STUDY PROTOCOL

Surveillance study of respiratory pathogens in adults hospitalised for SARI across Europe

A contribution of id.DRIVE, a public-private partnership.

Version 1.0

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

DOCUMENT HISTORY

Version control table

Version	Version date	Reason for new version
1.0	21 March 2024	Creation of first version of the protocol

TITLE PAGE

Abbreviated study title	id.DRIVE Surveillance study
Full study title	Surveillance study of respiratory pathogens in adults hospitalised for SARI across Europe
Study ID	01
HMA-EMA catalogue number	EUPAS1000000012
Protocol version	1.0
Date of protocol version	21 March 2024
Study Requestor(s)	AstraZeneca, Pfizer
Study status	Non-interventional
Research question and objectives	Primary objectives: 1. To calculate the proportion of laboratory samples positive for each viral respiratory pathogen of interest, among adult patients hospitalised with SARI; 2. To characterise adult SARI patients (including age, gender, protective- and risk factors, specific treatments, healthcare utilisation outcomes), overall and by viral respiratory pathogen of interest. Secondary objective: 3. To investigate the prevalence of co-infection with the viral respiratory pathogens of interest, in adult patients hospitalised with SARI, and the impact on healthcare utilisation outcomes. Exploratory objectives: 4. To calculate pathogen-specific SARI incidences and describe trends in adults (time period, country, level of severity); 5. To perform feasibility assessments for future respiratory disease studies within the id.DRIVE Study Network (e.g., effectiveness studies, impact studies).
Country(ies) of study	Belgium, Germany, Italy, Spain

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

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GLOSSARY

Term	Description
COVIDRIVE	means the public-private partnership for the estimation of brand-specific COVID-19 vaccine effectiveness in Europe organised under the Consortium Agreement.
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.
id.DRIVE	means the public-private partnership for conducting observational studies on infectious diseases, vaccines, related preventive measures and therapeutics for infectious diseases in Europe organised under the Consortium Agreement. For the avoidance of doubt, as of the Effective Date COVIDRIVE becomes a part of id.DRIVE as described in further detail in the Governance Charter.
Independent Scientific Committee (ISC)	means the body consisting of a limited number of external experts with relevant experience/expertise in the field of infectious diseases, vaccines, related preventive measures and therapeutics for infectious diseases. Scientific experts representing each of the Co-coordinators act as the secretariat of the ISC.
Partner	means a legal entity signatory of the Consortium Agreement. Partners are either Core Platform Partners or Pharmaceutical Company Partners.
Pharmaceutical Company Partner	means a Partner that is a pharmaceutical company.
Quality Assurance and Audit Committee (QAAC)	means the committee responsible for the quality management and auditing of the Studies, composed of one quality assurance expert from each Pharmaceutical Company Partners and one quality assurance expert from the Co-coordinators. The Co-Coordinators act as the secretariat of the QAAC.
Study Contributor	or “Study Site or “Site”, means an institution that collects/owns data of interest for studies and that signs a Study Contributor Agreement with P95 after being selected via a study-specific selection process.
Study Network	means the network of Study Contributors and potential new Study Contributors who have expressed interest to conduct Studies.
Study Requestor	means the Partner that requests to perform a specific Study.
Study Results Publication	means a scientific publication reporting on the Study including all Study objectives identified in the individual Study protocol(s).

Study Team (ST)	means the team that carries out the conduct of the Study. For Primary Data Use Studies, the Study Team includes experts from the Co-coordinators, Study Contributors and Study Requestors. • The Restricted Study Team (Restricted ST) is made up of experts from the Co-Coordinators and Study Contributors. • The Full Study Team (Full ST) is the Restricted ST plus the experts from the Study Requestors.

ABBREVIATIONS

BiPAP	Bi-level Intermittent Positive Airway Pressure
BMI	Body Mass Index
CIOMS	Council for International Organisations of Medical Sciences
CIRI-IT	Centro Interuniversitario per la Ricerca sull'Influenza – Italy
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus disease 2019
CPAP	Continuous Positive Airway Pressure
DALY	Disability-Adjusted Life Year
DMP	Data management plan
EDC	Electronic data capture
ECDC	European Centre for Disease Prevention and Control
ECMO	Extracorporeal Membrane Oxygenation
ED	Emergency Department
EMA	European Medicines Agency
ESLD	End stage liver disease
ESKD	End stage kidney disease
EU	European Union
EU/EEA	European Union/European Economic Area
GDPR	General Data Protection Regulation
GEP	Good Epidemiological Practice
GPP	Good Publication Practice
GTPUH	German Trias I Pujol University Hospital
HEV	Human EnteroVirus
HMA-EMA	Heads of Medicines Agencies - European Medicines Agency
hMPV	human MetaPneumoVirus
HRV	Human RhinoVirus
HUVH	Vall d'Hebron University Hospital
ICF	Informed consent form
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive care unit
IEC	Independent ethics committee
ILI	Influenza-Like Illness
IRB	Independent review board
ISC	Independent Scientific Committee
LAR	Legally acceptable representative
LRTI	Lower Respiratory Tract Infection
MAH	Marketing authorisation holder
PAS	Post-Authorisation Studies
QAAC	Quality Assurance and Audit Committee
RT-PCR	Reverse transcription polymerase chain reaction
RSV	Respiratory syncytial virus
SARI	Severe acute respiratory infection
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAP	Statistical analysis plan
ST	Study team
TMA	Transcription mediated amplification
UK	United Kingdom
US	United States
UZA	University Hospital Antwerp

VAHNSI	Valencia Hospital Surveillance Network for the Study of Influenza and Other Infectious Diseases
VE	Vaccine effectiveness
WHO	World Health Organisation

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ABSTRACT

Background

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

id. DRIVE is a public-private partnership which aims to conduct non-interventional studies on infectious diseases, vaccines, related preventive measures and therapeutics for infectious diseases in Europe (https://iddrive.eu). id.DRIVE's Study Network will be leveraged to continuously monitor SARI-causing pathogens (e.g., SARS-CoV-2, influenza, and respiratory syncytial virus), including virological and clinical trends, as well as burden of disease (e.g., pathogen-specific morbidity; in-hospital mortality), as detailed in this protocol. The surveillance of additional pathogens allows for study preparedness, with the potential to perform feasibility assessments for future impact and effectiveness studies within the id.DRIVE Study Network.

Research aim

Sentinel SARI surveillance for the continuous monitoring of virological and clinical trends, including pathogen-specific morbidity and in-hospital mortality in adults in Europe.

Objectives

This surveillance study aims to establish active surveillance for hospitalised SARI cases in adults in Europe.

The primary objectives are:

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

In addition, a secondary objective is:

3. To investigate the prevalence of co-infection with the viral respiratory pathogens of interest[1], in adult patients hospitalised with SARI, and the impact on healthcare utilisation outcomes[2].

[1] SARS-CoV-2 and/or SARS-CoV-2 specific variant, Influenza A/B, Respiratory Syncytial Virus (RSV) A/B, Adenovirus, Parainfluenza viruses (1-4), human metapneumovirus (hMPV), human rhinovirus (HRV), human enterovirus (HEV), human coronaviruses (229E/NL63/OC43/HKU1)

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

Exploratory objectives are:

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

Study methods

Study design: SARI-based surveillance study.

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

Data collection: Prospective

Study duration: From June 2024, with a minimum duration of 12 months.

Countries: The study will be conducted in Belgium, Spain, Italy, and Germany. Additional countries may be included during the study period.

Study participants: Adults (18 years and older) presenting at the participating hospitals during the study period who 1) are hospitalised and meet the SARI case definition AND who 2) meet the following criteria for:

- Inclusion: Willing and able to provide informed consent, when applicable, obtained from the patient or from the patient's Legally Acceptable Representative(s) (LAR)
- Exclusion: No exclusion criteria have been defined.

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

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

with symptom onset within the last 14 days prior to hospital admission. This SARI definition is modified from the latest European Centre for Disease Prevention and Control (ECDC) case definition (specifying "suspicion of respiratory infection") [3].

