id.DRIVE

Pilot study to assess the detection of RSV, hMPV and PIV when using multi-specimen collection compared to a single nasopharyngeal swab

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

Study Protocol

Version: 1.0

Date: 18 November 2025

1 TITLE PAGE

Title:	Pilot study to assess the detection of RSV, hMPV and PIV when using multi-specimen collection compared to a single nasopharyngeal swab
Study identifier:	1000000780
Protocol version and date:	V1.0 18 November 2025
Registration number:	EUPAS1000000780
Research question and objectives:	To assess the detection rates (%) of respiratory syncytial virus (RSV), human metapneumovirus (hMPV), and parainfluenza virus (PIV) in adult patients with acute respiratory infection (≥18 years), when using multi-specimen collection compared to a single nasopharyngeal swab, overall and by additional specimen type
Country of study:	Spain
Study Requestor(s):	**SANOFI WINTHROP INDUSTRIE** [redacted]
Sponsor:	P95, Clinical and Epidemiology Services Diestsevest 125 3000 Leuven Belgium
Author(s):	[redacted]
Review by:	[redacted]

2 RESPONSIBLE PARTIES

2.1 Project lead/coordinator

Name: [redacted]
Organization: Fundación Fomento de la Investigación Sanitaria y Biomédica de la Comunidad Valenciana
Address: [redacted]
E-mail: [redacted]

2.2 Study contributor Principal Investigators

Name: [redacted],
Organization: Hospital Dr Peset of Valencia
Address: [redacted]
E-mail: [redacted]

Name: [redacted]
Organization: Hospital Dr Peset of Valencia
Address: [redacted]
E-mail: [redacted]

Name: [redacted]
Organization: Hospital Dr Peset of Valencia
Address: [redacted]
E-mail: [redacted]

Name: [redacted]
Organization: Primary Care Center Malilla
Address: [redacted]
E-mail: [redacted]

2.3 Study Requestor

Name: [redacted]
Organization: SANOFI WINTHROP INDUSTRIE
Address: [redacted]
E-mail: [redacted]

2.4 Study Sponsor

Name: [redacted]
Organization P95 Clinical and Epidemiology Services

Address [redacted]
E-mail: [redacted]

2.5 Study contributor Team (Fisabio/VAHNSI)

Name	Role in the study	Email address
[redacted]	[redacted]	[redacted]

A complete list of the other members of the Study contributor team can be found in Annex 1.

2.6 P95 Research Team

Name	Role in the study	Email address
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

4 PROTOCOL SUMMARY

Title of study:

Pilot study to assess detection of RSV, hMPV and PIV when using multi-specimen collection compared to a single nasopharyngeal swab

Background and rationale:

Severe respiratory viral infections pose a significant health burden among adults, leading to substantial morbidity and mortality. Most incidence estimates are based on real-time polymerase chain reaction (RT-PCR) testing of nasopharyngeal swabs. However, the recent North American Multispecimen Study showed a several-fold increase in respiratory syncytial virus (RSV) diagnosis in adults when additional specimen types were added to nasopharyngeal swabs. This study as well as others demonstrate that the true RSV disease burden is underestimated in nasopharyngeal only studies [1-4].

With this study, we aim to gain insights into the possible underestimation RSV, human metapneumovirus (hMPV) and parainfluenza virus (PIV) detection rates in patients with an (severe) acute respiratory infection ((s)ARI) by using additional specimen types (oropharyngeal swabs, saliva, sputum and blood samples) and compare to the results by nasopharyngeal swabs only.

Objectives:

Primary objective:

1. To assess the detection rates (%) of RSV, hMPV and PIV in adult (s)ARI patients (≥18 years), when using multi-specimen collection compared to a single nasopharyngeal swab, overall and by additional specimen type.

Secondary objectives:

2. As primary objective, stratified by
   - Age categories: 18-49, 50-59, 60-74, 75+
   - Sex at birth
   - Time since symptom-onset categories
   - By setting (hospital, emergency department (ED) ward and primary care center (PCC))
   - By diagnosis (upper respiratory tract infection vs. lower respiratory tract infection and pneumonia, bronchitis, bronchiolitis, etc.)
   - By common comorbidities/ chronic conditions

3. As primary objective, stratified by
   - Vaccination status
     - RSV detection rates by RSV vaccination status (ever vaccinated or unvaccinated)

4. To assess the detection rates (%) of SARS-CoV-2 and Influenza in adult (s)ARI patients (≥18 years), when using multi-specimen collection compared to a single nasopharyngeal swab (overall and by additional specimen type), overall and stratified by:
   - SARS-CoV-2 detection rates (%) by SARS-CoV-2 vaccination status (vaccinated in the last 12 months or not vaccinated in the last 12 months)
   - Influenza detection rates (%) by Influenza vaccination status (vaccinated in the last 12 months or not vaccinated in the last 12 months).

Exploratory objectives:

5. To assess the detection rates (%) of co-infections (all pathogens tested) in adult (s)ARI patients (≥18 years), when using multi-specimen collection compared to a single nasopharyngeal swab, overall and by additional specimen type.
    - And stratify by disease severity (PCC, ED ward, hospitalization, death), if the sample size allows.

6. As primary objective, stratified by subtype or serotype (when applicable)
    - RSV detection rates by RSV subtype A and B
    - PIV detection rates by PIV serotype (1-4)

7. To assess the detection rates (%) of Influenza, SARS-CoV-2 and other viral pathogens tested for with the RT-PCR multiplex panel in adult (s)ARI patients (≥18 years), when using multi-specimen collection compared to a single nasopharyngeal swab, overall and by additional specimen type.

Study design:

Multi-setting (inpatient, ED ward and PCC) prospective cohort study of (s)ARI cases

Study duration:

Recruitment period: 7th of January 2026 – 30th of June 2026. Sample collection between 7th of January 2026 and 31st of July 2026.

Inpatient setting: baseline samples to be taken within 48 hours of hospital admission, as soon as possible after admission. Convalescent blood sample to be taken between 25 and 31 days after hospital admission.

ED and PCC setting: baseline samples to be taken within the initial consult.

