Study Protocol P2 C1-011

20/03/2024

Version 2.1

TABLE OF CONTENTS

DOCUMENT HISTORY

Version	Date	Description
V1.0	9th November 2023	**Submission to EMA**
V2.0	4th December 2023	**Updated version**
V2.1	20th March 2024	**EUPAS number added**

Study Title	DARWIN EU® - Age-specific incidence rates of RSV-related disease in Europe
Protocol version identifier	V2.1
Date of last version of protocol	20th March 2024
EU PAS register number	EUPAS107708
Active substance	N/A
Medicinal product	N/A
Research question and objectives	Research question What are the age-specific disease frequencies, hospitalization rates, and mortality rates related to Respiratory Syncytial Virus (RSV) infection in European countries over the past decade? Study objectives Objective 1: To estimate the incidence of RSV-related hospitalisation in the general population, stratified by year and age groups, during the period from January 1, 2013, to December 31, 2022. Objective 2: To estimate the duration of RSV-related hospitalisation among patients diagnosed with RSV infection, stratified by year and age groups, between January 1, 2013, and December 31, 2022. Objective 3: To estimate the prevalence of RSV-related intensive care unit (ICU) admissions among patients diagnosed with RSV infection, stratified by year and age groups, between January 1, 2013, and December 31, 2022. Objective 4: To estimate the prevalence of RSV co-infections with other common viral respiratory pathogens — such as Influenza Viruses, SARS-CoV-2, Parainfluenza Viruses, Adenoviruses, Metapneumovirus, Bocavirus, Rhinoviruses, Coxsackieviruses, Parechoviruses, and Echoviruses — in the general population, stratified by year and age groups, during the period from January 1, 2013, to December 31, 2022. Objective 5: To estimate RSV-related mortality rates among patients diagnosed with RSV infection, stratified by year and age groups, between January 1, 2013, and December 31, 2022.
Countries of study	Estonia, France, Germany, Spain, and United Kingdom.

	D2.2.2 - Study Protocol for P2 C1-011	
	Author(s): J.T. Arinze, K. Verhamme	**Version:** v2.1
		Dissemination level: Public

Author	Johnmary Arinze (j.arinze@darwin-eu.org) Katia Verhamme (k.verhamme@darwin-eu.org)

LIST OF ABBREVIATIONS

Acronyms/terms	Description
CDM	Common Data Model
CHUBX	Bordeaux University Hospital
CPRD GOLD	Clinical Practice Research Datalink GOLD
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real World Interrogation Network
EBB	Estonian Biobank
EGCUT	Estonian Genome Center at the University of Tartu
EHR	Electronic Healthcare Records
EMA	European Medicines Agency
GP	General Practitioner
LOINC	Logical Observation Identifiers Names and Codes
ID	Index date
ICU	Intensive Care Unit
IMASIS	Institut Municipal Assistencia Sanitaria Information System
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
RSV	Respiratory Syncytial Virus
SNOMED	Systemized Nomenclature of Medicine
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària

1. TITLE

DARWIN EU® - Age-specific incidence rates of RSV-related disease in Europe

2. RESPONSIBLE PARTIES – STUDY TEAM

Table 1 shows a description of the Study team by role, name and organization.

Table 1: Description of Study Team

Study team Role	Names	Organisation
Principal Investigator(s)/ Clinical Epidemiologists	Johnmary Arinze Katia Verhamme	Erasmus MC Erasmus MC
Data analysts	Cesar Barboza Ross Williams	Erasmus MC Erasmus MC
Data Partner*	**Names**	**Organization**
Local Study Coordinator/Data Analyst	Antonella Delmestri James Brash Romain Griffier Marek Oja Angela Leis Talita Duarte Salles	University of Oxford – CPRD IQVIA DA Germany CHUBX France University of Tartu - Estonian Biobank IMASIS Spain IDIAPJGol – SIDIAP

*Data partners' role is only to execute code at their data source. These people do not have an investigator role.

3. ABSTRACT (STAND-ALONE SUMMARY OF THE STUDY PROTOCOL)

Title

DARWIN EU® - Age-specific incidence rates of RSV-related disease in Europe

Rationale and Background

Severe acute respiratory infection (SARI) caused by respiratory syncytial virus (RSV) has gained recognition as a global health problem with a high burden of disease. In children under 5 years, it is estimated that 3.6 million hospital admissions, and 101,400 deaths were attributable to RSV worldwide in 2019. RSV infection also represents a substantial health burden in older adults. It is estimated that 470,000 hospitalisations, and 33,000 in-hospital deaths in ≥60-year-old adults were attributable to RSV-related disease in high-income countries.

There have been substantial advances in the development of RSV vaccines, with several prophylactic candidates reaching late-phase clinical development. As of July 2023, the European Medicines Agency (EMA) has recommended granting a marketing authorisation for Arexvy and Abrysvo vaccines for use in the European Union. Arexvy is indicated for active immunisation for the prevention of lower respiratory tract disease caused by RSV virus in adults ≥ 60 years. Abrysvo is indicated for the prevention of lower respiratory tract disease caused by RSV through: (a) passive protection in infants from birth through 6 months of age following maternal immunisation during pregnancy, (b) active immunisation of adults ≥ 60 years. More of these vaccines, using similar or different platforms, may be approved by EMA in the coming year(s). Therefore, accurate information about RSV burden in high-risk groups is essential for decision-making to support the continuous assessment of their benefit/risk profile.

This study is expected to generate evidence that is complementary to the work carried out by European initiatives such as IHI PROMISE.[1] Importantly, the objective is to explore the feasibility of capturing adequate RSV-specific endpoints in the DARWIN EU® data sources (for example, availability of laboratory testing data) to support the development of effectiveness studies as soon as possible once the vaccines are deployed and along their lifecycle, as part of the research agenda of the EU Vaccine Monitoring Platform, a collaboration between EMA and the ECDC.[2]

Research question and Objectives

Research question

What are the age-specific disease frequencies, hospitalization rates, and mortality rates related to Respiratory Syncytial Virus (RSV) infection in European countries over the past decade?

Study objectives

Objective 1: To estimate the incidence of RSV-related hospitalisation in the general population, stratified by year and age groups, during the period from January 1, 2013, to December 31, 2022.

Objective 2: To estimate the duration of RSV-related hospitalisation among patients diagnosed with RSV infection, stratified by year and age groups, between January 1, 2013, and December 31, 2022.

Objective 3: To estimate the prevalence of RSV-related intensive care unit (ICU) admissions among patients diagnosed with RSV infection, stratified by year and age groups, between January 1, 2013, and December 31, 2022.

Objective 4: To estimate the prevalence of RSV co-infections with other common viral respiratory pathogens — such as Influenza Viruses, SARS-CoV-2, Parainfluenza Viruses, Adenoviruses, Metapneumovirus, Bocavirus, Rhinoviruses, Coxsackieviruses, and Echoviruses — in the general population, stratified by year and age groups, during the period from January 1, 2013, to December 31, 2022.

Objective 5: To estimate RSV-related mortality rates among patients diagnosed with RSV infection, stratified by year and age groups, between January 1, 2013, and December 31, 2022.

Research Methods

Study design

Retrospective cohort study.

- Population-level cohort: Population-level descriptive epidemiology of the incidence of RSV-related hospitalisation (Objective 1), and prevalence of RSV co-infections with other respiratory pathogens (Objective 4) in the general population.
- Patient-level cohort: Patient-level characterisation to estimate duration of RSV-related hospitalisation (Objective 2), prevalence of RSV-related ICU admissions (Objective 3), and RSV-related mortality rates (Objective 5) in patients with diagnosed with RSV infection.

Population

Population-level descriptive epidemiology: This analysis will include all individuals in the respective databases from 2013 to 2022 (or the latest available date if earlier), with a minimum of 1 year of data visibility prior to study entry date. However, the latter requirement will not be applicable to children aged <1 year.

Patient-level characterization: This analysis will include all patients diagnosed with RSV infection between 2013 and 2022 (or the latest available date if earlier), with at least 1 year of data availability prior to their diagnosis. However, the latter requirement will not be applicable to children aged <1 year.

Variables

Drug of interest: Not applicable

Condition of interest: RSV infection identified through SNOMED disease codes and LOINC laboratory test codes.

Outcomes of interest: Study outcomes will include RSV-related hospitalisation, ICU admission, mortality rate, and co-infection with other respiratory pathogens (Influenza Viruses, Rhinoviruses, SARS-CoV-2, Parainfluenza Viruses, Adenoviruses, Metapneumovirus, and Enteroviruses).