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

Laboratory-confirmed infection: For each studied pathogen, a laboratory-confirmed infection is defined as a positive reverse transcription polymerase chain reaction (RT-PCR)[3] or multiplex RT-PCR on any respiratory specimen(s) collected between 14 days prior to and up to 72 hours after hospital admission. The absence of a laboratory-confirmed infection requires all samples collected in this time frame to be negative.

[3] Or another RNA amplification system with at least the same sensitivity as RT-PCR (e.g., transcription-mediated amplification (TMA)).

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

Laboratory testing

Clinical specimens will be taken from all SARI patients included in the study (within 72 hours after hospital admission). The preferred respiratory specimen is a nasopharyngeal swab. Additional respiratory specimens are accepted (e.g., nasal swab, oropharyngeal swab, bronchoalveolar lavage, aspirates). Sample type will be recorded.

The specimens will be tested for at least SARS-CoV-2, influenza A/B and respiratory syncytial virus (RSV) A/B, and preferably also for adenovirus, parainfluenza 1-4, human metapneumovirus (hMPV), human rhinovirus (HRV), human enterovirus (HEV), and human coronaviruses (229E/NL63/OC43/HKU1), by using validated RT-PCR or multiplex RT-PCR assays, or another RNA amplification system with at least the same sensitivity as RT-PCR (e.g., transcription-mediated amplification (TMA)).

Further genotyping or subtyping, if not available through local multiplex, will be performed on specimens that test-positive for:

- RSV:
  - Subtype A and B
- Influenza:
  - Type A and B
  - Subtypes A H1, Influenza A H3
- SARS-CoV-2:
  - Genotyping (pangolin lineage)

Covariates

Variables that will be collected include age, gender, history of medical diagnosis for selected morbidities of interest (chronic pulmonary disease (e.g., asthma, chronic obstructive pulmonary disease (COPD), emphysema), cardiovascular disease, hypertension, chronic liver disease, chronic renal disease, type 1 and type 2 diabetes, cancer, immunodeficiency disorders, obesity, and neurological disorders), body mass index (BMI), smoking history, previous SARS-CoV-2 infection, prior SARI hospitalisation and time since hospitalisation, vaccination against respiratory pathogens (SARS-CoV-2, influenza, RSV, pneumococcus; including brand and date of vaccination), calendar time, pregnancy (and term), respiratory support, intensive care unit (ICU) stay, in-hospital death, any use of preventive or therapeutic antivirals or virus-specific monoclonal antibodies prior or during hospitalisation, long-term care facility residence, and discharge destination.

Data collection

After study enrolment, data will be collected from primary (e.g., lab results) and secondary data sources (e.g., vaccination registries). Information to be collected at minimum include:

- SARI symptoms and onset date;
- date of sampling, outcome of specimen testing, assay used;
- date of hospital admission and discharge;
- Healthcare utilisation outcomes (in-hospital death, ICU admission, respiratory support, discharge destination, length of stay);
- covariates, including vaccination details (see Covariates section).

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

Statistical analysis

Clinical characteristics of the SARI patients will be provided, overall and by SARI-causing pathogen (type and/or subtype), including age groups, gender, symptoms, presence of chronic conditions, BMI, vaccination status, receipt of preventive monoclonal antibodies, pregnancy, smoking history, use of antiviral or virus-specific monoclonal antibody therapy, long-term care facility residence, and healthcare utilisation outcomes. Overall clinical characteristics will also be provided over time (monthly).

The total number of laboratory samples and proportion positive for each respiratory pathogen of interest and co-infections will be provided. Counts and proportions, along with 95% exact binomial confidence intervals, will be provided by calendar time, by Study Contributor, by country, and by age- and risk groups of interest. Co-infections will be described, by number of pathogens, by pathogen type and by healthcare utilization outcome.

Multinomial logistic regression will be used to explore the risk factors of pathogen-specific SARI hospitalisation, healthcare utilisation outcomes, and the presence of co-infections (by number of co-infections and involved pathogens, when feasible). Potential risk factors include age, gender, chronic conditions, and smoking. Stratified analyses will be performed by age groups, by gender, by presence of chronic conditions and specifically by those with pre-existing immunodeficiency disorders.

Pathogen-specific SARI incidence (per 100,000 person-years) will be derived from the percent pathogen positivity and the estimated catchment populations of the hospitals, if appropriate denominator data and comprehensive SARI surveillance to identify untested SARI events are both available. The feasibility of obtaining appropriate catchment population data and a complete SARI numerator will be assessed by site. If feasible, pathogen-specific SARI incidence will be calculated by calendar time, by Study Contributor, by country, and by age groups. Time trends will be explored treating calendar time as a categorical variable and as a continuous variable using penalised smoothing splines.

Reporting

Progress reports will be provided every two months from enrolment of the first participant. Progress reports will provide recruitment numbers, main demographic and clinical characteristics of SARI patients and pathogens detected. Study reports will be prepared once a year, covering the primary and secondary objectives. A final report will be prepared after 12 months of data collection.

Feasibility assessments for future respiratory disease effectiveness studies will be detailed in study feasibility reports and will be performed at the latest 12 months after start of the study data collection. Additional feasibility reports can be triggered (e.g., to evaluate any modifications to improve data quality, or upon major changes to the respiratory pathogen- and vaccine landscape).

Data management

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

Ethical considerations

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

Study limitations

When using sentinel surveillance, generalisability may be limited as social and demographic factors are usually not uniform across a country and thus the catchment population of a sentinel network may not be comparable with the remaining population of a country. Current active sites cover between 6.8% (Germany) to 16.2% (Belgium) of their countries' population, which is above the World Health Organization (WHO) recommended coverage for sentinel surveillance (at least 1-2% of a population) [1].

Under-detection of pathogens of interest may occur. RT-PCR sensitivity is influenced by several factors, including operator sampling technique, type of respiratory specimen, number of specimens collected, and timing of sampling [2, 3]. Assay sensitivity may also vary across pathogens. To limit under-detection, only assays with high sensitivity are used, sampling is performed in the first 72h after hospital admission, and information on the main factors influencing result RT-PCR are collected. Guidance on collecting and handling specimens for the diagnosis of viral respiratory pathogens are given as part of study staff training.

With RT-PCR, a positive result is highly specific for the presence of the viral pathogen nucleic acid of interest. However, RT-PCR does not differentiate between viable and nonviable virus, and a positive result may indicate an older infection, non-causal to the current SARI episode. Notably, as only results of specimens sampled within 72h after admission are included, inclusion of hospital-acquired infections will be avoided.

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

Incidence rates will be calculated by using a proxy denominator (hospital population catchment area and its demographics). Depending on each Study Contributor, the proportion of SARI captured and included in the study will vary. The proxy denominators used for the calculation of incidence rates will not allow for granularity e.g., calculation of incidence rates by e.g., specific chronic conditions. Thus, the feasibility of obtaining appropriate denominator numbers and comprehensive SARI surveillance to identify untested SARI events will be assessed.

Different SARI definitions are currently in use, limiting comparability of results. Here we apply a modified ECDC SARI case definition. Sensitivity analyses will be performed using alternative SARI-case definitions (e.g., WHO SARI definition, WHO extended SARI definition).

Dissemination

The generic protocol of this surveillance study and its substantial amendments will be posted on the id.DRIVE website (https://iddrive.eu/) and included in Heads of Medicines Agencies - European Medicines Agency (HMA-EMA) catalogue of real world data studies. Study Results Publications will be submitted to peer-reviewed open-source international journal(s).