Population, setting and eligibility criteria:

Study setting:

A pilot study will be conducted in one (1) hospital (Dr Peset, Valencia), one (1) ED ward (Dr. Peset, Valencia), and up to four (4) PCC, all based in Valencia, Spain.

Study participants: Patients are included if they are:

- Adults aged 18 years and older

  AND

- Meet the (s)ARI case definition

  AND

- Willing to have a nasopharyngeal and oropharyngeal swab collected as well as saliva. Sputum and serology are optional and will be consented for on the informed consent form (ICF) as separate items.

  AND

- Willing and able to provide informed consent, obtained from the patient or from the patient's Legally Acceptable Representative(s).

Individuals (patient) cannot be enrolled if:

- patient cannot be swabbed due to severe septum deviation, obstruction, or other conditions that contra-indicate swabbing,
- patient was previously enrolled in the study within 30 days of their current visit/admission,

- patient develops signs and symptoms of (s)ARI after being hospitalized.

(s)ARI case definition:

A (s)ARI case is defined as a patient 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 and symptoms occurring for at least 24 hours.

Patient recruitment:

In the hospital setting, (s)ARI patients will be recruited between Monday and Friday. Patients submitted during the weekend will be enrolled on Monday if sample collection can be performed within the allowed time frame. During January and February a maximum of 100 patients per month will be consecutively recruited during the week (Monday to Friday). Recruitment will be halted after 100 patients are recruited. During the other months with expected high hMPV and PIV circulation, all (s)ARI patients will be approached.

For both the ED ward and PCC setting, (s)ARI patients will be recruited consecutively during the week (Monday to Friday). Each week 12 (s)ARI patients will be recruited from each setting. During the peak season of respiratory illnesses, the targets will be reached before Friday after which recruitment will be halted for that week. In slower recruitment weeks, all patients will need to be approached to reach the target sample size of 12 (s)ARI patients.

Planned study recruitment period:

7 January 2026 – 30 June 2026

Last patient in on 30 June 2026, last sample taken by the 31st of July 2026.

Laboratory testing:

The following clinical specimens will be collected from all recruited patients during the study period:

Hospital setting:

At baseline: (as soon as possible, within 48 hours of hospital admission):

- 1x nasopharyngeal
- 1x oropharyngeal swab
- 1x Saliva
- Optional: 1x Sputum sample
- Optional: 1x Blood sample

At convalescence (28 days (+/- 3 days) after hospital admission)

- 1x Blood sample (if a baseline sample was taken)

ED ward and PCC

At baseline: (within the original of visit)

- 1x nasopharyngeal swab
- 1x oropharyngeal swab
- 1x Saliva
- Optional: 1x Sputum sample

Respiratory samples:

All respiratory samples (nasopharyngeal, oropharyngeal, saliva, and sputum samples) will be tested for RSV A and B, PIV serotypes 1-4, and hMPV, by using a commercial RT-PCR kit, which also tests for presence of SARS-CoV-2, Influenza A, Influenza B among others. Study Contributor will be requested to submit validation logs (summarizing the quality check process, results, timing and certificates of analysis for assays performed).

Blood samples:

Acute and convalescent paired blood specimens will be collected for serological testing for RSV A and B, hMPV and PIV 1-4. Blood samples will be centrifuged to separate the serum, which will be stored at -20°C until shipment to the central laboratory in Lyon for testing. Enzyme-Linked Immunosorbent Assay (ELISA) technique will be used to detect and quantify IgG antibody titers. Serology will be considered positive for a recent infection when a 4-fold or greater rise in virus specific IgG antibodies is found between the paired acute and convalescent blood samples.

The laboratory in Lyon will deliver the following variables:

- RSV-A IgG antibody titers baseline
- RSV-A IgG antibody titers convalescence
- RSV-B IgG antibody titers baseline
- RSV-B IgG antibody titers convalescence
- hMPV-A IgG antibody titers baseline
- hMPV-A IgG antibody titers convalescence
- hMPV-B IgG antibody titers baseline
- hMPV-B IgG antibody titers convalescence
- PIV1 IgG antibody titers baseline
- PIV1 IgG antibody titers convalescence
- PIV2 IgG antibody titers baseline
- PIV2 IgG antibody titers convalescence
- PIV3 IgG antibody titers baseline
- PIV3 IgG antibody titers convalescence
- PIV4 IgG antibody titers baseline
- PIV4 IgG antibody titers convalescence

Storage:

To support potential future analyses and ensure the integrity and reproducibility of study findings, multiple biological samples per participant will be collected and aliquots will be stored under controlled conditions for long-term preservation when there is specimen left over.

Variables:

At baseline, information on covariates will be collected from patients in all settings through an electronic Case Report Form (eCRF). Set-up and questions will be based on the eCRF used for the id.DRIVE surveillance project. The following variables will be collected:

- Age
- Sex at birth
- Setting id
- Diagnosis (upper respiratory tract infection or lower respiratory tract infection)
- Admitting diagnosis (Pneumonia, Bronchitis, Bronchiolitis)
- Chronic conditions/ Comorbidities:
    - chronic lung disease
    - chronic cardiovascular disease
    - hypertension
    - chronic liver disease
    - chronic renal disease
    - type 1 and type 2 diabetes
    - cancer
    - immunodeficiency disorders
    - obesity
    - neurological disorders
- Immunodeficiency (e.g., on immunosuppressants)
- Long-term care facility residence
- Vaccination status (RSV, Influenza, SARS-CoV-2), including date of last vaccination
- Specimen test results, specimen type, date of sampling
- Symptoms
- Date of symptom-onset

Data sources:

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

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

Study size:

Target sample size: 1074 (s)ARI patients (450 in hospital; 624 in PCC and ED):

Data analysis:

The rate of respiratory pathogen diagnosis from nasopharyngeal swab alone will be determined by dividing the count of patients in which the respiratory pathogen of interest was detected solely by nasopharyngeal swab by the total patient count involved in this study, thereby yielding detection rates. The same calculation will be performed for the other specimens, oropharyngeal swab, saliva, blood, and sputum, as well as the detection rates when different specimen types are combined. We will determine the increase in detection rates for each specimen added, using nasopharyngeal only as a reference point. Results will also be presented for different subgroups to explain potential heterogeneity. All included patients are required to have at least a nasopharyngeal swab, oropharyngeal swab and a saliva sample. Euler diagrams will be employed to illustrate respiratory pathogen diagnosis per specimen type. The sensitivity for each specimen type and combination thereof will also be computed.