Data sources

1. Clinical Data Warehouse of Bordeaux University Hospital (CHUBX), France
2. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
3. Estonian Biobank (EBB), Estonia
4. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
5. Institut Municipal Assistencia Sanitaria Information System (IMASIS), Spain
6. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain

Sample size

No sample size was calculated for this study as our primary objective is to describe the age-specific incidence rates of RSV-related disease outcomes in Europe using secondary data. Based on a preliminary feasibility assessment, the estimated number of individuals with RSV infection in the included databases varied, ranging from 1,000 (CPRD GOLD) to 16,400 (SIDIAP). Additionally, specific counts for other databases are as follows: 6,100 (EBB), 6,700 (CHUBX), 9,100 (IQVIA DA Germany), and 9,800 (IMASIS).

Data analysis

Data analysis will be conducted to estimate the number and rates of hospitalisation due to RSV infection (Objective 1) and the number and percentage of individuals with RSV co-infection with other respiratory pathogens (Objective 4) within the general population. Furthermore, the number and percentage of ICU admissions will be estimated among patients hospitalised due to with RSV infection (Objective 3).

The statistical analyses will be performed on OMOP-CDM mapped data using the *IncidencePrevalence* R package, and stratified by age, calendar year and database.

RSV-related mortality rates (Objective 5) will be calculated using the Kaplan-Meier (KM) method and survival will be calculated using data on time at risk of RSV-related death, defined as within 30 days of RSV infection. Results will be reported as plots of the estimated survival curves as well as the estimated probability of survival at 30 days. The lags between RSV detection and deaths is mostly between 1 to 31 days,[3] thus, we will estimate all-cause 30-day mortality rates following RSV infection. The statistical analysis will be performed on OMOP-CDM mapped data using the *CohortSurvival* R package, and stratified by age, calendar year and database.

The duration of hospitalisation (Objective 2) will be calculated between the date of in-patient care/ hospital stay and the date of hospital discharge in patients with RSV infection. This will include key metrics such as the median, interquartile range (p25 and p75), maximum, and minimum days of hospitalisation. Results will be provided stratified by age, calendar year and database.

For all analyses a minimum cell counts of 5 will be used when reporting results, with any smaller counts obscured.

4. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	04/12/2023	All	Update	Clarifications on some specific objectives and terminologies

5. MILESTONES

STUDY SPECIFIC DELIVERABLE	TIMELINE
Draft Study Protocol	9th November 2023
Final Study Protocol	4th December 2023
Creation of Analytical code	6th to 18th December 2023
Execution of Analytical Code on the data	9th to 16th January 2023
Interim Study Report (if applicable)	To be confirmed
Draft Study Report	26th January 2024
Final Study Report	To be confirmed

6. RATIONALE AND BACKGROUND

Respiratory Syncytial Virus (RSV) is a widespread viral pathogen affecting individuals across various age groups, with a growing recognition of its impact on both children and the elderly. While RSV frequently presents as an upper respiratory infection, it can progress to bronchiolitis in young children, characterized by small airway obstruction.[4] In severe cases, it can lead to more critical conditions, such as pneumonia, respiratory failure, apnea, and, in some instances, death.[4] RSV-induced Severe Acute Respiratory Infection (SARI) has emerged as a global health concern associated with a substantial disease burden.[5] Children under 5 years of age bore a considerable burden in 2019, with an estimated 3.6 million hospital admissions and 101,400 deaths attributed to RSV worldwide.[6] Furthermore, RSV remains a significant health concern among older adults, where high-income countries reported an estimated 470,000 hospitalizations and 33,000 in-hospital deaths in individuals aged 60 years and older due to RSV-related diseases.[7]

The causative agent of RSV is a single-stranded, negative-strand RNA virus classified within the *Paramyxoviridae* family and *Pneumovirus* genus. Originally identified in chimpanzees in 1955, RSV was later confirmed as a human pathogen.[8] The virus exhibits seasonal variations and spreads through respiratory droplets, targeting apical ciliated epithelial cells, leading to airway obstruction and other complications.[4] Contagiousness can persist for 3 to 8 days, with specific individuals capable of spreading the virus even after symptoms cease.[4] Preventative measures, such as thorough hand washing and environmental cleaning, are crucial to reducing transmission. Diagnosis of RSV infection primarily relies on clinical evaluation, though specific testing methods such as rapid antigen testing and PCR are essential in certain situations, especially when exploring differential diagnoses or co-infection with other respiratory pathogens.[9, 10] Clinical presentations vary, encompassing upper respiratory symptoms like rhinorrhea and cough to lower respiratory involvement, characterized by bronchiolitis, wheezing, and tachypnea.[11]

Prognosis for children hospitalized with RSV infection is generally positive, with most patients recovering within 3 to 4 days.[4] However, high-risk infants may need more extended hospitalization and have an increased likelihood of requiring mechanical ventilation.[12] Supportive care forms the cornerstone of RSV treatment, though antiviral medications and immune prophylaxis are considered for select cases. [13] Remarkable progress has been made in RSV vaccine development, with several candidates reaching late-phase clinical development. As of July 2023, the European Medicines Agency (EMA) has recommended granting marketing authorization for Arexvy and Abrysvo vaccines for use in the European Union.[14, 15] Similar approval has been granted by the United States Food and Drug Administration (FDA).[16] Arexvy is indicated for active immunization in adults ≥ 60 years to prevent lower respiratory tract disease caused by RSV, while Abrysvo is indicated for passive protection in infants from birth through 6 months of age following maternal immunization during pregnancy and active immunization in adults ≥ 60 years. The approval of these vaccines signifies a pivotal step in addressing the RSV burden, especially among high-risk groups. Nevertheless, accurate information about RSV burden in high-risk groups is paramount for decision-making and continuous assessment of the benefit/risk profile of these vaccines, contributing significantly to public health efforts in Europe.[17]

This study aims to describe age-specific disease frequencies, hospitalization rates, and mortality rates of RSV infection in European countries over the past decade. The findings of this study will provide essential complementary evidence to monitor the effectiveness of RSV vaccines during deployment and throughout their lifecycle.

7. RESEARCH QUESTION AND OBJECTIVES

Research question:

What are the age-specific disease frequencies, hospitalization rates, and mortality rates related to Respiratory Syncytial Virus (RSV) infection in European countries over the past decade?

Study objectives

Objective 1: To estimate the incidence of RSV-related hospitalisation in the general population, stratified by year and age groups, during the period from January 1, 2013, to December 31, 2022.

Objective 2: To estimate the duration of RSV-related hospitalisation among patients diagnosed with RSV infection, stratified by year and age groups, between January 1, 2013, and December 31, 2022.

Objective 3: To estimate the prevalence of RSV-related intensive care unit (ICU) admissions among patients diagnosed with RSV infection, stratified by year and age groups, between January 1, 2013, and December 31, 2022.

Objective 4: To estimate the prevalence of RSV co-infections with other common viral respiratory pathogens — such as Influenza Viruses, SARS-CoV-2, Parainfluenza Viruses, Adenoviruses, Metapneumovirus, Bocavirus, Rhinoviruses, Coxsackieviruses, Parechoviruses, and Echoviruses — in the general population, stratified by year and age groups, during the period from January 1, 2013, to December 31, 2022.

Objective 5: To estimate RSV-related mortality rates among patients diagnosed with RSV infection, stratified by year and age groups, between January 1, 2013, and December 31, 2022.

Table 2: Primary and secondary research questions and objective

Objectives:	To estimate the incidence of RSV-related hospitalizations and the prevalence of RSV co-infections with other respiratory pathogens (such as Influenza Viruses, SARS-CoV-2, Parainfluenza Viruses, Adenoviruses, Metapneumovirus, Bocavirus, Rhinoviruses, Coxsackieviruses, Parechoviruses, and Echoviruses) in the general population, stratified by year and age groups. To estimate the duration of RSV-related hospitalizations, the prevalence of RSV-related intensive care unit (ICU) admissions, and RSV-related mortality rates among patients diagnosed with RSV infection, stratified by year and age groups.
Hypothesis:	Not applicable
Population ***(mention key inclusion-exclusion criteria):***	Population-level descriptive epidemiology: All individuals in the databases between 2013 and 2022 (or the most recent available date if earlier). A minimum of 1 year of data visibility before the study entry date is required for inclusion except in children under 1 year of age. Patient-level characterization: All individuals diagnosed with RSV infection between 2013 and 2022. To be included, patients must have at least 1 year of data availability before their diagnosis.