Funding

The id.DRIVE Study Network has been funded by current and previous Pharmaceutical Company Partners of the id.DRIVE consortium (for details refer to the section id.DRIVE consortium). This study and its protocol have been further financed by id.DRIVE Study Requestors, namely AstraZeneca and Pfizer. Other partners (Pharmaceutical Company Partners or other public institutions) may join the id.DRIVE consortium as per id.DRIVE Consortium Agreement and participate in the study's funding. All funding will be transparently acknowledged in study communications.
id.DRIVE consortium
id.DRIVE is a not-for-profit open public-private partnership. Current consortium members are FISABIO (Spain), P95 (Belgium), AstraZeneca (UK), Janssen (Belgium), GSK (UK), Novavax (US), Pfizer (US) and Valneva (Austria). Past members include Bavarian Nordic (Denmark), Moderna (US), Sanofi (France), THL (Finland) and CureVac (Germany).
Study Sponsor
P95
Study status
Non-interventional

MILESTONES

Milestone	Planned date
Registration of study protocol in the HMA-EMA catalogue of real world data studies	March 2024
Start of data collection	June 2024
End of data collection	May 2025
Study progress reports	Every 2 months
Feasibility report	Q3 2025
Final report	Q3 2025
Manuscript	Q4 2025
Registration of study results in the HMA-EMA catalogue of real world data studies	Q1 2026

1 RATIONALE AND BACKGROUND

The latest, pre-COVID-19, report on lower respiratory tract infections (LRTIs) by the Global Burden of Disease Study [4] showed that LRTIs resulted in almost 66 million hospitalisations worldwide and caused 2.4 million deaths in people of all ages, accounting for 4.4% of all-cause mortality. A total of 91,844,600 disability-adjusted life years (DALYs) were estimated to have been attributable to LRTIs in 2016 [4]. LRTIs can be caused by a broad array of pathogens, including various respiratory viruses such as influenza A and B, SARS-CoV-2, respiratory syncytial virus (RSV), adenovirus, or Parainfluenza viruses. Most often, infection with any of these pathogens causes mild illness, such as a cold, but in some cases infection results in serious illness requiring hospitalisation.

Influenza is one of the most contagious seasonal respiratory diseases [5], estimated to have caused over 54 million disease episodes worldwide in 2017, with over 145 000 deaths [6]. Lafond et al [7] estimated in their meta-analysis that influenza viruses are associated with over 5 million hospitalisations worldwide per year in adults, with hospitalisation rates of 437/100,000 person-years in those aged ≥65 years. The Global Burden of Disease Study even estimated almost 9.5 million hospitalisations in 2017 [6]. Following the influenza pandemic in 2009, the World Health Organization (WHO) recommended the integration of severe acute respiratory infections (SARI) surveillance among hospitalised patients into existing public health systems, in addition to the already established Influenza-like illness (ILI) surveillance in outpatients [8].

In late 2019 the world was startled by the emergence of a new virus causing severe respiratory disease, SARS-CoV-2, which spread rapidly across the world. The first cases were identified in December 2019 in China, and WHO declared a pandemic on March 11, 2020 [9]. WHO reports that up to 12 April 2023, there have been over 762 million confirmed cases of COVID-19, caused by SARS-CoV-2, including almost 7 million deaths globally [10]. In response to the enormous burden of the COVID-19 pandemic, vaccines were developed at rapid speed, with the first vaccine approved in the European Union/European Economic Area (EU/EEA) by December 2020. Although the large peaks in disease incidence seem behind us [10], the disease burden persists as the pandemic evolves to endemicity.

The common human coronaviruses (HcoV-229E, HcoV-OC43, HcoV-NL63, and HKU1) are conventionally known to cause the common cold. These viruses cause less severe morbidity than SARS-CoV-2, and often only cause of mild upper respiratory tract infections in adults. However, in high-risk populations, such as elderly or immunocompromised, these viruses can cause severe bronchiolitis and pneumonia [11].

Next to the known burden of COVID-19 and influenza on healthcare, there is increasing evidence that in addition to the known burden in children, RSV is a significant cause of SARI in adults, in particular in the elderly population [12-16]. Ackerson et al [17] showed in a retrospective cohort study that RSV is an important cause of respiratory morbidity and mortality among older adults, causing comparable and more severe morbidity than influenza, resulting in increased duration of hospitalisation and higher risk of pulmonary complications. Falsey et al [15] also showed significant use of medical resources for RSV. However, there is still limited data on the clinical presentation, management, outcomes, and health care utilisation of RSV infection in this at-risk population. In addition, it is estimated that the incidence of RSV hospitalisation in older adults is underestimated by at least 2.2-

fold in current studies, due to case under-ascertainment [3, 18], indicating additional uncertainty with regards to the currently available burden estimates. Note that the burden of RSV in paediatrics is out of scope of this project.

Finally, the attributable proportion of SARI due to other respiratory viruses such as Parainfluenza and adenoviruses, or the burden of respiratory co-infections is not clear. Also, the impact of SARS-CoV-2 on the epidemiological trends of other respiratory viruses is still under investigation.

Continuous monitoring of respiratory pathogens is essential to monitor clinical and virological trends, for epidemic and pandemic preparedness, to guide pathogen and strain selection for vaccine development, to evaluate the impact of interventions (e.g., mass vaccination campaigns, novel therapeutics or vaccines, combined vaccines, or co-administration of vaccines), and to support respiratory virus vaccine effectiveness (VE) studies. The first RSV vaccine for active immunisation of older adults has been approved within the EU in June 2023 (Arexvy) [19], the second one (Abrysvo) received a positive opinion from EMA in July 2023 [20], and more RSV vaccines are expected to apply for marketing authorisation in the EU in the near future. These RSV vaccines will complement the set of currently available vaccines aiming to decrease respiratory morbidity and mortality, including COVID-19, influenza, pneumococcal and pertussis vaccines. Also, several new influenza vaccines are currently in phase 3 of clinical development and are expected to complement the available influenza vaccines in the near future.

Next to ILI surveillance, SARI surveillance has become an international standard for monitoring influenza-associated morbidity and mortality [21], and was extended to the monitoring of SARS-CoV-2 during the COVID-19 pandemic. With the generalisation of the use of multiplex PCR assays (laboratory tests allowing for the simultaneous detection of multiple pathogens on a single sample) following ECDC recommendations [22], SARI surveillance systems could now also be used to study additional respiratory pathogens, such as RSV. Moreover, SARI surveillance networks could potentially be used for additional viral respiratory VE studies, as has been previously done for influenza and COVID-19. Notably, when extending SARI-based influenza surveillance to include SARS-CoV-2, the ECDC "traditional" case definition was modified to fit the specificities of the novel virus: the current ECDC SARI case definition no longer includes fever as an obligatory symptom, increasing the case-definition sensitivity [23]. A more sensitive case definition may be better adapted to the monitoring of other viral respiratory pathogens, particularly RSV, as RSV-related disease will present without fever in a significant fraction of young children and elderly (often >50%) [24].

id.DRIVE is a public-private partnership built upon DRIVE[4] [25] and COVIDRIVE monitoring COVID-19 VE since September 2021 (Home - IDDRIVE). Using SARI data collected across Europe, COVIDRIVE was conducting brand-specific COVID-19 VE studies for Market Authorisation Holders (MAHs) as part of their European regulatory obligations, with methodological alignment across the different post-authorisation studies (PAS). Leveraging its expertise in influenza and COVID-19 VE studies, the partnership is now expanding its scope of research to become an infectious disease study platform with primary focus on viral respiratory disease in adults. This protocol describes a surveillance study

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

to monitor the burden of disease of multiple viral respiratory pathogens and to study preparedness for future impact and effectiveness studies. Data will be collected through a wide network of hospitals located in several European countries, using a common data collection model already in-place from ongoing COVID-19 VE studies.

2 RESEARCH QUESTIONS AND OBJECTIVES

This surveillance study aims to establish active surveillance for hospitalised SARI cases in adults in Europe.

2.1 Primary objectives

1 To calculate the proportion of laboratory samples positive for each viral respiratory pathogen of interest[1], among adult patients hospitalised with SARI;

2 To characterise adult SARI patients (including age, gender, protective- and risk factors, specific treatments, and healthcare utilisation outcomes), overall and by viral respiratory pathogen of interest[1].

2.2 Secondary objectives

3 To investigate the prevalence of co-infection with the viral respiratory pathogens of interest[1], in adult patients hospitalised with SARI, and the impact on healthcare utilisation outcomes[2].

2.3 Exploratory objectives

4 To calculate pathogen-specific SARI incidences and describe trends in hospitalised adults (time period, country, level of severity);

5. To perform feasibility assessments for future respiratory disease studies within the id.DRIVE Study Network (e.g., effectiveness studies, impact studies).