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.

Quality control:

Within the data analysis workflow and quality control process, one statistician will develop the R code, and a second statistician will review it to confirm accuracy, reproducibility, and compliance with coding standards. Following the coding QC, the results are reviewed by epidemiologists to assess their validity, interpretability, and relevance in the context of the study's design and public health implications.

Limitations of the research methods:

- Limited samples size, especially as some pathogen (subtypes) are rarely detected.
- RT-PCR offer high specificity. However, a positive RT-PCR result may not indicate causality for (s)ARI (persistent nucleic acid from previous infection, or asymptomatic carriage).
- Despite good sensitivity and specificity of the selected serology assays, false-negative (e.g., immunodeficiency disorder) and false-positive (e.g., cross-reactivity) test results are possible.
- The second blood sample will be collected approximately four weeks after hospital admission when the majority of patients will be home again. A nurse will be hired to follow-up with patients at home or patients will be provided with transportation costs to increase the likelihood of getting all required samples, however there still might be patients that are lost to follow-up.
- Viral load is variable and usually decreased over time. Delays between symptom onset and sample collection could affect detection rates and diagnostic accuracy.

References:

1. C. Onwuchekwa et al. (2023) Underascertainment of Respiratory Syncytial Virus Infection in Adults Due to Diagnostic Testing Limitations: A Systematic Literature Review and Meta-analysis. J Infect Dis. 228(2):173-184. doi: 10.1093/infdis/jiad012.
2. E. Begier et al. (2025) Detection of RSV using nasopharyngeal swabs alone underestimates RSV-related hospitalization incidence in adults: the Multispecimen study's Final Analysis. Preprint. https://doi.org/10.1101/2025.01.14.25320406
3. Y. Li 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):1137–1149. doi: 10.1007/s40121-023-00792-3
4. Zhang et al. (2016) Serology Enhances Molecular Diagnosis of Respiratory Virus Infections Other than Influenza in Children and Adults Hospitalized with Community-Acquired Pneumonia. J Clin Microbiol. 55(1):79-89. DOI: 10.1128/JCM.01701-16

5 MILESTONES

Milestone	Planned date
Registration of study protocol in the HMA-EMA catalogue of real world data studies	November 2026
Start of data collection	January 2026
End of data collection	July 2026
Interim report	April 2026
Final report on study results	September 2026

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7 VERSION HISTORY

Version	Date	Description of changes
1.0	18-NOV-2025	Creation of first version of the protocol

8 LIST OF ABBREVIATIONS

Abbreviation	Definition
ARD	Acute respiratory disease
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
DALY	Disability-adjusted life year
DMP	Data management plan
eCRF	Electronic case report form
ED	Emergency department
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
FISABIO	Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana.
GDPR	General data protection regulation
GPP	Good publication practice
hMPV	human metapneumovirus
ICF	Informed consent form
ICMJE	International committee of medical journal editors
IEC	Independent ethics committee
IgG	Immunoglobulin
IRB	Institutional review board
LRTI	Lower respiratory tract infection
mAb	Monoclonal antibody
PCC	Primary care center
PI	Principal Investigator
PIV	Parainfluenza virus
QC	Quality control
RSV	Respiratory syncytial virus
RT-PCR	Real-time polymerase chain reaction
SAP	Statistical analysis plan
(s)ARI	(Severe) Acute respiratory infection
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
URTI	Upper respiratory tract infection
VAHSNI	Valencia Hospital Surveillance Network for the Study of Influenza and Other Infectious Diseases

9 GLOSSARY

Term	Description
Co-Coordinators	means FISABIO and P95, both Partners, that are the Co-coordinators.
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 organized under the Consortium Agreement. For the avoidance of doubt, as of January 2024 COVIDRIVE became a part of id.DRIVE as described in further detail in the Governance Charter.
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 Results Publication	means a scientific publication reporting on the Study including all Study objectives identified in the individual Study protocol(s).
Study Team	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.

10 BACKGROUND & RATIONALE

According to the Global Burden of Disease Study (pre-COVID-19), lower respiratory tract infections (LRTIs) caused nearly 66 million hospitalizations and 2.4 million deaths globally, accounting for 4.4% of all-cause mortality [1]. In 2016, LRTIs were responsible for over 91 million disability-adjusted life years (DALYs) [1]. Also, upper respiratory tract infections (URTIs) reached more than 17 billion incident cases in 2019, accounting for about 43% cases of the global disease burden and injuries, and caused about 64 million DALYs in 2019 globally [2].

Both LRTIs and URTIs are caused by a wide range of pathogens, including respiratory viruses such as influenza, RSV, hMPV, and PIVs. While many infections result in mild illness, some progress to severe disease requiring hospitalization or even resulting in death.

A recent global analysis of RSV burden found that mortality rates in individuals aged 70 years and older exceeded those in children under five, highlighting the burden of RSV among older adults [3]. In contrast, the burden of other respiratory viruses—such as parainfluenza and adenoviruses—remains poorly understood. A cross-sectional study in the United States assessed the burden of RSV, hMPV, PIV, and influenza using medical records [4]. Pooled estimates indicated that RSV, hMPV, and PIV were associated with severe respiratory disease and prolonged hospital stays in adults. The study also noted potential under-testing and underdiagnosis, suggesting that the true burden may be underestimated.

Most incidence estimates rely on RT-PCR testing of nasopharyngeal swabs. However, several studies suggest that RSV hospitalization rates in older adults may be underestimated by at least 2.2-fold due to case under-ascertainment when using nasopharyngeal swabs alone [5-8]. Similarly, detection rates for hMPV and PIV may also be underestimated when relying solely on nasopharyngeal swabs [8].

Despite growing evidence of underdiagnosis, few studies have systematically assessed the limitations of nasopharyngeal swab-based detection for RSV, hMPV and PIV, in medically-attended adults for acute respiratory infections.

With this study, we aim to gain insights into the possible underestimation of RSV, hMPV, PIV detection rates in patients with (severe) acute respiratory infections ((s)ARI) by using nasopharyngeal swabs alone compared to the use of multiple specimens (oropharyngeal, saliva, sputum and blood samples).