	Nevertheless, children under 1 year of age will not be required to meet this criterion.
Exposure:	Not applicable
Comparator:	None
Outcome:	RSV-related hospitalization, ICU admission, mortality rate, and co-infection with a range of other respiratory pathogens, including Influenza Viruses, SARS-CoV-2, Parainfluenza Viruses, Adenoviruses, Metapneumovirus, Bocavirus, Rhinoviruses, Coxsackieviruses, Parechoviruses, and Echoviruses.
Time *(when follow up begins and ends):*	Population-level descriptive epidemiology: Follow-up will start when participants fulfil inclusion criteria (i.e., present in the database between 1st of January 2013 and 31st of December 2022 and with at least 1 year of data visibility except in children under one year of age). Patient-level characterization: Follow-up will start from the date of RSV diagnosis during the study period. End of follow-up will be defined as the earliest of loss to follow-up, end of data availability, death, or end of study period (31st December 2022), whatever comes first.
Setting:	Inpatient and outpatient setting using data from the following 6 data sources: CHUBX (France), CPRD GOLD (UK), EBB (Estonia), IQVIA DA (Germany), IMASIS (Spain) and SIDIAP (Spain).
Main measure of effect:	Incidence and duration of RSV-related hospitalisation Prevalence of RSV-related ICU admission Prevalence of RSV co-infection with other respiratory pathogens RSV-related mortality rate

8. RESEARCH METHODS

8.1 Study Design

A cohort study will be conducted using routinely collected health data from 6 databases. The study will comprise two consecutive parts:

- Population-level cohort study: This part will estimate the incidence of RSV-related hospitalizations (Objective 1) and the prevalence of RSV co-infections with other respiratory pathogens (Objective 4) in the general population.

- Patient-level characterisation: This part aims to estimate the duration of RSV-related hospitalizations (Objective 2), the prevalence of RSV-related ICU admissions (Objective 3), and RSV-related mortality rates (Objective 5) among patients diagnosed with RSV infection.

Table 3. Description of Potential Study Types and Related Study Designs

STUDY TYPE	STUDY DESIGN	STUDY CLASSIFICATION
Population-level descriptive epidemiology	Population-level cohort	Off-the-shelf (C1)
Patient-level characterisation	Patient-level cohort	Off the shelf (C1)

8.2 Study Setting and data sources

This study will be conducted using routinely collected data from 6 databases in 5 European countries (4 EU countries and United Kingdom). All databases were previously mapped to the OMOP CDM.

1. Clinical Data Warehouse of Bordeaux University Hospital (CHUBX), France
2. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
3. Estonian Biobank (EBB), Estonia
4. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
5. Institut Municipal Assistencia Sanitaria Information System (IMASIS), Spain
6. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain

For this study, we have carefully selected six databases from the ten databases available on DARWIN EU® in 2022. The selection process was based on data reliability and relevance to the research question at hand. These selected databases demonstrate substantial record counts for RSV infection. Moreover, they offer a good geographical spread and includ diverse regions of Europe.

These included databases met the requirements for conducting both population-level descriptive epidemiology study and patient-level characterisation, enabling the investigation of various endpoints of RSV-related disease in Europe. Additionally, by including databases from different settings, we can effectively capture both inpatient and outpatient RSV disease estimates and outcomes..

However, it is important to note that that specific study objectives can only be explored in certain databases due to variations in settings and data availability. For example, to ensure the appropriate denominator population, the co-prevalence of RSV infection and other respiratory pathogens (Objective 4) will be examined in population-based databases (CPRD, EBB, SIDIAP, and IQVIA Germany), and in hospital-based databases (CHUBX and IMASIS) using a different denominator population (all patients hospitalised during the study period). Likewise, the incidence of RSV-related hospitalisation (Objective 1) will be confined to population-based databases with strong linkage to secondary care (SIDIAP and EBB) and in hospital-based databases (CHUBX and IMASIS) using a different denominator population (all patients hospitalised during the study period). Notably, CPRD Gold and IQVIA Germany do not include information on hospitalisations. Furthermore, the estimation of the duration of RSV-related hospitalisation (Objective 2) will be restricted to secondary care databases (CHUBX and IMASIS), and population-based databases with good linkage to

secondary care (SIDIAP). Also, the prevalence of RSV-related ICU admission (Objective 3) will be limited to secondary care databases (CHUBX and IMASIS). In terms of RSV-related mortality (Objective 5), it will be reported in all included databases except for the IQVIA DA Germany database, which lacks information regarding the date of death. **Table 4a** outlines specific study objectives that can be investigated within specific databases.

Table 4a. Description of specific study objectives that can be investigated within specific databases.

Databases	Objective 1	Objective 2	Objective 3	Objective 4	Objective 5
	Incidence rate of hospitalisation	Duration of hospitalisation	Prevalence of ICU admissions	Prevalence of RSV co-infection	Mortality rates in individuals diagnosed with RSV bronchiolitis
CHUBX	P*	P	P	P#	P
CPRD GOLD	NF	NF	NF	P	P
EBB	P	NF	NF	P	P
IQVIA DA Germany	NF	NF	NF	P	NF
IMASIS	P*	P	P	P#	P
SIDIAP	P	P	NF	P	P

P = Possible; NF = Not feasible; *Denominator population includes all patients hospitalised during the study period. #Denominator population includes all patients with RSV infection during the study period.

Information on the data source(s) with a justification for their choice in terms of ability to capture the relevant data is described in a **Table 4b**.

To ensure data quality, data partners describe their internal data quality processes during the DARWIN EU onboarding procedure. As part of onboarding, we employ the Achilles tool, which systematically characterizes the data and presents it in a dashboard format for inspection. This tool allows for the comparison of data characteristics, such as age distribution, condition prevalence per year, data density, and measurement value distribution, against data quality expectations. Furthermore, the data quality dashboard (DQD) provides objective checks on plausibility consistently across the data sources.

In terms of relevance of data for a specific study question, we have developed a more general-purpose diagnostic tool, *CohortDiagnostics*, which evaluates phenotype algorithms for OMOP CDM datasets. This tool offers a standard set of analytics for understanding patient capture and data generation, providing additional insights into cohort characteristics, record counts, and index event misclassification. To ensure data timeliness, we monitor dataset release dates and the expected refresh cycle (typically quarterly or half-yearly). Additionally, it is essential to have a clear understanding of the time period covered by each released

database, which can vary across different domains. For this purpose, the *CdmOnboarding* (and *Achilles*) packages include a 'data density' plot, displaying the number of records per OMOP domain on a monthly basis. This plot aids in understanding when data collection commenced, when new data sources were added, and when data was last included.

Table 4b. Description of data sources

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Data lock for the last update
France	CHUBX	Covers hospital care setting for RSV-related duration of hospitalisation, ICU admission, and mortality rates. Laboratory testing for RSV infection available.	Secondary care (in and outpatients)	EHR	2.1 million	05/04/2023
UK	CPRD GOLD	Covers primary care setting for RSV co-infection and mortality rates. Laboratory testing for RSV infection available.	Primary care	EHR	3 million	01/01/2023
Estonia	EBB	Covers both primary and secondary care settings for RSV-related hospitalisation, co-infection, and mortality rates. Laboratory testing for RSV infection available.	Biobank	Claims data	0.2 million	31/03/2022
Germany	IQVIA DA Germany	Covers primary care and secondary care setting for RSV-related co-infection rates.	Primary care and outpatient specialist care	EHR	8.5 million	01/04/2023
Spain	IMASIS	Covers hospital care setting for RSV-related duration of hospitalisation, ICU admission, and mortality rates. Laboratory testing for RSV infection available.	Secondary care (in and outpatient)	EHR	0.6 million	13/05/2023
Spain	SIDIAP	Covers primary care settings for RSV-related hospitalisation, co-infection, and mortality rates.	Primary care	EHR	8.3 million	30/09/2022

Bordeaux University Hospital (CHUBX), France

The clinical data warehouse of the Bordeaux University Hospital comprises electronic health records on more than 2 million patients with data collection starting in 2005. The hospital complex is made up of three main sites and comprises a total of 3,041 beds (2021 figures). The database currently holds information about the person (demographics), visits (inpatient and outpatient), conditions and procedures (billing codes), drugs (outpatient prescriptions and inpatient orders and administrations), measurements (laboratory tests and vital signs) and dates of death (in or out-hospital death).[18]

Clinical Practice Research Datalink GOLD, United Kingdom (University of Oxford)

The Clinical Practice Research Datalink (CPRD) is a governmental, not-for-profit research service, jointly funded by the National Institute for Health and Care Research and the Medicines and Healthcare products Regulatory Agency, a part of the Department of Health, United Kingdom (UK) (https://cprd.com). CPRD GOLD[19] comprises computerized records of all clinical and referral events in primary care in addition to comprehensive demographic information and medication prescription data in a sample of UK patients (predominantly from Scotland (52% of practices) and Wales (28% of practices). The prescription records include information on the type of product, date of prescription, strength, dosage, quantity, and route of administration. Data from contributing practices are collected and processed into research databases. Additionally, CPRD records were also linked to the ONS (Office for National Statistics) database, which records annual mortality data registered by age, sex and selected underlying cause of death.[20] Quality checks on patient and practice level are applied during the initial processing. Data are available for 20 million patients, including 3.2 million currently registered patients. Access to CPRD GOLD data requires approval via the Research Data Governance Process.