[1] SARS-CoV-2 and/or SARS-CoV-2 specific variant, Influenza A/B, Respiratory Syncytial Virus (RSV) A/B, Adenovirus, Parainfluenza viruses (1-4), human metapneumovirus (hMPV), human rhinovirus (HRV), human enterovirus (HEV), human coronaviruses (229E/NL63/OC43/HKU1)

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

3 RESEARCH METHODS

3.1 Study design

This study is a non-interventional multi-country, multi-centre, hospital-based surveillance study of viral respiratory pathogens in adults hospitalised for SARI.

A combination of primary (e.g., lab results) and secondary data collection (e.g., vaccination registries) will be used to obtain the relevant data.

3.2 Study Contributors (study sites)

This is a multi-country, multi-centre study, with hospital sites in Europe. The participating Study Contributors (also referred to as study sites) are described in Table 1. Additional countries, and or Study Contributors may be included during the study period.

The participating Study Contributors are either individual hospitals or hospital networks. The data collection will be a prospective data collection from primary and secondary data sources, and in some sites, data will additionally be retrieved from the existing hospital databases and linked data.

Table 1. Participating Study Contributors.

Country	Study Contributor[1]	Number of hospitals	No. of hospital beds/ICU beds	Recruitment wards
Spain	VAHNSI	5 hospitals	3347/143	ED
	GTPUH	1 hospital	794/95	All, through hospital records
	HUVH	1 hospital	1154/56	All, through hospital records
	Hospital Clínic de Barcelona	1 hospital	767/63	ED
	Hospital Clínico Universitario de Santiago de Compostela	1 hospital	1511/38	All, through hospital records
	Hospital Universitario La Paz	1 hospital	1308/31	Through hospital records
Italy	CIRI-IT	6 hospitals	5623/281	ED
	Luigi Sacco Hospital	1 hospital	507/20	ED
Belgium	UZA	1 hospital	605/45	ED
	St. Pierre	1 hospital	600/32	Infectious diseases

Germany	Univeritätsklinikum Ulm	1 hospital	1000/30	Infectious diseases
	Universitätsklinikum Frankfurt	1 hospital	1250/96	ED
	Universitätsklinikum Freiburg	1 hospital	2180/48	ED and hospital records

Abbreviations: ICU, intensive care unit; GTPUH, German Trias I Pujol University Hospital; HUVH, Vall d'Hebron University Hospital; CIRI-IT, Centro Interuniversitario per la Ricerca sull'Influenza – Italy; UZA, University Hospital Antwerp; ED, emergency department
[1]Study Contributor selection may differ by Study Requestor

3.3 Study population

The study population consists of adults aged 18 years and older (patients), presenting at the participating hospitals during the study period, who

- meet the inclusion criteria (see Section 3.3.1)

AND

- are hospitalised and meet the SARI case definition (see Section 3.6.2).

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

3.3.1 Inclusion criteria

Individuals (patients) that meet the study population criteria need to fulfil the following inclusion criterion:

- Willing and able to provide informed consent, when applicable, obtained from the patient or from the patient's legally acceptable representative(s) (LAR).

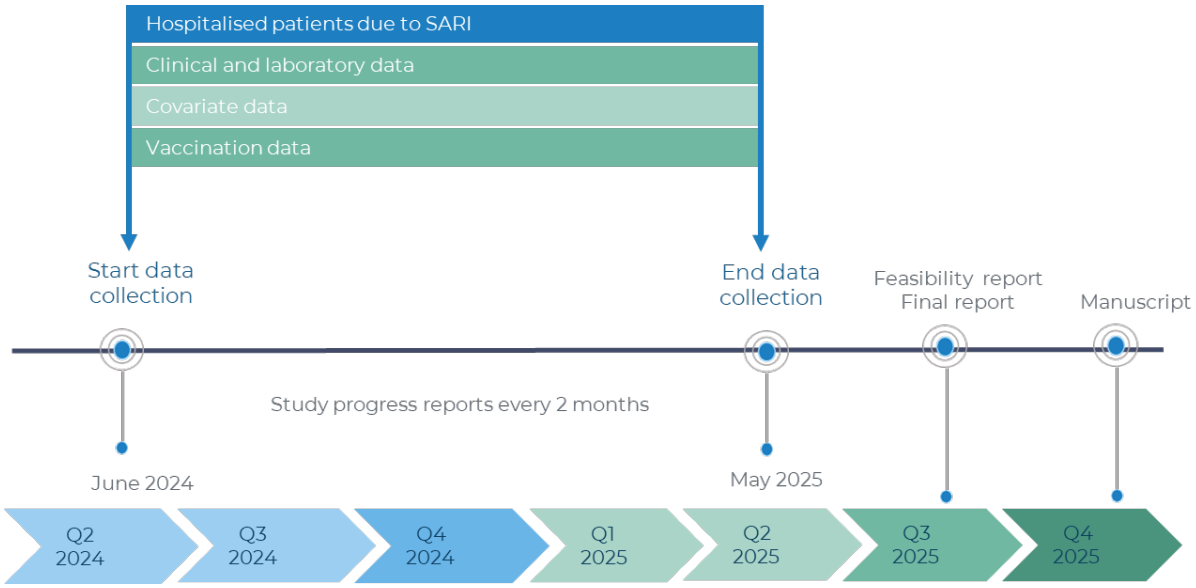
3.3.2 Exclusion criteria

No exclusion criteria have been defined.

3.4 Study period

From June 2024, with a minimum duration of 12 months and an expected duration of two years.
A graphical visualisation of the study timelines is provided in the figure below (Figure 1):

Figure 1: Study timelines



3.5 Study outcomes

The outcome of interest for the primary objectives will be **laboratory-confirmed infection** (Section 3.6.3) with one of the viral respiratory pathogens of interest (see section 3.8.1) in patients hospitalised with SARI symptoms, and laboratory-confirmed co-infection (section 3.6.4) for the secondary objective.

For the second secondary objectives, healthcare utilisation outcomes of interest are:

- **Level of severity** (Section 3.6.5.1).
- **Discharge destination** (Section 3.6.5.2)
- **Length of stay** (section 3.6.5.3)

Pathogen-specific SARI incidences will be calculated to address the first exploratory objective (see section 3.13.5). The denominator will be based on the sum of the catchment populations covered by the Study Contributors [26].

For the second exploratory objective, **feasibility assessments** for future respiratory disease impact and effectiveness studies will be made as described in Section 3.13.6.

3.6 Definitions

3.6.1 Hospitalised patient

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

another hospital, the date of hospital admission is defined as the date of first admission (i.e., admission to the referring hospital).

3.6.2 SARI patient

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

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

with **symptom onset within the last 14 days** prior to hospital admission. This SARI definition is modified from the latest ECDC case definition (specifying "suspicion of respiratory infection") [23].

3.6.3 Laboratory-confirmed infection

For each studied pathogen, a laboratory-confirmed infection is a positive reverse transcription polymerase chain reaction (RT-PCR)[3] or multiplex RT-PCR on a respiratory specimen(s) collected between 14 days prior to and up to 72 hours after hospital admission. If all samples collected in this time frame are negative, the patient is considered as not having any laboratory-confirmed infection.

3.6.4 Laboratory-confirmed co-infection

Laboratory-confirmed co-infection is defined as two or more laboratory-confirmed infections (Section 3.6.3) on any respiratory sample taken in the accepted timeframe (collected between 14 days prior to and up to 72 hours after hospital admission).

3.6.5 Healthcare utilisation outcomes

3.6.5.1 Level of severity

Severity will be assessed in 2 ways, first by 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] Or another RNA amplification system with at least the same sensitivity as RT-PCR (e.g., transcription-mediated amplification (TMA)).

3. In-hospital death
    a. during ICU stay
    b. outside of ICU stay

Respiratory support:

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).

3.6.5.2 Discharge destination

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

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

3.6.5.3 Length of stay

Length of stay is defined as the number of days between date of admission and date of discharge or in-hospital death.

