contributor heterogeneity and was in line with the heterogeneity seen in a previous database study[21]. Note that decreasing the value of this parameter lead to a decrease in the sample size requirements. The expected value of the VE over the Study Contributors is then equal to $100 \times \left(1 - \exp\left(\log\left(1 - \frac{VE_{x,overall}}{100}\right) + \frac{0.05}{2}\right)\right)$.

Effect of additional dose vaccination

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

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

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

Estimates and data obtained for each simulation

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

[21] THOMPSON, M. G., STENEHJEM, E., GRANNIS, S., et al. (2021). Effectiveness of Covid-19 Vaccines in Ambulatory and Inpatient Care Settings. N Engl J Med, 385(15):1355-71.
DOI: https://doi.org/10.1056/NEJMoa2110362.

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

- The simulated dataset is restricted to represent the data of interest.
- The Study Contributor-specific expected OR on the log-scale of the (relative) treatment effect is calculated using a logistic regression model with the disease status as the outcome and the exposure status as a covariate.
- The Study Contributor-specific log OR estimates are combined using a random-effects meta-analysis (RE-MA) model. More particularly, the log OR estimates are combined using the Hartung-Knapp-Sidik-Jonkman estimator to obtain an estimate of the median overall log OR and the corresponding two-sided 95% CI.
- The pooled log OR and the corresponding CI are then back-transformed to obtain an estimate and 95% CI of the median overall VE.
- The overall VE estimate and the length of the CI are stored for each simulation.

Generalised estimation equations (GEE)

- The simulated dataset is restricted to represent the data of interest.
- The expected OR on the log-scale of the treatment effect is estimated using a logistic regression model with the disease status as the outcome and the exposure as a covariate. The estimates are obtained using the GEE method in which the Study Contributors are considered as clusters and the variances are calculated using a robust sandwich estimator.
- The estimated log OR and the corresponding CI are then back-transformed to obtain an estimate of the mean overall (r)VE and its 95% CI.
- The overall (r)VE estimate and the length of the CI are stored for each simulation.

Generalised linear model/generalised additive model (GLM/GAM)

- The simulated dataset is restricted to represent the data of interest.
- The expected OR on the log-scale of the treatment effect is estimated using a logistic regression model with the disease status as the outcome and the exposure as a covariate.
- The estimates are obtained using the GLM/GAM method in which the Study Contributors are considered as fixed effects.
- The estimated log OR and the corresponding CI are then back-transformed to obtain an estimate of the mean overall (r)VE and its 95% CI.
- The overall (r)VE estimate and the length of the CI are stored for each simulation.

Number of simulations performed

For each combination of parameter settings, a total of 500 simulations are recommended. On empirical basis, this number of simulation runs leads to stable Monte Carlo CIs while limiting the computational burden.

Summary measures of the simulation study

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

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

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