Estonian Biobank – University of Tartu (Estonia)

The Estonian Biobank (EBB) is a population-based biobank of the Estonian Genome Center at the University of Tartu (EGCUT). Its cohort size is currently close to 200,000 participants (“gene donors” >= 18 years of age) which closely reflects the age, sex, and geographical distribution of the Estonian adult population. Genomic GWAS analysis have been performed on all gene donors. The database also covers health insurance claims, digital prescriptions, discharge reports, information about incident cancer cases and causes of death from national sources for each donor. [21, 22]

IQVIA Disease Analyser (DA) Germany, Germany

DA Germany is collected from extracts of patient management software used by GPs and specialists practicing in ambulatory care settings[23]. Data coverage includes more than 34M distinct person records out of at total population of 80M (42.5%) in the country and collected from 2,734 providers. Patient visiting more than one provider are not cross identified for data protection reasons and therefore recorded as separate in the system. Dates of service include from 1992 through present. Observation time is defined by the first and last consultation dates. Germany has no mandatory GP system and patient have free choice of specialist. As a result, data are collected from visits to 28.8% General, 13.4% Orthopaedic Surgery, 11.8% Otolaryngology, 11.2% Dermatology, 7.7% Obstetrics/Gynaecology, 6.2% various Neurology and Psychiatry 7.0% Paediatric, 4.6% Urology, 3.7% Cardiology, 3.5% Gastroenterology, 1.5% Pulmonary and 0.7% Rheumatology practices. Drugs are recorded as prescriptions of marketed products. Death it is not reliably captured. No registration or approval is required for drug utilisation studies.

Information System for Research in Primary Care (SIDIAP), Spain (IDIAP Jordi Gol)

SIDIAP is collected from EHR records of patients receiving primary care delivered through Primary Care Teams (PCT), consisting of GPs, nurses and non-clinical staff[24]. The Catalan Health Institute manages 286 out of

370 such PCT with a coverage of 5.6M patients, out of 7.8M people in the Catalan population (74%). The database started to collect data in 2006. The mean follow-up is 10 years. The observation period for a patient can be the start of the database (2006), or when a person is assigned to a Catalan Health Institute primary care centre. Date of exit can be when a person is transferred-out to a primary care centre that does not pertain to the Catalan Health Institute, or date of death, or date of end of follow-up in the database. Additionally, SIDIAP contains information on date of death and high-quality data on all-cause mortality.[25] Drug information is available from prescriptions and from dispensing records in pharmacies. Drugs not prescribed in the GP setting might be underreported; and disease diagnoses made at specialist care settings are not included. Studies using SIDIAP data require previous approval by both a Scientific and an Ethics Committee.

Institut Municipal Assistencia Sanitaria Information System (IMASIS), Spain

The Institut Municipal Assistència Sanitària Information System (IMASIS) is the Electronic Health Record (EHR) system of Parc de Salut Mar Barcelona (PSMar) which is a complete healthcare services organisation. Currently, this information system includes and shares the clinical information of two general hospitals (Hospital del Mar and Hospital de l'Esperança), one mental health care centre (Centre Dr. Emili Mira) and one social-healthcare centre (Centre Fòrum) including emergency room settings, which are offering specific and different services in the Barcelona city area (Spain). At present, IMASIS includes clinical information more than 1 million patients with at least one diagnosis and who have used the services of this healthcare system since 1990 and from different settings such as admissions, outpatients, emergency room and major ambulatory surgery. The diagnoses are coded using The International Classification of Diseases ICD-9-CM and ICD-10-CM. The average follow-up period per patient in years is 6.37 (SD±6.82). IMASIS-2 is the anonymized relational database of IMASIS which is used for mapping to OMOP including additional sources of information such as the date of death and Tumours Registry. [26]

8.3 Study Period

The study period will be from 1st of January 2013 until the earliest of 31st December 2022 or the respective data lock for the last database update (see **Table 4b** for more details) to capture changes in healthcare use / testing for respiratory infections due to the COVID-19 pandemic.

8.4 Follow-up

For population-level descriptive epidemiology, follow-up will start when participants fulfil inclusion criteria (i.e., present in the database between 1st of January 2013 and 31st of December 2022 and with at least 1 year of data visibility except in children under one year of age) until the earliest of loss to follow-up, end of data availability, death, or end of study period (31st December 2022).

For patient-level characterization, follow-up will start from the date of RSV diagnosis until the earliest of loss to follow-up, end of data availability, death, or end of study period (31st December 2022).

The operational definition of start of follow-up is described in **Table 5**.

Table 5: Operational Definition of Time 0 (index date) and other primary time anchors

Study population name(s)	Time Anchor Description (e.g., time 0)	Number of entries	Type of entry	Washout window	Care Setting[1]	Code Type[2]	Diagnosis position	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
All individuals from the respective databases with at least 1 year of valid database history.	Study entry date	Multiple	Incident	[30]	IP and OP	n/a	n/a	RSV-related hospitalisation	n/a	n/a
All patients with diagnosis of RSV infection	Date of RSV diagnosis	Multiple	Incident	[30]	IP and OP	n/a	n/a	RSV diagnosis	n/a	n/a

[1] IP = inpatient, OP = outpatient, n/a = not applicable.

8.5 Study population with inclusion and exclusion criteria

For population-level descriptive epidemiology (Objectives 1 and 4), the study population will include all individuals in the respective databases between 2013 and 2022 (or the most recent available date if earlier), with a minimum of 1 year of data visibility before study entry except for children < 1 year.

For patient-level characterization (Objectives 2, 3, and 5), the study population will include all patients diagnosed with RSV infection between 2013 and 2022 (or the most recent available date if earlier), with a minimum of 1 year of data visibility before their diagnosis. This 1 year of database history does not hold for children < 1 year.

Table 6. Operational Definitions of Inclusion Criteria

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics /validation	Source for algorithm
Prior database history	Study participants will be required to have a year of prior history observed before contributing observation time. This criterion does not hold for children < 1 year.	After	1 year	IP, OP, OT	N/A	N/A	All individuals in the respective databases	N/A	N/A

[1] IP = inpatient, OP = outpatient, OT = other, n/a = not applicable

8.6 Variables

8.6.1 Exposure n/a

8.6.2 Outcome/s

This study will examine the following four primary outcomes of interest.

- RSV-related hospitalisation

RSV-related hospitalisation as an outcome will be identified through SNOMED and/or LOINC codes for RSV infection occurring within 7 days before hospital admission, during the hospitalisation period, or within 7 days following discharge. Instances meeting these criteria will be considered cases of RSV-related hospitalisation.

- Duration of RSV-related hospitalisation

The date difference (in days) between the date of hospital admission due to RSV infection, as previously defined, and the date of hospital discharge.

- RSV-related ICU admission

Of those patients hospitalised for RSV related hospitalisation, we will provide the proportion of individuals who were admitted to ICU.

- RSV co-infection with other respiratory pathogens

RSV co-infection with other respiratory pathogens, including Influenza Viruses, SARS-CoV-2, Parainfluenza Viruses, Adenoviruses, Metapneumovirus, Bocavirus, Rhinoviruses, Coxsackieviruses, Parechoviruses, and Echoviruses, will be identified through the SNOMED and/or LOINC codes for these other respiratory pathogens occurring within 7 days before, on, or 7 days after the date of RSV diagnosis.

- RSV-related Mortality

Overall survival in patients with RSV will also be calculated within 30 days of diagnosis, based on the registered date of death.

Table 7. Operational Definitions of Outcomes

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings[1]	Code Type	Diagnosis Position	Applied to study populations	Measurement characteristics/validation	Source of algorithm
RSV infection	Based on condition or lab tests within OMOP-CDM	Yes	Binary	N/A	IP and OP care	SNOMED and/or LOINC	N/A	All eligible individuals	N/A	N/A
Hospitalisation rate	Based on visit type within OMOP-CDM	Yes	Time	N/A	IP and OP care	Visit	N/A	All eligible individuals	N/A	N/A
ICU admission	Based on visit type within OMOP-CDM	Yes	%	N/A	IP and OP care	Visit	N/A	All patients with RSV diagnosis	N/A	N/A
Mortality rate	Based on date of death	Yes	Time	N/A	IP and OP care	Date of death	N/A	All patients with RSV diagnosis	N/A	N/A

[1] IP = inpatient, OP = outpatient, n/a = not applicable.