Length of ICU stay is defined as the number of days between date of admission to the ICU and date of discharge from ICU or in-hospital death.

3.6.6 Risk groups

Risk groups will consist of those patients with specific chronic conditions (e.g., immunocompromised), long-term care facility residents, and the elderly. A specific categorisation of risk groups will be provided in the SAP.

3.7 SARI patient identification

Hospitalised SARI patients will be identified based on the defined SARI definition (3.6.2). Depending on the Study Contributor, the SARI patient's point of identification will be different (e.g., during consultation in the emergency department (ED), or at admission to infectious disease or internal medicine ward). For every participating study site, the patient flow will be documented in detail.

3.8 Pathogens of interest and laboratory testing

3.8.1 Pathogens of interest

The pathogens of interest are as follows:

- Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)
- Influenza
    - Influenza A
        - A-H1
        - A-H3
    - Influenza B
- Respiratory Syncytial Virus (RSV)
    - RSV A and RSV B
- Parainfluenza
    - Type 1-4
- Human Metapneumovirus (hMPV)
- Human Rhinovirus (HRV)
- Human Enterovirus (HEV)
- Adenovirus
- Human coronavirus
    - Types 229E, NL63, OC43 and HKU1

At minimum, sites should have testing capacity for SARS-CoV-2, Influenza A and B, and RSV A and B. Additional pathogens may be added to the study depending on epidemiological trends (e.g., inclusion of an emerging pathogen).

3.8.2 Laboratory testing

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

The specimens will be tested within the local laboratory infrastructures of the participating Study Contributors, for at least SARS-CoV-2, influenza A/B and RSV A/B, and preferably also for adenovirus,

Parainfluenza 1-4, human metapneumovirus (hMPV), human rhinovirus (HRV), human enterovirus (HEV), and human coronaviruses (229E/NL63/OC43/HKU1), by using validated RT-PCR or multiplex RT-PCR assays, or another RNA amplification system with at least the same sensitivity as RT-PCR (e.g., transcription-mediated amplification (TMA)). Assays used are either commercial assays with known high sensitivity, specificity and/or concordance, or in-house developed assays that have undergone quality and/or validation processes. Study Contributors will be requested to submit validation logs (summarising the quality check process, results, timing and certificates of analysis for assays performed) to the Study Team.

Table 2. Multiplex assays (brand, panel, and number of pathogens) used by Study Contributors

Study Contributor, Country	Brand	Panel	Number of pathogens tested
VAHNSI, Spain	In-house	In-house	20
Val d´Hebron, Spain	SeeGene Cepheid GeneExpert	Allplex RP 1-3 Xpert® Xpress CoV-2/FLU/RSV plus	19 4
GHTiP, Spain	SeeGene	Allplex SARS-CoV-2/FLU/RSV Allplex RP 1-3	4 19
Hospital Clínico Universitario de Santiago de Compostela, Spain	BioFire	FilmArray	18
Hospital Clínic de Barcelona, Spain	GeneXpert	TBC	
Hospital Universitario La Paz, Spain	BioFire Cepheid GeneXpert	TBC	
CIRI-IT, Italy	SeeGene (Bari, Genoa) In-house (Milan) TBC (Sienna, Pisa)	Allplex RP 1-3	19
Luigi Sacco Hospital, Italy	SeeGene	Allplex RP	21
UZA, Belgium	Pathofinder	Respifinder 2smart	18
St Pierre, Belgium	Qiagen Qiastat Abbott Alinity m RESP 4-plex TaqMan	RP SARS-CoV-2 In-house	18 4 17
Universitäts-klinikum Frankfurt, Germany	SeeGene BioFire	Allplex RP 1-3 FilmArray RP2.1	19 18
Universitäts-klinikum Ulm, Germany	SeeGene / GeneXpert	TBC	

Study Contributor, Country	Brand	Panel	Number of pathogens tested
Universitäts-klinikum Freiburg, Germany	Pathofinder	Respifinder 2smart	18

**CIRI-IT location Rome does not use multiplex yet, but is considering implementation of SeeGene Allplex or Roche ePlex (to be finalised in June 2024); TBC, to be confirmed*

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

- RSV:
  - Subtype A and B (if not available through local multiplex)
- Influenza:
  - Type A and B (if not available through local multiplex)
  - Subtypes A H1, Influenza A H3 (if not available through local multiplex)
- SARS-CoV-2:
  - Genotyping (pangolin lineage)

Genomic sequencing will be performed by whole genome sequencing or next generation sequencing using commercially available molecular kits. Sites will be requested to communicate to the Study Team the sequencing methodology applied, software version used, and the references of the laboratory performing the test.

3.9 Covariates and healthcare use

The complete dataset can be found in the id.DRIVE Common dataset case report form and is summarised in Table 3.

Table 3. Study covariates and healthcare use

Covariate	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

Covariate	Description
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.
Immunodeficiency (or organ transplant)	Binary. If yes, specification of subcategories: Solid organ or islets transplant, Haematopoietic stem cell transplantation, Primary immunodeficiency, Advanced or untreated HIV infection, Iatrogenic immunodeficiency, other. If yes solid organ or islets transplant, specification of subcategories: Kidney, Liver, Intestines, Heart, Lung, Pancreas, Other, No information
Neurological disorders	Binary
Pregnancy	Binary. If yes, specification of trimester: first, second, third
Body mass index (BMI)	Continuous
Smoking history	Never smoker, ex-smoker, occasional smoker, daily smoker, no information
Vaccination history influenza last 12 months	Vaccination details of Influenza vaccination within 12 months prior to SARI hospital admission, date, brand
Vaccination history COVID-19	Vaccination history of COVID-19 vaccinations, date, brand
Vaccination history RSV	Vaccination history of RSV vaccinations, date, brand
Vaccination pneumococcus	Vaccination details of any pneumococcal vaccination, date, brand
Previous SARI hospitalisation in last 12 months	Binary
Time since previous SARI hospitalisation	<14 days, 14 days-3 months, >3 months, No information
Time between symptom onset and hospitalisation	Days, continuous
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
Respiratory support	None, oxygen therapy, non-invasive ventilation, mechanical ventilation, extra corporeal membrane oxygenation (ECMO), other
Cumulative number of days of non-invasive ventilation, invasive ventilation, or ECMO	Days, continuous
Length of hospital stay	Days, continuous
Admission to ICU	Binary
Length of ICU stay	Days, continuous
In-hospital death	Binary

Covariate	Description
Post-discharge destination	Home, Home with nursing care, Transfer to another hospital, Rehabilitation centre, Nursing home or other long-term care facility, Other
Treatments received during hospital stay for the management of SARI episode	Antibiotics, Antiviral drug(s), Corticosteroid(s), Immune-modulator(s), Anti-SARS-CoV-2 antibodies, Other monoclonal antibodies, None of the above. Brand name if anti-SARS-CoV-2 antibodies received during hospital stay
Treatments received prior to hospital admission for the management of current SARI episode	Antibiotics, Antiviral drug(s), Corticosteroid(s), Immune-modulator(s), Anti-SARS-CoV-2 antibodies, Other monoclonal antibodies, None of the above. Brand name if anti-SARS-CoV-2 antibodies received during hospital stay
Medicinal product for the prevention of SARS-CoV-2 (pre- or post-exposure prophylaxis) in the 12 months prior to current hospitalisation	Binary. If yes, type (Antiviral drug, Anti-SARS-CoV-2 antibodies, Other), brand and date (month/year) if SARS-CoV-2 monoclonal antibody
Medicinal products 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 RSV monoclonal antibody

**Definitions for each chronic conditions are specified in the id.DRIVE Common dataset case report form*

§ At VAHNSI, long-term care facility residents are excluded

3.10 Sample size

WHO advises that sentinel surveillance should cover at least 1-2% of a population [1]. Current active sites as described in section 3.2 cover between 6.8% (Germany) to 16.2% (Belgium) of their countries' population. The primary objective of this surveillance study is to determine the proportion of relevant pathogens among the admitted SARI patients. Through a feasibility assessment, we anticipate recruiting 300 patients per hospital, totalling 6,600 SARI patients (300 patients per hospital across 22 hospitals) for the upcoming season. Further assuming a 10% drop-off rate, the final patient size is estimated to be around 5,940. Table 4 below demonstrates the anticipated precision (by Binomial Exact method at 95% confidence interval) regarding the prevalence corresponding to the expected proportion of each primary pathogen of interest.