This study is conducted by the id.DRIVE public-private partnership, a consortium created to facilitate the conduct of observational studies on infectious diseases, vaccines, related preventive measures, therapeutics, and diagnostics for infectious diseases. id.DRIVE evolved from the COVIDRIVE consortium launched in September 2021, to address the joint need to monitor COVID-19 vaccination programs for public health institutes and assess brand-specific COVID-19 vaccine effectiveness for vaccine companies as part of their regulatory obligations. Current id.DRIVE members are FISABIO (Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana, Spain), P95 (Belgium), AstraZeneca (United Kingdom), Novavax (US), Pfizer (US) and Sanofi (France). Past members are THL (Finnish institute for Health and Welfare, Finland), GSK

(GlaxoSmithKline, UK), Janssen (Belgium), Valneva (Austria), CureVac (Germany), Moderna (US), and Bavarian Nordic (Denmark). This pilot project is performed at the request of Sanofi (France).

11 OBJECTIVES

11.1 Primary Objective(s)

1. To assess the detection rates (%) of RSV, hMPV and PIV in adult (s)ARI patients (≥18 years), when using multi-specimen collection compared to a single nasopharyngeal swab, overall and by additional specimen type.

11.2 Secondary Objective(s)

2. As primary objective, stratified by:
   - Age categories: 18-49, 50-59, 60-74, 75+
   - Sex at birth
   - Time since symptom-onset categories
   - By setting (hospital, ED ward and PCC)
   - By diagnosis (upper respiratory tract infection vs. lower respiratory tract infection and pneumonia, bronchitis, bronchiolitis, etc.)
   - By common comorbidities/ chronic conditions

3. As primary objective, stratified by:
   - Vaccination status
     - RSV detection rates by RSV vaccination status (ever vaccinated or unvaccinated)

4. To assess the detection rates (%) of SARS-CoV-2 and Influenza in adult (s)ARI patients (≥18 years), when using multi-specimen collection compared to a single nasopharyngeal swab (overall and by additional specimen type), overall and stratified by:
   - SARS-CoV-2 detection rates by SARS-CoV-2 vaccination status (vaccinated in the last 12 months or not vaccinated in the last 12 months)
   - Influenza detection rates by Influenza vaccination status (vaccinated in the last 12 months or not vaccinated in the last 12 months).

11.3 Exploratory Objective(s)

5. To assess the detection rates (%) of co-infections (all pathogens tested) in adult (s)ARI patients (≥18 years), when using multi-specimen collection compared to a single nasopharyngeal swab, overall and by additional specimen type.
   - And stratify by disease severity (setting: PCC, ED ward, hospitalization, death), if the sample size allows.

6. As primary objective, stratified by subtype or serotype (when applicable)
   - RSV detection rates by RSV subtype A and B
   - PIV detection rates by PIV serotype (1-4)

7. To assess the detection rates of Influenza, SARS-CoV-2 and other viral pathogens tested for with the RT-PCR multiplex panel in adult (s)ARI patients (≥18 years), when using multi-specimen collection compared to a single nasopharyngeal swab, overall and by additional specimen type.

12 METHODS

12.1 Study Design

This study is a multi-setting (inpatient, ED ward and PCC) prospective cohort study of (s)ARI cases.

The outcome of interest for the study will be laboratory-confirmed infection (with one of the viral respiratory pathogens of interest) in patients visiting PCC and ED or hospitalized because of (s)ARI.

12.2 Study Setting

This is a multicenter pilot study taking place in Spain, involving up to four PCCs and one hospital—including emergency departments—in the Valencia region.

The following centers are involved:

- Hospital Dr. Peset, part of the VAHNSI hospital network (inpatient and ED ward).
- PCCs based in Valencia, Spain

12.3 Study Population

The study population consists of adults aged 18 years and older, presenting at one of the participating Study Contributors during the study period, who

- meet the inclusion criteria and does not present with any exclusion criteria

AND

- meet the (s)ARI case definition (see Section 12.3.1)

12.3.1 Case definition

For the purposes of this study, the case definition of (s)ARI will serve as the main definition for identifying cases across all healthcare settings involved—hospitals, PCC, and ED. Recognizing that the classical (s)ARI definition includes hospitalization as a criterion, which is not applicable in PCC and ED contexts, we will adopt the notation (s)ARI to reflect that not all patients have severe illness. The presence of the same symptoms will be used to trigger enrolment in the study in all settings.

A (s)ARI case is defined as a patient 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 and symptoms occurring for at least 24 hours.

12.3.2 Inclusion Criteria

Individual patients need to fulfil the following inclusion criteria:

- Adults aged 18 years and older

AND

- Meet the (s)ARI case definition

AND

- Willing to have a nasopharyngeal and oropharyngeal swab collected as well as saliva.

AND

- Willing and able to provide informed consent, obtained from the patient or from the patient's Legally Acceptable Representative(s).

Patients are also asked to provide sputum and blood samples for paired serology testing; however, this is optional and consent is provided separately on the ICF.

12.3.3 Exclusion Criteria

Individuals (patient) cannot be enrolled if:

- patient cannot be swabbed due to severe septum deviation, obstruction, or other conditions that contra-indicate swabbing,
- patient was previously enrolled in the study within 30 days of their current visit/admission,
- patient develops signs and symptoms of (s)ARI after being hospitalized.

12.3.4 Definitions

Medically attended patients (PCCs and ED):

Persons who sought medical care at an ED or PCCs but are not admitted for an overnight hospital stay or admitted to the hospital directly. This includes individuals who are evaluated, treated, or managed during a single visit and discharged the same day.

Hospitalized patients:

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

12.4 Study Period

Patients will be recruited from January 2026 until end of June 2026. Recruitment targets are set per setting and month based on logistics and average number of patients at each setting during the previous years.

During January and February, a maximum of 100 (s)ARI inpatients per month will be consecutively recruited during the week (Monday to Friday). Recruitment will be

halted after 100 patients are recruited. During the other months with expected high hMPV and PIV circulation, all (s)ARI patients will be approached.