8.6.3 Other covariates, including confounders, effect modifiers and other variables (where relevant)

Age at study entry will be characterized and categorized as follows:

- Elderly: 60 years and above
- Adults: 18 to 59 years
- Children: 6 to 17 years
- Children under 1 to 5 years
- Children under 1 year

The sex (male/ female) of study participants will also be identified.

8.6.4 Study size

No sample size was calculated for this study as our primary objective is to describe the age-specific incidence rates of RSV-related disease outcomes in Europe using secondary data. Based on a preliminary feasibility assessment, the estimated number of individuals with RSV infection in the included databases varied, ranging from 1,000 (CPRD GOLD) to 16,400 (SIDIAP). Additionally, specific counts for other databases are as follows: 6,100 (EBB), 6,700 (CHUBX), 9,100 (IQVIA DA Germany), and 9,800 (IMASIS).

8.7 Analysis

Table 8. Description of Study Types and Type of analysis

STUDY TYPE	STUDY CLASSIFICATION	TYPE OF ANALYSIS
Population-level descriptive epidemiology	Off-the-shelf (C1)	- Incidence of RSV-related hospitalisation - Prevalence of RSV co-infection with other respiratory pathogens
Patient Level characterisation	Off-the-shelf (C1)	- Duration of RSV-related hospitalisation - Prevalence of RSV-related ICU admission - Mortality rates in individuals with RSV

8.7.1 Federated Network Analyses

Analyses will be conducted separately for each database. Before study initiation, test runs of the analytics are performed on a subset of the data sources or on a simulated set of patients and quality control checks are performed. Once all the tests are passed, the final package is released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally execute the analytics against the OMOP-CDM in R Studio and review and approve the by default aggregated results before returning them to the Coordination Centre. Sometimes multiple execution iterations are performed, and additional fine tuning of the code base is needed. A service desk will be available during the study execution for support.

The study results of all data sources are checked after which they are made available to the team and the Study Dissemination Phase can start. All results are locked and timestamped for reproducibility and transparency.

8.7.2 Patient privacy protection

Cell suppression will be applied as required by databases to protect people's privacy. Cell counts < 5 will be masked.

8.7.3 Statistical model specification and assumptions of the analytical approach considered

R-packages

We will use the R package "*IncidencePrevalence*"[27] for the population-level estimation of incidence of RSV-related hospitalisation and prevalence of RSV co-infection with other respiratory pathogens. "*PatientProfile*" package will be used for the patient-level characterization of duration of RSV-related hospitalisation, prevalence of RSV-related ICU admission.

30-day survival will be calculated as time from the date of diagnosis of RSV infection to death (due any cause). Proportion of patients who died will be reported and survival curves will be estimated using the Kaplan-Meier (KM) method. Individuals who are lost to follow-up will be censored at the time of loss of follow-up.

8.7.4 Methods to derive parameters of interest

Calendar time

Calendar time will be based on the calendar year of the index date.

Age

Age at study entry will be calculated using January 1st of the year of birth as proxy for the actual birthday, and categorized as follows:

- Elderly: 60 years and above
- Adults: 18 to 59 years
- Children: 6 to 17 years
- Children under 1 to 5 years
- Children under 1 year

Sex

Results will be presented stratified by sex.

8.7.5 Methods to obtain point estimates with confidence intervals of measures of occurrence

8.7.5.1 Population level disease epidemiology study

Prevalence of RSV co-infections with other respiratory pathogens and incidence of RSV-related hospitalisations will be calculated.

Prevalence calculations

The prevalence of RSV co-infections will be calculated as the number of patients with RSV co-infection divided by the total number of individuals available during that year. Binomial 95% confidence intervals will be calculated. Results will be stratified by calendar year, age categories, and database.

Incidence calculations

Annual incidence rates of RSV-related hospitalisation will be calculated as the of number of hospitalisations due to RSV infection per 100,000 person-years of the population at risk during the period for each calendar year. Those study participants who enter the denominator population will then contribute time at risk up to their first RSV-related hospitalisation during the study period, with a wash-out period of 30 days after which they become eligible to contribute time for another or subsequent

event of hospitalisation. If they do not have RSV-related hospitalisation, they will contribute time at risk up to the end of follow-up. Incidence rates will be reported together with 95% Poisson confidence intervals.

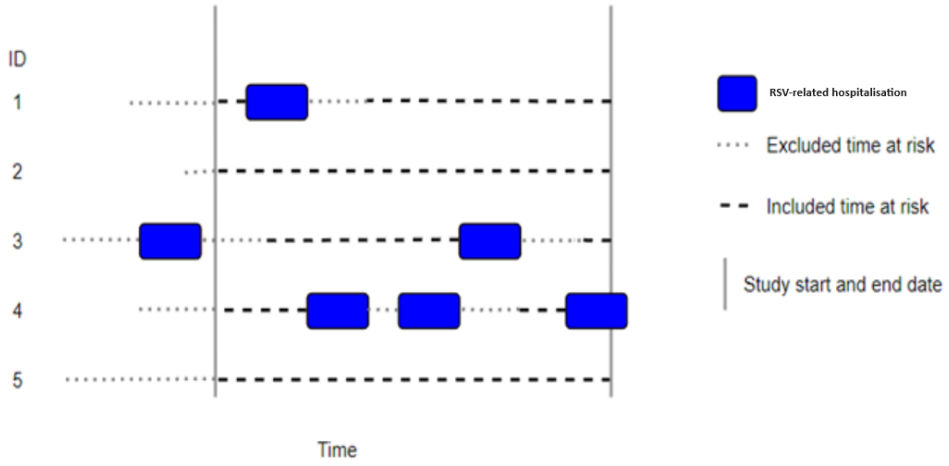

Figure 1: example of incidence rate estimation

8.7.5.2 Patient level characterisation

The prevalence of RSV-related ICU admission will be calculated as the number of patients with RSV-related ICU admission divided by the RSV patient population being hospitalised during that year. Binomial 95% confidence intervals will be calculated. Results will be stratified by calendar year, age categories, and database.

Mortality rate will be calculated using the Kaplan-Meier (KM) method and survival will be calculated using data on time at risk of RSV-related death, defined as within 30 days of RSV infection. Results will be reported as plots of the estimated survival curves as well as the estimated probability of survival at 30 days. Results will be stratified by calendar year, age categories, and database.

Duration of RSV-related hospitalisation will be calculated as the date difference between the date of hospital discharge and the date of RSV-related hospitalisation. The median, interquartile range (p25 and p75), maximum, and minimum days of hospitalization will be calculated. Results will be stratified by calendar year, age categories, and database.

8.7.5.3 Minimum cell count of 5

For all analyses, results will be reported with a minimum cell count of 5, and any counts smaller than 5 will be obscured to ensure privacy and confidentiality.

8.8 Sensitivity analyses

The diagnosis of RSV infection primarily relies on clinical evaluation. Laboratory testing is conducted selectively. Consequently, SNOMED codes for RSV infection may not necessarily indicate laboratory-confirmed cases of RSV infection.[4] The analyses outlined in objectives 1, 2, 3, 4, and 5 will be repeated, whenever possible, restricted exclusively to laboratory-confirmed cases of RSV infection. These cases will be identified using LOINC codes.

8.9 Missing data

The population included within these real-world databases is dynamic, meaning that patients may enter and leave the database at any moment in time. To address potential differences in follow-up time, we will provide the median follow-up time by database. Differences in follow-up time will be accounted for in the incidence rate and mortality rate analyses, as the denominator will consist of person-years.

In light of the observational nature of this study which will be conducted within a dynamic population, it is crucial to acknowledge the inevitability of cohort attrition during the follow-up period. This may result in a loss of valuable information concerning RSV estimates and their associated outcomes due to potential missing data. It is essential to note, however, that we operate under the assumption that the probability of data being missing is consistent across all cases within the respective databases.

9 DATA MANAGEMENT

9.1 Data management

All databases are mapped to the OMOP common data model. This enables the use of standardised analytics and tools across the network since the structure of the data and the terminology system is harmonised. The OMOP CDM is developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org

The analytic code for this study will be written in R. Each data partner will execute the study code against their database containing patient-level data and will then return the results set which will only contain aggregated data. The results from each of the contributing data sites will then be combined in tables and figures for the study report.

9.2 Data storage and protection

For this study, participants from various EU member states will process personal data from patients which is collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All databases used in this study are already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to. In agreement with these regulations, rather than combining person

level data and performing only a central analysis, local analyses will be run, which generate non-identifiable aggregate summary results.

The output files are stored in the DARWIN Digital Research Environment (DRE). These output files do not contain any data that allow identification of subjects included in the study. The DRE implements further security measures in order to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/20161 in the various member states.