Table 4. Anticipated precision regarding the prevalence corresponding to the expected proportion of the pathogens of interest

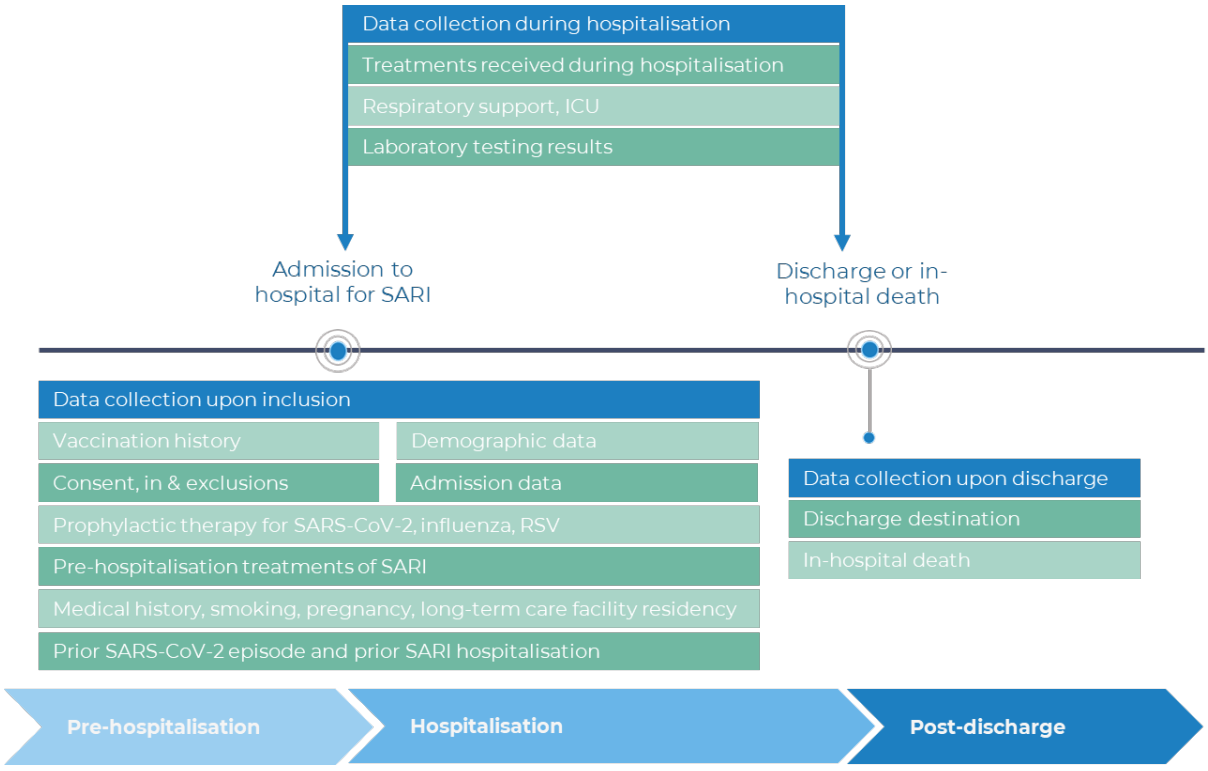
Pathogen of interest	Minimum expectation		Maximum expectation	
	Prevalence case among admitted SARI patients	Precision	Prevalence case among admitted SARI patients	Precision
COVID	20%	1.025%	25%	1.109%
RSV	2%	0.365%	7%	0.657%
Influenza	7%	0.657%	12%	0.835%

The precision provided by this patient size is within an acceptable range. The precision will increase if the actual enrolled patient size is smaller than expected. Further sample size justifications for the other objectives will be provided in the SAP.

3.11 Flow chart of data collection

The figure below indicates the timelines for which data will be collected (Figure 2).

Figure 2: Flow chart of data collection



All data are collected from pre-existing medical files (registries and/or patient files), and are therefore considered as a secondary data collection, except for laboratory results that will be collected specifically for the purpose of the study and are considered as a primary data collection (Section 3.5, Section 3.8 and Section 3.9).

3.12 Data management

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

3.12.1 Data management at Study Contributor level

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

3.12.2 Data flow

1. The Study Contributor collects the data and enters/uploads it in the Castor® electronic data capture (EDC).
2. The Study Sponsor validates the data, raises applicable queries and the Study Contributor responds to data queries by updating or confirming the data.
3. The Study Sponsor imports the data from all participating Study Contributors in a secure environment using the EDC system's export functionality.
4. The Study Sponsor transforms all data to generate the output as pre-specified in the SAP within the secure environment.

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

A data management plan (DMP) is written prior to the start of the data collection to describe data management at the central level. The DMP describes all functions, processes, responsibilities and specifications for data collection, data storage, quality checking, transfer, cleaning, and validation. The DMP is updated regularly. All statistical analyses will be conducted in the id.DRIVE Research Server.

3.13 Data analysis

A SAP will be developed prior to the conduct of the analysis. The SAP specifies all statistical analyses, including sensitivity analyses, to be conducted and will include table shells and mock figures. There will be one common SAP for all Study Requestors.

3.13.1 Attrition diagram

An attrition diagram will be created, describing the number of records excluded from the statistical analyses, by reason of exclusion.

3.13.2 Total SARI and pathogen-specific SARI numbers

The total number and proportion of positive laboratory samples for each respiratory pathogen of interest (see section 3.8.1) and co-infections (see section 3.6.4) will be provided. Counts and proportions (%, along with 95% exact binomial confidence intervals) will be provided by calendar time, by Study Contributor, by country and by age- and risk groups of interest. Co-infections (%) will be described, by number of pathogens, by pathogen type and by healthcare utilisation outcomes. Visualisations of these counts and percentages over time will be provided.

3.13.3 Demographic and clinical characteristics of SARI

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

3.13.4 Healthcare utilisation outcomes

Multinomial logistic regression will be used to explore risk factors of pathogen-specific SARI hospitalisation, healthcare utilisation outcomes (as defined in Section 3.6.5), and the presence of co-infections (by number of co-infections and involved pathogens, when feasible). Potential risk factors include age, gender, chronic conditions, smoking). Stratified analyses will be performed by age groups, by gender, by presence of chronic condition and specifically by those with pre-existing immunodeficiency disorders.

3.13.5 Incidence rates

As part of the exploratory objectives, pathogen-specific SARI incidence rates (per 100,000 person-years) will be calculated and monitored over time to identify trends using the following formula [27]:

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

The number of events in a specific period will be calculated by multiplying the percentage of SARI patients testing positive for a specific pathogen within the selected time period with the total number of SARI patients (included in the Surveillance Study and missed SARI patients identified by screening logs). Alternatively, the untested SARI events may be accounted for by multiple imputation of expected testing results (e.g., for RSV [2, 3]).

Incidence estimates will not be calculated unless formal denominator mapping can be performed and there is an accurate process for identifying SARI events that were missed by active surveillance. Denominator data will be based on the hospital-reported catchment population of each hospital. The

total number of hospital beds in a region corresponding to the Study Contributor's catchment region will be obtained, and the percentage of hospital beds caught by the specific Study Contributor will be calculated. The percentage of hospital beds caught by the Study Contributor will be used to calculate the hospital's catchment population. The catchment population of each hospital is expected to reflect the average number of persons at risk during that same time period Official regional (or national if not available) population gender- and age-specific distributions will be obtained to model these characteristics for the Study Contributor-specific catchment populations. These modelled data will be used to calculate gender- and age-specific incidence rates of SARI by pathogen. Further, incidence rates will also be adjusted for events missed due to lower diagnostic testing sensitivity of single specimens among older adults as seen in several recent incidence meta-analyses [28, 18]. Details will be provided in the SAP.