For both the ED ward and PCC setting, (s)ARI patients will be recruited consecutively during the week (Monday to Friday). Each week 12 (s)ARI patients will be recruited from each setting. During the peak season of respiratory illnesses, the targets might be reached before Friday and then recruitment will be halted for that week. In slower recruitment weeks, all patients will need to be approached to reach the target sample size of 12 (s)ARI patients.

12.5 Variables

12.5.1 Outcome(s)

12.5.1.1 Primary Outcome – Laboratory-confirmed respiratory infection

A laboratory-confirmed respiratory infection is defined as either:

- a positive RT-PCR result from the nasopharyngeal, oropharyngeal, sputum or saliva respiratory sample, and/or
- a positive serology result from paired blood samples (hospitalized patients only).

The outcome of interest for the primary objectives is a laboratory-confirmed infection with one of the viral respiratory pathogens of interest:

- RSV:
  - Subtype A
  - Subtype B
- PIV
  - Serotype 1
  - Serotype 2
  - Serotype 3
  - Serotype 4
- hMPV

The RT-PCR commercial kit will be used on the nasopharyngeal, oropharyngeal, sputum or saliva respiratory samples and will test for additional pathogens as well including Influenza A and B and SARS-CoV-2.

There will be no results for these additional pathogens on the blood samples.

12.5.2 Other Variables and Covariates

At baseline, information on covariates will be collected from patients in all settings through an electronic Case Report Form (eCRF). The complete dataset can be found in the annotated eCRF and is summarized in Table 1.

Table 1. Study covariates

Covariate	Description
Age	DD-MMM-YYYY
Sex at birth	Male, female
Setting id	Hospitalized, ED ward or PCC

Covariate	Description
Symptom onset-date	DD-MMM-YYYY
Date of visit or admission	DD-MMM-YYYY
Diagnosis	Upper respiratory tract infection (URTI) or lower respiratory tract infection (LRTI)
Admitting diagnosis	ICD-10 code
Chronic conditions/ Comorbidities:	
Asthma	Binary, yes/no
Chronic lung disease	Binary, yes/no
Chronic obstructive pulmonary disease (COPD)	Binary, yes/no
Chronic cardiovascular disease	Binary, yes/no
Hypertension	Binary, yes/no
Chronic liver disease	Binary, yes/no
Chronic renal disease	Binary, yes/no
Type 1 and type 2 diabetes	Binary, yes/no
Cancer	Binary, yes/no
Obesity	Binary, yes/no
Immunodeficiency disorders	Binary, yes/no
Neurological disorder	Binary, yes/no
Immunodeficiency or organ transplant	Binary, yes/no
Long-term care facility residence	Binary, yes/no
Admission to intensive care unit	Binary, yes/no
In-hospital death	Binary, yes/no
Vaccination status:	
RSV	Vaccination history of RSV vaccinations, vaccination date
Influenza	Vaccination details of Influenza vaccination within 12 months prior to (s)ARI medical attendance, vaccination date
SARS-CoV-2	Vaccination history of COVID-19 vaccinations, vaccination date
Symptoms and signs	Nasal congestion/rhinorrhea: Sore throat/hoarseness; Sinus pain/pressure tenderness; Chest pain; New or increased cough; New or increased sputum; New or increased dyspnea (shortness of breath); New or increased wheezing (reported by study participant or investigator); New or increased crackles/ rhonchi/ rales based on chest auscultation (reported by investigator); Tachypnea: respiratory rate ≥ 20 respirations/min (reported by investigator); Hypoxemia: Low or decreased oxygen saturation (O2 saturation < 95% or ≤90% if baseline is <95%) (reported by investigator); Need for oxygen supplementation (reported by investigator); Fever (temperature ≥38°C by any route; self-reported by patient in the case of use of fever lowering medication); Feverishness (Feeling of having fever if temperature is not

Covariate	Description
	measured or forgotten); Fatigue; Body aches; Headache; Anorexia/decreased appetite

12.6 Data Sources

After study enrolment, data will be collected from primary (e.g., laboratory results) and secondary data sources (e.g., vaccination registries, medical files). Chronic conditions and comorbidities will be collected using the medical files. The symptoms and signs a patient is experiencing are collected from the medical files as well as from the intake conversation with the treating physician.

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

12.7 Study Procedures

Patients attending to PCC, ED and patients hospitalized will be screened to select eligible (s)ARI patients[1]. These patients will be approached for written informed consent. Those willing to participate in the study will be asked to provide saliva, nasopharyngeal swabs and oropharyngeal swabs, with optional sputum samples. Blood samples are collected only from hospitalized patients, with paired serology used to confirm recent infection. Study samples will be collected by trained personnel following instructions for proper identification, hygiene procedures, and sample labelling which will be outlined in the Study Assessments and Procedures form.

No treatment is provided as part of this study; routine clinical management and standard-of-care therapies will be provided to the study participants.

The following samples are taken to identify the pathogen causing the respiratory infection:

Table 2. Sample collection by setting

Sample type	ED and PCCs setting	Hospitalized
Nasopharyngeal	Required	Required
Oropharyngeal	Required	Required

[1] In the hospital setting, during January and February a maximum of 100 patients per month will be consecutively recruited during the week (Monday to Friday). During the other months with expected high hMPV and PIV circulation, all (s)ARI patients will be approached (including weekends).
For both the ED ward and PCC setting, (s)ARI patients will be recruited consecutively during the week (Monday to Friday). Each week 12 (s)ARI patients will be recruited per setting. During the peak season of respiratory illnesses, the targets will be reached before Friday after which recruitment will be halted for that week. In slower recruitment weeks, all patients will need to be approached to reach the target sample size of 12 (s)ARI patients.

Sample type	ED and PCCs setting	Hospitalized
Saliva	Required	Required
Sputum (optional)	Optional	Optional
Blood sample taken at baseline in hospital (optional)	Not collected	Optional
At convalescence: Blood sample taken 28 (+/- 3 days) days after hospital admission (if baseline sample was taken)	Not collected	If baseline is taken

Respiratory samples

A laboratory-confirmed infection is a positive multiplex RT-PCR on a respiratory sample collected between hospital admission and up to 48 hours after hospital admission, preferably as soon as possible. For ED/PCC patients, sample should be collected at time of the initial visit.