10. QUALITY CONTROL

General database quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). In particular, it is expected that data partners will have run the OHDSI Data Quality Dashboard tool (https://github.com/OHDSI/DataQualityDashboard). This tool provides numerous checks relating to the conformance, completeness and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories has one or more subcategories and are evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

When defining RSV infection, a systematic search of possible codes for inclusion will be identified using *CodelistGenerator* R package (https://github.com/darwin-eu/CodelistGenerator). This software allows the user to define a search strategy and using this will then query the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. In addition, the *CohortDiagnostics* R package (https://github.com/OHDSI/CohortDiagnostics) will be run to assess the use of different codes across the databases contributing to the study and identify any codes potentially omitted in error. This will allow for a consideration of the validity of the study cohort of patients with RSV in each of the databases and inform decisions around whether multiple definitions are required.

The study code will be based on three R packages namely the *IncidencePrevalence*, the *CohortSurvival*, and the *PatientProfile* Packages. These packages will include numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R package will be made publicly available via GitHub.

11. LIMITATIONS OF THE RESEARCH METHODS

The study will be conducted using routinely collected healthcare data, and it is crucial to acknowledge several inherent limitations and considerations. These limitations may impact the interpretation and generalizability of the study findings.

Firstly, there is a potential underreporting of mortality data, which could affect the accuracy of estimates related to mortality outcomes associated with RSV. Mortality data, especially in the context of respiratory infections, may not be comprehensively captured in healthcare databases, leading to potential underestimation of the true impact.

Secondly, the diagnostic and coding practices for RSV-related endpoints may not have been universally validated in healthcare databases. Variability in diagnostic coding standards and practices across different healthcare systems could introduce uncertainty and affect the reliability of RSV-related data.

To estimate the incidence of RSV, there is a risk of misclassification, where prevalent cases may be erroneously categorized as incident cases due to incomplete inclusion of the patient's entire medical history. This misclassification may impact the accuracy of incidence rates and skew the understanding of the temporal trends in RSV infection.

Moreover, the ongoing COVID-19 pandemic (from 2020-present) introduces a unique challenge. Changes in healthcare utilization patterns, routine clinical practices, and information recording during the pandemic might potentially distort estimates for the years 2020 and 2021. Disruptions in healthcare services and altered patient behaviours could influence the representation of RSV-related data during this period.

The study relies on specific clinical databases in different countries, raising concerns about the generalizability of findings to a broader population. The study population may not fully represent all individuals with RSV infection due to potential biases introduced by the selection of specific databases.

Additionally, certain databases, such as CPRD GOLD and IQVIA Germany, lack information on hospitalization, limiting the estimation of RSV-related hospitalization outcomes. The absence of comprehensive documentation of laboratory-confirmed RSV cases in participating databases, particularly in SIDIAP and IQVIA DA Germany, poses another challenge. While the primary analyses encompass both RSV disease codes and/or laboratory-confirmed cases, additional sensitivity analyses focusing solely on laboratory-confirmed cases will be conducted to enhance statistical power and ensure the validity of the RSV infection cases included in the study.

In cases where information on the date of discharge and date of admission is missing within the hospital data, the duration of hospitalization cannot be accurately calculated, introducing potential uncertainties in assessing this critical aspect of RSV-related outcomes. These limitations underscore the need for cautious interpretation of study results and the importance of considering the context in which the data were collected..

12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions will not be collected or analyzed as part of this evaluation. The nature of this non-interventional evaluation, through the use of secondary data, and not investigating any medicinal product as a study objective, does not fulfill the criteria for reporting adverse events, according to module VI, VI.C.1.2.1.2 of the Good Pharmacovigilance Practices.

13. GOVERNANCE BOARD ASPECTS

All data sources require approval from their respective IRB boards, with the exception of IQVIA DA Germany which will not require any further specific approvals to undertake this study.

14. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

14.1 Study Report

A report including an executive summary, and the specified tables and/or figures will be submitted to EMA by the DARWIN EU® CC upon completion of the study.

An interactive dashboard incorporating all the results (tables and figures) will be provided alongside the pdf report. The full set of underlying aggregated data used in the dashboard will also be made available if requested.

15. OTHER RESULTS

N/A

16. REFERENCES

1. IMI-Promise, *Preparing for RSV Immunisation and Surveillance in Europe*. 2023.
2. EMA, *Vaccine Monitoring Platform*. 2023, European Medicines Agency: Amsterdam.
3. Li, Y., et al., *Unveiling the Risk Period for Death After Respiratory Syncytial Virus Illness in Young Children Using a Self-Controlled Case Series Design.* The Journal of Infectious Diseases, 2020. **222**(Supplement_7): p. S634-S639.
4. Jain, H., J.W. Schweitzer, and N.A. Justice, *Respiratory Syncytial Virus Infection*, in *StatPearls*. 2023, StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC.: Treasure Island (FL) ineligible companies. Disclosure: John Schweitzer declares no relevant financial relationships with ineligible companies. Disclosure: Nathaniel Justice declares no relevant financial relationships with ineligible companies.
5. Mazur, N.I., et al., *The respiratory syncytial virus vaccine landscape: lessons from the graveyard and promising candidates.* Lancet Infect Dis, 2018. **18**(10): p. e295-e311.
6. Li, Y., et al., *Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis.* Lancet, 2022. **399**(10340): p. 2047-2064.
7. Savic, M., et al., *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, 2023. **17**(1): p. e13031.
8. Battles, M.B. and J.S. McLellan, *Respiratory syncytial virus entry and how to block it.* Nat Rev Microbiol, 2019. **17**(4): p. 233-245.
9. Ye, S. and T. Wang, *Laboratory epidemiology of respiratory viruses in a large children's hospital: A STROBE-compliant article.* Medicine (Baltimore), 2018. **97**(30): p. e11385.
10. Popow-Kraupp, T. and J.H. Aberle, *Diagnosis of respiratory syncytial virus infection.* Open Microbiol J, 2011. **5**: p. 128-34.
11. Pickles, R.J. and J.P. DeVincenzo, *Respiratory syncytial virus (RSV) and its propensity for causing bronchiolitis.* J Pathol, 2015. **235**(2): p. 266-76.
12. Khuri-Bulos, N., et al., *Severe outcomes associated with respiratory viruses in newborns and infants: a prospective viral surveillance study in Jordan.* BMJ Open, 2018. **8**(5): p. e021898.
13. Gatt, D., et al., *Prevention and Treatment Strategies for Respiratory Syncytial Virus (RSV).* Pathogens, 2023. **12**(2).
14. EMA, *First RSV vaccine to protect infants up to 6 months of age and older adults*. 2023, European Medicines Agency.
15. EMA, *First vaccine to protect older adults from respiratory syncytial virus (RSV) infection*. 2023, European Medicines Agency.
16. *Two vaccines (Arexvy and Abrysvo) for prevention of RSV disease.* Med Lett Drugs Ther, 2023. **65**(1686): p. 155-156.
17. Teirlinck, A.C., et al., *Recommendations for respiratory syncytial virus surveillance at national level.* European Respiratory Journal, 2021: p. 2003766.
18. Brat, G.A., et al., *International electronic health record-derived COVID-19 clinical course profiles: the 4CE consortium.* NPJ Digit Med, 2020. **3**: p. 109.
19. Herrett, E., et al., *Data Resource Profile: Clinical Practice Research Datalink (CPRD).* Int J Epidemiol, 2015. **44**(3): p. 827-36.
20. Gallagher, A.M., et al., *The accuracy of date of death recording in the Clinical Practice Research Datalink GOLD database in England compared with the Office for National Statistics death registrations.* Pharmacoepidemiology and Drug Safety, 2019. **28**(5): p. 563-569.

21. Krebs, K., et al., *Genome-wide Study Identifies Association between HLA-B(*)55:01 and Self-Reported Penicillin Allergy.* Am J Hum Genet, 2020. **107**(4): p. 612-621.
22. Leitsalu, L., et al., *Cohort Profile: Estonian Biobank of the Estonian Genome Center, University of Tartu.* Int J Epidemiol, 2015. **44**(4): p. 1137-47.
23. Rathmann, W., et al., *Basic characteristics and representativeness of the German Disease Analyzer database.* Int J Clin Pharmacol Ther, 2018. **56**(10): p. 459-466.
24. Garcia-Gil Mdel, M., et al., *Construction and validation of a scoring system for the selection of high-quality data in a Spanish population primary care database (SIDIAP).* Informatics in primary care, 2011. **19**(3): p. 135-45.
25. Recalde, M., et al., *Data Resource Profile: The Information System for Research in Primary Care (SIDIAP).* Int J Epidemiol, 2022. **51**(6): p. e324-e336.
26. Reyes, C., et al., *Characteristics and outcomes of patients with COVID-19 with and without prevalent hypertension: a multinational cohort study.* BMJ Open, 2021. **11**(12): p. e057632.
27. Burn, E., *IncidencePrevalence: Estimate Incidence and Prevalence using the OMOP Common Data Model. Version: 0.3.0. Published: 2023-05-07* https://cran.r-project.org/web/packages/IncidencePrevalence/index.html.