3.13.6 Feasibility assessments

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

4 QUALITY MANAGEMENT

4.1 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 surveillance studies.

The roles and responsibilities of the ISC are the following:

- reviews and makes recommendations for study documents (protocols and SAPs);
- reviews and makes recommendations for study reports;
- reviews and formulates recommendations for the master scientific documents, which are co-developed by the id.DRIVE partners to harmonise methodology.

4.2 Quality Assurance and Audit Committee

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

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

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

4.3 Monitoring

Monitoring activities include:

- Before study start, the Study Contributor will be asked to complete a quality management questionnaire to inform the Study Team on all aspects of the study conduct.
- Before study start, a site initiation visit will be organised by the Study Team.
- During study conduct, regular Study Contributor contacts will be organised to monitor study progress (number of patients enrolled), to ensure regular data input to the id.DRIVE electronic data capture (EDC) system and to discuss potential protocol deviations or other issues related to the study conduct.

- Sites will be asked to keep high-level screening logs (including number of SARI patients missed or not consented for the study with age group 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. Efforts will be made to maintain participant confidentiality at all times.

4.4 Data quality checks at central level

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

5 LIMITATIONS OF THE RESEARCH METHODS

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

- With sentinel surveillance, generalisability may be limited as social and demographic factors are usually not uniform across a country and therefore the catchment population of a sentinel network may not be comparable with the remaining population of a country. However, this could be circumvented by ensuring that demographic and socioeconomic characteristics of the patients are representative of the general population [27]. WHO advises that sentinel surveillance should cover at least 1-2% of a population [1]. Current active sites as described in section 3.2 cover between 6.8% (Germany) to 16.2% (Belgium) of their countries' population.
- Under-detection of pathogens of interest may occur. RT-PCR sensitivity is influenced by several factors, including operator sampling technique, type of respiratory specimen, laboratory assay, and timing of sampling. Assay sensitivity may also vary across pathogens, with larger under-detection rates for certain viruses, such as RSV [29]. To limit under-detection, only assays with high sensitivity are used, sampling is performed in the first 72h after hospital admission, and information on the main factors influencing result RT-PCR are collected [18]. Moreover, to ensure good testing procedure, guidance on collecting and handling specimens for the diagnosis of viral respiratory pathogens are given as part of study staff training.
- With RT-PCR, a positive result is highly specific for the presence of the viral pathogen nucleic acid of interest. False positives only occur in the rare event of laboratory contamination. However, RT-PCR does not differentiate between viable and nonviable virus, and a positive result may indicate an older infection, non-causal to the current SARI episode. This would be more frequent with prolonged viral shedding, such as COVID-19 [30]. Notably, as only results of specimens sampled within 72h after admission are included, inclusion of hospital-acquired infections will be avoided.
- The use of different RT-PCR or multiplex assays across Study Contributors may impact the comparability across sites or with other surveillance systems. However, the laboratory tests used by the Study Contributors are those used for the diagnostic work-up of patients admitted and are either commercial assays with known high sensitivity, specificity and/or concordance [31] or in-house developed assays that have undergone quality and/or validation processes.
- Incidence rates will be calculated by using a proxy denominator (hospital population catchment area and its demographics). Depending on each Study Contributor, the proportion of SARI captured and included in the study will vary. The feasibility of obtaining incidence rates will be assessed and incidence will only be reported once considered valid.
- The proxy denominators used for the calculation of incidence rates will not allow for granularity e.g., calculation of incidence rates by e.g., specific chronic condition. However, even without proper denominator data, the surveillance data will nevertheless be valuable and can be used to e.g., calculate the proportional contribution of certain chronic conditions for a specific pathogen and compare these proportions with the proportions for other pathogens.
- Different SARI definitions are currently in use (WHO SARI definition, WHO extended SARI definition, ECDC SARI definition) with disparate sensitivity levels, limiting comparability of results. Here we apply a modified ECDC SARI case definition. As SARI symptom and date of symptom-onset are collected, sensitivity analysis will be performed to restrict cases to those that would meet the WHO SARI or WHO extended SARI definition.

- Genotyping for some viral pathogens (for example, whole genome sequencing for SARS-CoV-2) requires additional laboratory processing of clinical specimens. Some clinical specimens may be inadequate or unsuitable for additional genotyping.

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

6.1 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) [32], Good Epidemiological Practice (GEP) [33], the ethical principles that have their origins in the Declaration of Helsinki and any applicable national laws, regulations and guidelines.

This is an non-interventional study. There is no direct benefit to the participants. Nevertheless, there are important potential societal benefits derived from this surveillance study. Insight in SARI pathogen distribution and clinical presentation are key to identify vaccine targets, marketing authorisation, and vaccination policies.

6.2 Ethics approval

The Study Contributor-specific protocols will be submitted to relevant independent ethics committee(s) (IECs) following local regulations and the Declaration of Helsinki. Copies of the appropriate IEC approvals will be collected from each Study Contributor and archived according to the local regulations, but at least for 5 years. The only exception is where the study is part of an ongoing routine 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.

6.3 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.

6.4 Independent ethics committee/Institutional review board

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

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

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

6.5 Participant's confidentiality

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

6.6 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.

6.7 Secondary data use

The data generated as part of this study may be used for future research related to the expansion of the knowledge, prevention and control of infectious diseases. For this secondary use of data the id.DRIVE governance principles will be respected as detailed in the id.DRIVE Governance Charter. The Governance Charter can be made available by the Co-Coordinators upon written request.

7 STUDY MANAGEMENT AND LOGISTICAL ASPECTS

This study will be performed by the Study Contributor investigator(s), with guidance, input, review, and approval of the Study Team, including development of materials, recruitment, training, management of network sites, EDC, data management and analysis.

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

7.1 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.

7.2 Data capture

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

7.3 Retention

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

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

7.4 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.

7.5 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.

8 REPORTING AND DISSEMINATION OF RESULTS

8.1 Study protocol

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

8.2 Management and reporting of adverse events/adverse reactions

This is an epidemiological study for the surveillance of SARI-causing viral respiratory pathogens, based on primary and secondary data collection (3.10). 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.

8.3 Progress reports, study reports and feasibility reports

Progress reports will be provided every two months since enrolment of the first participant. Progress reports will provide recruitment numbers, main characteristics of SARI patients and pathogens detected.

Study reports will be prepared once a year covering the primary and secondary objectives. A final report will be prepared after 12 months of data collection.

Feasibility assessments (section 3.13.6) detailed in Study feasibility reports will be prepared 12 months after the start of data collection. Additional feasibility reports can be triggered (e.g., to evaluate any modifications to improve data quality, upon major changes to the respiratory pathogen- and vaccine landscape).

Progress reports, study reports and feasibility reports will be Study Requestor specific, based on Study Contributor selection of each Study Requestor.

8.4 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.

9 FUNDING

The id.DRIVE Study Network has been funded by the current and previous Pharmaceutical Company Partners of the id.DRIVE consortium. The id.DRIVE consortium is a not-for-profit open public-private partnership. Current consortium members are FISABIO (Spain), P95 (Belgium), AstraZeneca (UK), Janssen (Belgium), GSK (UK), Novavax (US), Pfizer (US) and Valneva (Austria). Past members include Bavarian Nordic (Denmark), Moderna (US), Sanofi (France), THL (Finland) and CureVac (Germany).

This surveillance study and its protocol are further financed by AstraZeneca and Pfizer. Other partners (Pharmaceutical Company Partners or other Institutions) may join the id.DRIVE partnership as per governance and participate in the study's funding. All funding will be transparently acknowledged in study communications.

10 REFERENCES

1. WHO (2016). WHO Expert Working Group Meeting on RSV Surveillance based on the GISRS Platform. Available from: https://apps.who.int/iris/bitstream/handle/10665/252625/WHO-OHE-PED-GIP-2016.7-eng.pdf?sequence=1 [Accessed: 12-06-2023].

2. ONWUCHEKWA, C., MOREO, L. M., MENON, S., et al. (2023). Under-ascertainment of Respiratory Syncytial Virus infection in adults due to diagnostic testing limitations: A systematic literature review and meta-analysis. J Infect Dis, DOI: https://doi.org/10.1093/infdis/jiad012.