All respiratory samples (nasopharyngeal, oropharyngeal , sputum and saliva samples) will be tested using a commercial RT-PCR kit, which has undergone quality and/or validation processes. Study Contributor will be requested to submit validation logs summarizing the quality check process, results, timing and certificates of analysis for assays performed.

Blood samples

Blood samples will be collected only from hospitalized (s)ARI patients. A baseline sample is taken at admission (within 48 hours), and a convalescent sample is requested 28 days (+/- 3 days) after hospital admission. If the patients have already been discharged from the hospital for the second blood sample, a study nurse will visit them at their homes to collect the required samples and information or transport will be arranged for the study participant to come to the hospital. The serum sample must be stored and transported at -20°C. Every month a batch of blood samples will be transported to the central laboratory in Lyon, France. Whenever possible, blood taken as part of the standard of care will be salvaged for this study.

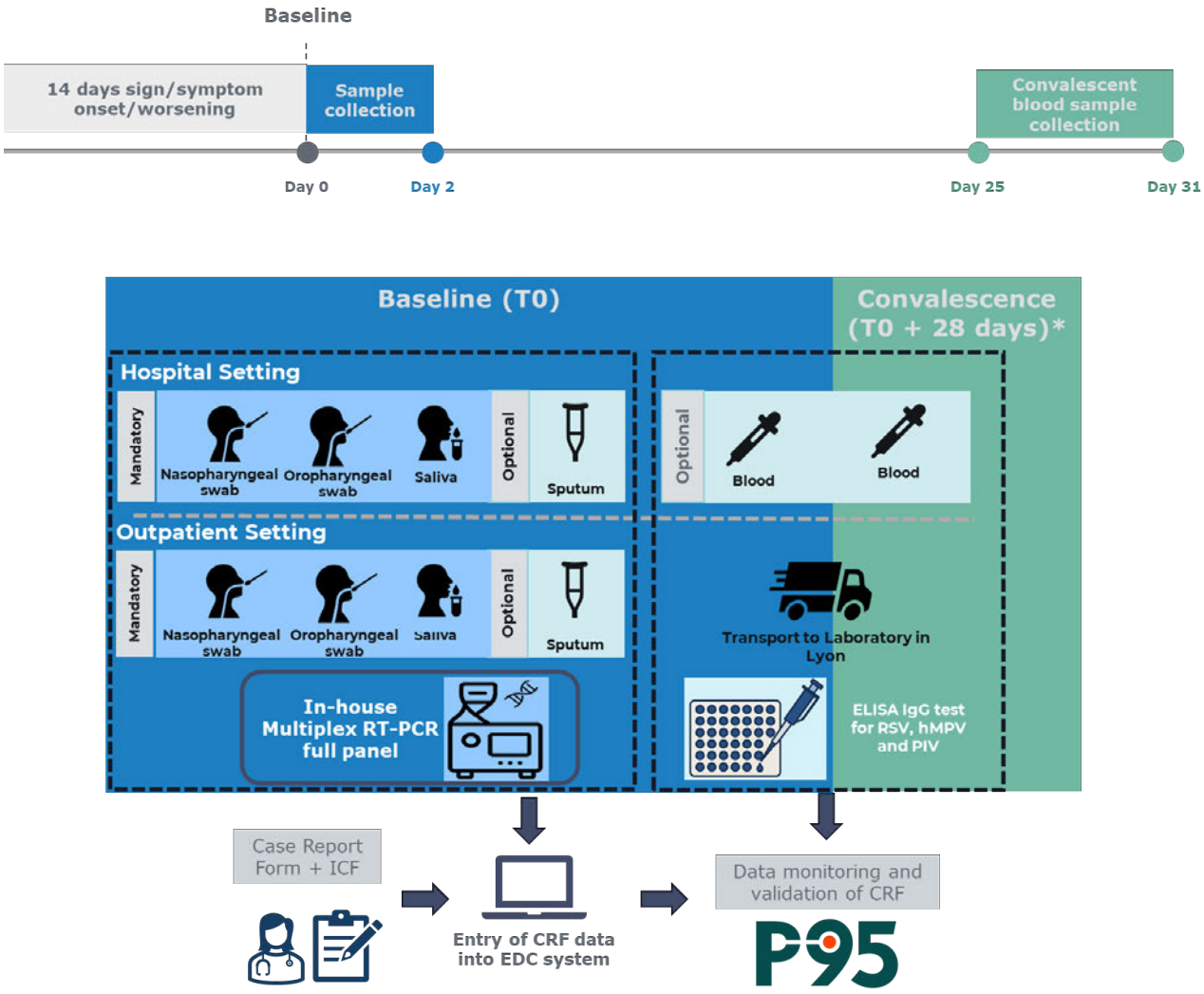
ELISA technique will be used to detect and quantify IgG antibody titers. The following antibody titers will be tested:

- RSV-A IgG antibody titers baseline
- RSV-A IgG antibody titers convalescence
- RSV-B IgG antibody titers baseline
- RSV-B IgG antibody titers convalescence
- hMPV-A IgG antibody titers baseline
- hMPV-A IgG antibody titers convalescence
- hMPV-B IgG antibody titers baseline
- hMPV-B IgG antibody titers convalescence
- PIV1 IgG antibody titers baseline

- PIV1 IgG antibody titers convalescence
- PIV2 IgG antibody titers baseline
- PIV2 IgG antibody titers convalescence
- PIV3 IgG antibody titers baseline
- PIV3 IgG antibody titers convalescence
- PIV4 IgG antibody titers baseline
- PIV4 IgG antibody titers convalescence

See Figure 1 for the schematic overview of the samples that will be taken and the test to be performed.

Figure 1. Study procedure overview



12.7.1 Sample storage

To support potential future analyses and ensure the integrity and reproducibility of study findings, aliquots of any leftover material from the biological samples collected will be stored under controlled conditions for long-term preservation. This approach enables the possibility of retesting or conducting additional analyses as new methodologies or research questions arise. All samples will be aliquoted to

minimize freeze-thaw cycles and stored at validated temperatures in accordance with Good Clinical Practice and applicable biobanking standards. Participants will be providing informed consent for the storage and potential future use of their samples, which will be maintained in secure, access-controlled facilities for the duration specified in the study protocol.