17. ANNEXES

Appendix I: List of Stand-Alone documents (e.g., lists with concept codes (conditions & drugs etc.)

Appendix II: ENCePP checklist for study protocols

APPENDIX I – LIST WITH PRELIMINARY CONCEPT DEFINITIONS

RSV infection (SNOMED)

Concept id	Concept name
437222	Respiratory syncytial virus infection
254058	Acute bronchiolitis due to respiratory syncytial virus
4237921	Respiratory syncytial virus bronchiolitis
436145	Pneumonia due to respiratory syncytial virus
4110484	Acute respiratory syncytial virus bronchitis
46269721	Bronchopneumonia due to respiratory syncytial virus
4237184	Healthcare associated respiratory syncytial virus disease
46270075	Positive sputum culture for hRSV (Human respiratory syncytial virus)
4195736	Respiratory syncytial virus bronchitis
4218289	Respiratory syncytial virus laryngotracheobronchitis
4150370	Respiratory syncytial virus pharyngitis

RSV infection (LOINC)

concept_id	concept_name
3017198	Bovine respiratory syncytial virus Ag [Presence] in Lung
3009489	Bovine respiratory syncytial virus Ag [Presence] in Lung by Immune stain
3014709	Bovine respiratory syncytial virus Ag [Presence] in Lung by Immunoassay
3009146	Bovine respiratory syncytial virus Ag [Presence] in Lung by Immunofluorescence
3013744	Bovine respiratory syncytial virus Ag [Presence] in Specimen
36660160	Bovine respiratory syncytial virus Ag [Presence] in Tissue by Immune stain
36659983	Bovine respiratory syncytial virus [Presence] in Specimen by Organism specific culture
21493384	Respiratory syncytial virus A 5' UTR RNA [Presence] in Nasopharynx by NAA with probe detection
46236090	Respiratory syncytial virus Ag [Presence] in Bronchoalveolar lavage by Immunofluorescence
36304759	Respiratory syncytial virus Ag [Presence] in Lower respiratory specimen by Immunofluorescence
40771500	Respiratory syncytial virus Ag [Presence] in Nasopharynx by Immunoassay
46236091	Respiratory syncytial virus Ag [Presence] in Nasopharynx by Immunofluorescence
43534059	Respiratory syncytial virus Ag [Presence] in Nasopharynx by Rapid immunoassay
3046856	Respiratory syncytial virus Ag [Presence] in Nose
3027791	Respiratory syncytial virus Ag [Presence] in Nose by Immunofluorescence
3001684	Respiratory syncytial virus Ag [Presence] in Specimen
3020426	Respiratory syncytial virus Ag [Presence] in Specimen by Immunoassay
3005444	Respiratory syncytial virus Ag [Presence] in Specimen by Immunofluorescence
3021508	Respiratory syncytial virus Ag [Presence] in Throat

concept_id	concept_name
3023609	Respiratory syncytial virus Ag [Presence] in Throat by Immunoassay
3019907	Respiratory syncytial virus Ag [Presence] in Throat by Immunofluorescence
3032425	Respiratory syncytial virus Ag [Presence] in Tissue by Immune stain
36303588	Respiratory syncytial virus A RNA [Presence] in Lower respiratory specimen by NAA with probe detection
46234982	Respiratory syncytial virus A RNA [Presence] in Nasopharynx by NAA with probe detection
3005156	Respiratory syncytial virus A RNA [Presence] in Specimen by NAA with probe detection
37019510	Respiratory syncytial virus A RNA [Presence] in Upper respiratory specimen by NAA with probe detection
21493385	Respiratory syncytial virus B F gene [Presence] in Nasopharynx by NAA with probe detection
36304133	Respiratory syncytial virus B RNA [Presence] in Lower respiratory specimen by NAA with probe detection
46234983	Respiratory syncytial virus B RNA [Presence] in Nasopharynx by NAA with probe detection
3000108	Respiratory syncytial virus B RNA [Presence] in Specimen by NAA with probe detection
37019752	Respiratory syncytial virus B RNA [Presence] in Upper respiratory specimen by NAA with probe detection
3000122	Respiratory syncytial virus identified in Specimen by Organism specific culture
37019563	Respiratory syncytial virus [Presence] in Lower respiratory specimen by Organism specific culture
3001226	Respiratory syncytial virus [Presence] in Nose by Organism specific culture
40758230	Respiratory syncytial virus [Presence] in Specimen by Organism specific culture
37020439	Respiratory syncytial virus [Presence] in Upper respiratory specimen by Organism specific culture
3043924	Respiratory syncytial virus RNA [Identifier] in Specimen by NAA with probe detection
46235767	Respiratory syncytial virus RNA [Presence] in Bronchoalveolar lavage by NAA with probe detection
40763326	Respiratory syncytial virus RNA [Presence] in Isolate by NAA with probe detection
37019493	Respiratory syncytial virus RNA [Presence] in Lower respiratory specimen by NAA with non-probe detection
1176171	Respiratory syncytial virus RNA [Presence] in Lower respiratory specimen by NAA with probe detection
21493342	Respiratory syncytial virus RNA [Presence] in Nasopharynx by NAA with non-probe detection
46235794	Respiratory syncytial virus RNA [Presence] in Nasopharynx by NAA with probe detection
37021152	Respiratory syncytial virus RNA [Presence] in Respiratory specimen by NAA with probe detection
3044254	Respiratory syncytial virus RNA [Presence] in Specimen by NAA with probe detection
36203323	Respiratory syncytial virus RNA [Presence] in Upper respiratory specimen by NAA with probe detection

Influenza Viruses (LOINC)

concept_id	concept_name
37020635	Influenza virus A RNA [Presence] in Respiratory specimen by NAA with probe detection
37021252	Influenza virus B RNA [Presence] in Respiratory specimen by NAA with probe detection
21492988	Influenza virus A Ag [Presence] in Upper respiratory specimen by Rapid immunoassay
21492989	Influenza virus B Ag [Presence] in Upper respiratory specimen by Rapid immunoassay
3032213	Influenza virus A.adamantane resistance [Presence]
40757371	Influenza virus Ag [Presence] in Specimen
3000251	Influenza virus B Ag [Presence] in Throat
3002523	Influenza virus A Ag [Presence] in Specimen
3002707	Influenza virus C Ag [Presence] in Specimen
3003551	Influenza virus A Ag [Presence] in Throat
3003740	Influenza virus B Ag [Presence] in Specimen
3017256	Equine influenza virus Ag [Presence] in Nose
3043891	Influenza virus A Ag [Presence] in Nose
3044141	Influenza virus A Ag [Presence] in Nasopharynx
3045831	Influenza virus B Ag [Presence] in Nasopharynx
3045856	Influenza virus B Ag [Presence] in Nose
40757372	Influenza virus B Ag [Presence] in Isolate
3022193	Influenza virus A+B Ag [Presence] in Throat
3024891	Influenza virus A+B Ag [Presence] in Specimen
3029458	Influenza virus A+B Ag [Presence] in Nasopharynx
3033032	Influenza virus A.adamantane resistance [Presence] by Phenotype method
3043038	Influenza virus B Ag [Presence] in Bronchial specimen
3044408	Influenza virus A+B Ag [Presence] in Nose
3047276	Influenza virus A Ag [Presence] in Bronchial specimen
3001664	Influenza virus C Ag [Presence] in Specimen by Immunofluorescence
3003682	Swine influenza virus Ag [Presence] in Tissue by Immunofluorescence
3010845	Influenza virus B Ag [Presence] in Throat by Immunofluorescence
3011688	Influenza virus B Ag [Presence] in Specimen by Immunoassay
3013704	Influenza virus B Ag [Presence] in Specimen by Immunofluorescence
3020370	Equine influenza virus Ag [Presence] in Nose by Immunoassay
3023210	Influenza virus A+B+C Ag [Presence] in Throat
3023444	Influenza virus A+B+C Ag [Presence] in Specimen
3024400	Influenza virus A Ag [Presence] in Specimen by Immunofluorescence
3024940	Influenza virus B Ag [Presence] in Throat by Immunoassay
3026784	Influenza virus A Ag [Presence] in Throat by Immunoassay
3028162	Influenza virus A Ag [Presence] in Throat by Immunofluorescence
3028459	Influenza virus A Ag [Presence] in Specimen by Immunoassay