3. RAMIREZ, J., CARRICO, R., WILDE, A., et al. (2023). Diagnosis of Respiratory Syncytial Virus in Adults Substantially Increases When Adding Sputum, Saliva, and Serology Testing to Nasopharyngeal Swab RT-PCR. Infect Dis Ther:1-11. DOI: 10.1007/s40121-023-00805-1.

4. GLOBAL BURDEN OF DISEASE LOWER RESPIRATORY INFECTIONS COLLABORATORS (2018). Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Infect Dis, 18(11):1191-210. DOI: 10.1016/s1473-3099(18)30310-4.

5. KRAMMER, F., SMITH, G. J. D., FOUCHIER, R. A. M., et al. (2018). Influenza. Nat Rev Dis Primers, 4(1):3. DOI: 10.1038/s41572-018-0002-y.

6. GBD 2017 INFLUENZA COLLABORATORS (2019). Mortality, morbidity, and hospitalisations due to influenza lower respiratory tract infections, 2017: an analysis for the Global Burden of Disease Study 2017. Lancet Respir Med, 7(1):69-89. DOI: 10.1016/s2213-2600(18)30496-x.

7. LAFOND, K. E., PORTER, R. M., WHALEY, M. J., et al. (2021). Global burden of influenza-associated lower respiratory tract infections and hospitalizations among adults: A systematic review and meta-analysis. PLoS Med, 18(3):e1003550. DOI: 10.1371/journal.pmed.1003550.

8. WHO (2013). Global epidemiological surveillance standards for influenza. Available from: https://www.who.int/publications/i/item/9789241506601 [Accessed: 12-06-2023].

9. WHO (2020). WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020 [Accessed: 12-06-2023].

10. WHO (2023). Coronavirus (COVID-19) Dashboard. DOI.

11. LIU, D. X., LIANG, J. Q. & FUNG, T. S. (2021). Human Coronavirus-229E, -OC43, -NL63, and -HKU1 (Coronaviridae). In: BAMFORD, D. H. & ZUCKERMAN, M. (eds.) Encyclopedia of Virology (Fourth Edition). Oxford: Academic Press.

12. KORSTEN, K., ADRIAENSSENS, N., COENEN, S., et al. (2021). Burden of respiratory syncytial virus infection in community-dwelling older adults in Europe (RESCEU): an international prospective cohort study. Eur Respir J, 57(4)DOI: 10.1183/13993003.02688-2020.

13. SAVIC, M., PENDERS, Y., SHI, T., et al. (2023). Respiratory syncytial virus disease burden in adults aged 60 years and older in high-income countries: A systematic literature review and meta-analysis. Influenza Other Respir Viruses, 17(1):e13031. DOI: 10.1111/irv.13031.

14. SHI, T., DENOUEL, A., TIETJEN, A. K., et al. (2020). Global Disease Burden Estimates of Respiratory Syncytial Virus-Associated Acute Respiratory Infection in Older Adults in 2015: A Systematic Review and Meta-Analysis. J Infect Dis, 222(Suppl 7):S577-s83. DOI: 10.1093/infdis/jiz059.

15. FALSEY, A. R., WALSH, E. E., HOUSE, S., et al. (2021). Risk Factors and Medical Resource Utilization of Respiratory Syncytial Virus, Human Metapneumovirus, and Influenza-Related Hospitalizations in Adults-A Global Study During the 2017-2019 Epidemic Seasons (Hospitalized Acute Respiratory Tract Infection [HARTI] Study). Open Forum Infect Dis, 8(11):ofab491. DOI: 10.1093/ofid/ofab491.

16. TIN TIN HTAR, M., YERRAMALLA, M. S., MOÏSI, J. C., et al. (2020). The burden of respiratory syncytial virus in adults: a systematic review and meta-analysis. Epidemiology & Infection, 148:e48. DOI: 10.1017/S0950268820000400.

17. ACKERSON, B., TSENG, H. F., SY, L. S., et al. (2019). Severe Morbidity and Mortality Associated With Respiratory Syncytial Virus Versus Influenza Infection in Hospitalized Older Adults. Clin Infect Dis, 69(2):197-203. DOI: 10.1093/cid/ciy991.

18. LI, Y., KULKARNI, D., BEGIER, E., et al. (2023). Adjusting for Case Under-Ascertainment in Estimating RSV Hospitalisation Burden of Older Adults in High-Income Countries: a Systematic Review and Modelling Study. Infect Dis Ther, 12(4):1137-49. DOI: 10.1007/s40121-023-00792-3.

19. EUROPEAN MEDICINES AGENCY (2023). Arexvy - Recombinant respiratory syncytial virus pre-fusion F protein, adjuvanted with AS01E. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/arexvy [Accessed: 21-07-2023].

20. EUROPEAN MEDICINES AGENCY (2023). Abrysvo - Respiratory syncytial virus vaccines. Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/abrysvo [Accessed: 24-07-2023].

21. EUROPEAN CENTER FOR DISEASE CONTROL (2023). Global Influenza Surveillance and Virus Sharing. Available from: https://www.ecdc.europa.eu/en/seasonal-influenza/surveillance-and-disease-data/facts-global-surveillance [Accessed: 12-06-2023].

22. EUROPEAN CENTER FOR DISEASE CONTROL (2023). Considerations for infection prevention and control practices in relation to respiratory viral infections in healthcare settings. Available from: https://www.ecdc.europa.eu/en/publications-data/considerations-infection-prevention-and-control-practices-relation-respiratory [Accessed: 12-06-2023].

23. 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].

24. WORLD HEALT ORGANIZATION (2019). WHO strategy for global respiratory syncytial virus surveillance project based on the influenza platform. Available from: https://www.who.int/publications/i/item/who-strategy-for-global-respiratory-syncytial-virus-surveillance-project-based-on-the-influenza-platform [Accessed: 17-08-2023].

25. DRIVE CONSORTIUM (2021). DRIVE – Development of Robust and Innovative Vaccine Effectiveness. Available from: https://www.drive-eu.org/ [Accessed: 16-03-2021].

26. EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL (2020). Strategies for the surveillance of COVID-19. Available from: https://www.ecdc.europa.eu/en/publications-data/strategies-surveillance-covid-19 [Accessed:

27. WHO (2015). A Manual for Estimating Disease Burden Associated With Seasonal Influenza. Available from: https://www.who.int/publications/i/item/9789241549301 [Accessed:

28. MCLAUGHLIN, J. M., KHAN, F., BEGIER, E., et al. (2022). Rates of Medically Attended RSV Among US Adults: A Systematic Review and Meta-analysis. Open Forum Infect Dis, 9(7):ofac300. DOI: 10.1093/ofid/ofac300.

29. WANG, W., XU, Y., GAO, R., et al. (2020). Detection of SARS-CoV-2 in Different Types of Clinical Specimens. JAMA, 323(18):1843-4. DOI: https://doi.org/10.1001/jama.2020.3786.

30. CEVIK, M., TATE, M., LLOYD, O., et al. (2021). SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. Lancet Microbe, 2(1):e13-e22. DOI: 10.1016/s2666-5247(20)30172-5.

31. JOHNSON, G., ZUBRZYCKI, A., HENRY, M., et al. (2021). Clinical evaluation of the GeneXpert® Xpert® Xpress SARS-CoV-2/Flu/RSV combination test. J Clin Virol Plus, 1(1):100014. DOI: 10.1016/j.jcvp.2021.100014.

32. COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES (CIOMS) (2009). International Ethical Guidelines for Epidemiological Studies. Available from: https://cioms.ch/wp-content/uploads/2017/01/International_Ethical_Guidelines_LR.pdf [Accessed:

33. HOFFMANN, W., LATZA, U., BAUMEISTER, S. E., et al. (2019). Guidelines and recommendations for ensuring Good Epidemiological Practice (GEP): a guideline developed by the German Society for Epidemiology. Eur J Epidemiol, 34(3):301-17. DOI: 10.1007/s10654-019-00500-x.