12.8 Study Management

The study will be conducted by the Study Contributor investigator(s) with input, review, and approval from the P95 Research Team, including support for material development, study contributor recruitment and training, network management, electronic data capture (EDC), and data handling.

All study activities will follow the final approved protocol. The rights, safety, and well-being of patients will take precedence over scientific or societal interests. All personnel must be appropriately qualified by education, training, and experience.

12.8.1 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.

12.8.2 Data Capture

The data will be collected using the electronic data capture system Viedoc. Viedoc will be set up following the annotated case report form (CRF).

12.9 Statistical Methods

A statistical analysis plan (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.

12.9.1 Sample Size Considerations

Sample size were calculated assuming paired designs across various scenarios, assuming the addition of one extra specimen per patient and the simplifying assumption that all positives by Method A are also positive by Method B (i.e., the gain equals the proportion A-/B+). These calculations were based on pathogen incidence rates ranging from 1% to 10% and varying levels of improved detection with an additional sample. Across all settings, we expect data from over 1,000 patients with at least two specimens available (approximately 450 inpatients and 624 outpatients).

Under these assumptions, with the planned combined samples (N≈1,074), we have adequate precision to assess a doubling of detection rates — consistent with the Pfizer North America Multispecimen Study [6] — for pathogens with an incidence between 1% -7% range. For such doublings, the 95% confidence intervals on the gain are expected to be approximately ± 0.6 and ± 1.8 percentage points overall (interval with ≈1.2—3.6 pp), depending on the baseline incidence.

While analyses stratified by settings will be possible, they will have wider confidence intervals due to smaller sample sizes.

The analysis of the 150 patients with available serology data will be exploratory, with limited statistical power, as we expect only a small number of PIV and/or hMPV cases in this subgroup.

12.9.2 Descriptive Analyses

12.9.2.1 Attrition diagram

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

12.9.2.2 Descriptive analysis of demographics and baseline characteristics of included patients

We will describe the demographic and clinical characteristics of the patients both overall and by respiratory pathogen. Counts and proportions (%, along with 95% exact binominal confidence intervals) will be presented for several variables, including age group, sex, diagnosis, symptoms, chronic conditions, vaccination status and residence in long-term care facilities.

Euler diagrams will be used to visually represent the overlap in pathogen detection across specimen types. In the SAP, visualization and presentation of results will be further defined.

12.9.3 Data Analysis

12.9.3.1 Detection rates of respiratory pathogens

Positive laboratory results for each respiratory pathogen of interest will be reported by specimen type. This includes nasopharyngeal swabs, saliva, blood, and sputum. Serology is considered positive for recent infection if a fourfold or greater rise in virus-specific IgG antibodies is observed between paired samples. If all samples (respiratory and blood samples) collected in the time frame are negative, the patient is considered as not having any laboratory-confirmed infection.

For each specimen type, the percentage of positive diagnoses will be calculated by dividing the number of patients in whom the pathogen was detected using that specimen (alone or in combination) by the total number of included patients. Detection rates in sputum and blood samples will be calculated by dividing the number of patients in whom the pathogen was detected using that specimen (alone or in combination) by the total number of included patients who provided sputum or blood samples.

Comparative detection rates will be assessed by calculating the percentage increase in positivity when additional specimen types are included, using nasopharyngeal as the reference. This will allow evaluation of the incremental diagnostic value of each specimen type.

12.9.4 Subgroups

The primary objective will be investigated stratifying by several subgroups to investigate heterogeneity. The following stratifications will be pursued.

- Age categories:
  - 18-49 years old
  - 50-59 years old
  - 60-74 years old
  - 75+ years old
- Sex at birth
- Time since symptom-onset categories
- By setting
  - Hospitalized patients
  - ED ward
  - PCCs
- By diagnosis:
  - Upper respiratory tract infection (URTI)
  - Lower respiratory tract infection (LRTI)
- By admitting diagnosis (ICD-10 code)
  - Pneumonia
  - Bronchitis
  - Bronchiolitis
- By common comorbidities/ chronic conditions
- Subtypes of respiratory pathogens

12.9.5 Case definition

The (s)ARI case definition will be used to select patients that could be enrolled in the current study. To investigate the influence of the case definition, the symptoms and signs for the Sanofi acute respiratory disease (ARD) case definition will be collected, to enable a sensitivity analysis in those patients who also fit the ARD case definition.

ARD case definition

A patient will be considered as having ARD when:

- At least **2 respiratory symptoms/signs** for at least 24 hours
  OR
- At least **1 respiratory symptom/sign AND 1 systemic symptom/sign** for at least 24 hours.

Respiratory symptoms/signs	**Systemic symptom/sign**
• Nasal congestion/rhinorrhea • Sore throat/hoarseness • Sinus pain/pressure tenderness • Chest pain • New or increased cough • New of increased sputum	• Fever (temperature ≥38°C by any route; self-reported by patient in the case of use of fever lowering medication) • Feverishness (Feeling of having fever if temperature is not measured or forgotten)

Respiratory symptoms/signs	Systemic symptom/sign
• New or increased dyspnea (shortness of breath) • New or increased wheezing (reported by study participant or investigator) • New or increased crackles/rhonchi/rales based on chest auscultation (reported by investigator) • Tachypnea: respiratory rate ≥20 respirations/min (reported by investigator) • Hypoxemia: Low or decreased oxygen saturation <95% or ≤90% if baseline is <95% (reported by investigator) • Need for oxygen supplementation (reported by investigator)	• Fatigue • Body aches • Headache • Anorexia/decreased appetite

12.10 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. Data collected at the Study Contributor will be checked for quality and transferred to a dedicated, secured central server hosted by P95.

Data Flow:

1. The Study Contributor collects the data and enters/uploads it in the EDC system. The Study Contributor is responsible for the data collection and data management of their patient-level study data.
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.

A 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. P95 reviews the imported variables on monthly basis.

12.11 Quality Management

Programmed checks are run on the EDC-extracted data and the identified data issues will be queried regularly using the EDC platform Viedoc. After the Study Contributor responds to the queries by updating or confirming the data entered in eCRF, P95 closes the queries. All the queries should be closed before database lock.

As part of the data analysis workflow, R coding undergoes a QC review by an independent statistician to ensure accuracy, reproducibility, and adherence to coding standards. Following the coding QC, the results are reviewed by epidemiologists to assess their validity, interpretability, and relevance in the context of the study's design and public health implications.

12.11.1 Monitoring

Monitoring activities include:

- Before study start, a site initiation visit will be organized by the Study Team.
- During study conduct, regular Study Contributor contacts will be organized to monitor study progress (number of patients enrolled), to ensure regular data input to the Viedoc 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 (s)ARI 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 study specific Monitoring Plan.

The Study Contributor investigators must permit any external auditor mandated by the Study Requestor, or auditors and representatives from regulatory authorities direct access to all study-related documents. Efforts will be made to maintain participant confidentiality at all times.

12.12 Limitations of the Research Methods

- The overall sample size and study period are limited, and certain respiratory pathogens or subtypes may occur infrequently, reducing the statistical power to detect associations or draw conclusions for these specific agents.
- RT-PCR offer high specificity. However, a positive RT-PCR result may not indicate causality for a respiratory infection (persistent nucleic acid from previous infection, or asymptomatic carriage).
- This study will be performed in one geographical area which may result in a limited diversity of patients when considering age, race, social economic status, chronic medical conditions and vaccinations status. The generalizability of the study might therefore be limited.
- Although the study period was selected to coincide with the high season of the pathogens of interest in the Valencia region, previous published studies have shown high seasonal variability and the circulation of the pathogens of interest might differ from the expectations.

- Despite good sensitivity and specificity of the selected serology assays, false-negative (e.g., immunodeficiency disorder) and false-positive (e.g., cross-reactivity) test results are possible.
- The second blood sample is scheduled approximately four weeks after hospital admission, when most patients are expected to have returned home. To facilitate follow-up, a nurse will be hired to visit patients at home, or transportation costs will be reimbursed. Nonetheless, some patients may still be lost to follow-up
- Timing of specimen collection: Delays between symptom onset and sample collection may result in declining viral loads, potentially affecting detection rates and diagnostic accuracy.

13 ETHICAL CONSIDERATIONS

13.1 Guiding Principles

To ensure the quality and integrity of research, this study will be conducted under the International Ethical Guidelines on Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS) [9], Good Epidemiological Practice (GEP) [10], the ethical principles that have their origins in the Declaration of Helsinki and any applicable national laws, regulations and guidelines.

This is a non-interventional study. There is no direct benefit to the patients. Nevertheless, this study provides key scientific insights and could provide directions to identify the best specimen type for diagnosis.

13.2 Informed Consent

Written informed consent will be obtained from all patients/guardians as specified by the national/regional independent ethics committee (IEC), if applicable. The following information should be specified in the 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 recruited patients, 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 is not required, the reason will be stated.

13.2.1 Discontinuation or withdrawal from the Study

Patients enter this study voluntary and may withdraw from the study at any time for any reason. Withdrawal or discontinuation from this study will not affect the quality of the medical care or the relationship with their treating physician(s). Efforts will be made to understand and document the primary reason for the withdrawal. Already collected data may still be included in the analysis.

13.2.2 Loss to Follow-up

Information from patients included from the PCC and ED ward setting is expected to be complete as all information and samples will be collected within the initial visit. However, in the hospital setting it is possible that patients have been discharged before the CRF has been completed or all samples have been collected. The ICF for the hospital setting will include giving permission to be contacted at home for additional samples and collection of additional data. For patients who provided a first blood sample, a study nurse will go to the patient's home to collect the second blood sample. If the second blood sample could not be collected, the patient will still be included in the analysis as the information from the other specimen types can still be used.

13.3 Patients' Privacy Protection and Confidentiality

Data will be pseudonymized at the study contributor-level prior to data transfer to P95. All parties will ensure protection of patients´ personal data and will not include patient 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, recruited patients 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 patient data. Every effort will be made to protect patient confidentiality according to Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons regarding the processing of personal data and on the free movement of such data and repealing Directive 95/46/EC (General Data Protection Regulation; GDPR).

13.4 Independent Ethics Committee/Institutional Review Board

Consistent with local regulations and prior to enrolment of patients 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. Patient enrolment will not start before the Study Contributor has obtained written confirmation of a favorable opinion/approval from the relevant central or local IRB/IEC. The Study Contributor will promptly and before first patient 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 favorable opinion/approval was given that clearly identifies the study, the protocol version, and the ICF version reviewed.

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

13.5 Protocol Amendments

Changes to the protocol will be documented in written protocol amendments. Such protocol changes will be discussed and agreed upon with the Study Team prior to their implementation. Major (i.e., substantial, significant) amendments will

usually require submission to the relevant IRB/IEC for approval or favorable opinion and to the relevant regulatory authorities, if applicable. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.
Minor (non-substantial) protocol amendments, including administrative changes, will be filed at each participating Study Contributor and will be submitted to the relevant IRB/IEC or regulatory authorities where required by pertinent regulations.

13.6 Protocol Deviations

Protocol deviations will be reported by the Study Contributor and will be discussed with the Study Team.

14 MANAGEMENTOF STUDY RELATED INCIDENTS AND REPORTING OF ADVERSE EVENTS

During study visits, patients may experience procedure-related incidents. The PI will provide emergency care or first aid if needed, prioritizing patient safety and well-being. Any such incidents will be documented in the source records and reported to the Sponsor. As this is an observational study with no investigational medicinal products involved, adverse event reporting is not part of the data collection.

15 REPORTING AND DISSEMINATION OF STUDY RESULTS

15.1 Registration of Study Protocol

This study is registered in the EMA-HMA catalogue (EUPAS1000000780).

15.2 Reports

Two study reports will be prepared covering the objectives described in this study protocol (if sample numbers allow).

The interim report will be prepared after 3 months of data collection. The final report will be prepared after end of study period when all data has been collected and analyzed.

15.3 Publications

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

16 SOURCES OF 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.

This pilot study and its protocol are financed by Sanofi. All funding will be transparently acknowledged in study communications.

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ANNEX 1 - ADDITIONAL FISABIO STUDY TEAM