concept_id	concept_name
3030438	Influenza virus B Ag [Presence] in Isolate by Immunofluorescence
3032966	Influenza virus A Ag [Presence] in Isolate by Immunofluorescence
3042913	Influenza virus B Ag [Presence] in Trachea by Immunofluorescence
3043362	Influenza virus B Ag [Presence] in Nasopharynx by Immunoassay
3044123	Influenza virus A Ag [Presence] in Nose by Immunofluorescence
3045609	Influenza virus A+B Ag [Presence] in Bronchial specimen
3045936	Influenza virus A Ag [Presence] in Nasopharynx by Immunofluorescence
3046105	Influenza virus A Ag [Presence] in Trachea by Immunofluorescence
3046253	Influenza virus B Ag [Presence] in Nose by Immunoassay
3046445	Influenza virus B Ag [Presence] in Nose by Immunofluorescence
3046524	Influenza virus A Ag [Presence] in Nasopharynx by Immunoassay
3046769	Influenza virus B Ag [Presence] in Nasopharynx by Immunofluorescence
3047225	Influenza virus A Ag [Presence] in Nose by Immunoassay
36204255	Influenza virus A Ag [Presence] in Tissue by Immunofluorescence
36305960	Influenza virus B Ag [Presence] in Tissue by Immunofluorescence
3002646	Swine influenza virus Ag [Presence] in Tissue by Immune stain
3010064	Influenza virus A+B Ag [Presence] in Specimen by Immunofluorescence
3011852	Influenza virus A+B Ag [Presence] in Throat by Immunoassay
3012646	Influenza virus A+B Ag [Presence] in Specimen by Immunoassay
3026753	Influenza virus A+B Ag [Presence] in Throat by Immunofluorescence
3029009	Influenza virus A H3 Ag [Presence] in Isolate by Immunofluorescence
3029215	Influenza virus A H1 Ag [Presence] in Isolate by Immunofluorescence
3029677	Influenza virus A nucleoprotein RNA [Presence] in Isolate by Sequencing
3042756	Influenza virus B Ag [Presence] in Bronchial specimen by Immunofluorescence
3042763	Influenza virus A Ag [Presence] in Bronchial specimen by Immunofluorescence
3048627	Influenza virus B [Presence] in Specimen by Organism specific culture
3048858	Influenza virus A [Presence] in Specimen by Organism specific culture
36660167	Equine influenza virus [Presence] in Specimen by Organism specific culture
46235793	Influenza virus A Ag [Presence] in Bronchoalveolar lavage by Immunofluorescence
46236085	Influenza virus B Ag [Presence] in Bronchoalveolar lavage by Immunofluorescence
3002601	Influenza virus A Ag [Presence] in Specimen by Immune diffusion (ID)
3002988	Porcine influenza virus A Ag [Presence] in Tissue by Immune stain
3010601	Influenza virus A+B+C Ag [Presence] in Throat by Immunoassay
3012817	Influenza virus A+B+C Ag [Presence] in Specimen by Immunoassay
3026290	Influenza virus A+B+C Ag [Presence] in Throat by Immunofluorescence
3027335	Influenza virus A+B+C Ag [Presence] in Specimen by Immunofluorescence
3029994	Influenza virus A polymerase A RNA [Presence] in Isolate by Sequencing
3030205	Influenza virus A polymerase B2 RNA [Presence] in Isolate by Sequencing
3030291	Influenza virus A polymerase B1 cDNA [Presence] in Isolate by Sequencing
3032391	Influenza virus A.adamantane resistant RNA [Presence] by NAA with probe detection

concept_id	concept_name
3033064	Influenza virus A matrix protein RNA [Presence] in Isolate by Sequencing
36303582	Influenza virus B Ag [Presence] in Lower respiratory specimen by Immunofluorescence
36304868	Influenza virus A Ag [Presence] in Lower respiratory specimen by Immunofluorescence
43054998	Influenza virus A+B Ag [Presence] in Nose by Rapid immunoassay
3030134	Influenza virus B RNA [Presence] in Isolate by NAA with probe detection
3030235	Influenza virus A non-structural protein RNA [Presence] in Isolate by Sequencing
3032475	Influenza virus A RNA [Presence] in Isolate by NAA with probe detection
3038288	Influenza virus B RNA [Presence] in Specimen by NAA with probe detection
3044938	Influenza virus A RNA [Presence] in Specimen by NAA with probe detection
3047713	Influenza virus A cDNA [Presence] in Specimen by NAA with probe detection
36203621	Influenza virus B Victoria lineage Ag [Presence] in Isolate by Hemagglutination inhibition
36203943	Influenza virus B Yamagata lineage Ag [Presence] in Isolate by Hemagglutination inhibition
36204259	Influenza virus A RNA [Presence] in Tissue by NAA with probe detection
36204262	Influenza virus B RNA [Presence] in Tissue by NAA with probe detection
40763322	Influenza virus C RNA [Presence] in Isolate by NAA with probe detection
40765592	Influenza virus C RNA [Presence] in Specimen by NAA with probe detection
46235757	Influenza virus A RNA [Presence] in Nasopharynx by NAA with probe detection
46235759	Influenza virus B RNA [Presence] in Nasopharynx by NAA with probe detection
3028957	Influenza virus A H7 RNA [Presence] in Isolate by NAA with probe detection
3030120	Influenza virus A H1 RNA [Presence] in Specimen by NAA with probe detection
3031905	Influenza virus A H1 RNA [Presence] in Isolate by NAA with probe detection
3031919	Influenza virus A H3 RNA [Presence] in Isolate by NAA with probe detection
3032221	Influenza virus A H5 RNA [Presence] in Isolate by NAA with probe detection
3032731	Influenza virus A H3 RNA [Presence] in Specimen by NAA with probe detection
3032788	Influenza virus A H9 RNA [Presence] in Specimen by NAA with probe detection
3036107	Influenza virus A H5 RNA [Presence] in Specimen by NAA with probe detection
3036420	Influenza virus A H6 RNA [Presence] in Specimen by NAA with probe detection
3036725	Influenza virus A H7 RNA [Presence] in Specimen by NAA with probe detection
1988089	Influenza virus A N1 RNA [Presence] in Specimen by NAA with probe detection
21493332	Influenza virus A RNA [Presence] in Nasopharynx by NAA with non-probe detection
21493336	Influenza virus B RNA [Presence] in Nasopharynx by NAA with non-probe detection
21493375	Influenza virus A M gene [Presence] in Nasopharynx by NAA with probe detection
21493378	Influenza virus B NS gene [Presence] in Nasopharynx by NAA with probe detection
40761091	Influenza virus A H2 RNA [Presence] in Specimen by NAA with probe detection
40763584	Influenza virus A H9 RNA [Presence] in Isolate by NAA with probe detection
40765199	Influenza virus A+B RNA [Presence] in Specimen by NAA with probe detection
40771512	Influenza virus A H5a RNA [Presence] in Specimen by NAA with probe detection
40771513	Influenza virus A H5b RNA [Presence] in Specimen by NAA with probe detection
46235756	Influenza virus A RNA [Presence] in Bronchoalveolar lavage by NAA with probe detection
46235758	Influenza virus B RNA [Presence] in Bronchoalveolar lavage by NAA with probe detection

concept_id	concept_name
46236736	Influenza virus A H1 RNA [Presence] in Nasopharynx by NAA with probe detection
46236737	Influenza virus A H3 RNA [Presence] in Nasopharynx by NAA with probe detection
3047040	Influenza virus A H5 Asian RNA [Presence] in Specimen by NAA with probe detection
36203321	Influenza virus A RNA [Presence] in Upper respiratory specimen by NAA with probe detection
36203322	Influenza virus B RNA [Presence] in Upper respiratory specimen by NAA with probe detection
36031498	Influenza virus A H7 Eurasia RNA [Presence] in Specimen by NAA with probe detection
21493333	Influenza virus A H1 RNA [Presence] in Nasopharynx by NAA with non-probe detection
21493335	Influenza virus A H3 RNA [Presence] in Nasopharynx by NAA with non-probe detection
21493376	Influenza virus A H1 HA gene [Presence] in Nasopharynx by NAA with probe detection
21493377	Influenza virus A H3 HA gene [Presence] in Nasopharynx by NAA with probe detection
36304919	Influenza virus B RNA [Presence] in Lower respiratory specimen by NAA with probe detection
36305662	Influenza virus A RNA [Presence] in Lower respiratory specimen by NAA with probe detection
40758593	Influenza virus A swine origin RNA [Presence] in Specimen by NAA with probe detection
44816683	Influenza virus B Victoria lineage RNA [Presence] in Specimen by NAA with probe detection
44816684	Influenza virus B Yamagata lineage RNA [Presence] in Specimen by NAA with probe detection
36660213	Influenza virus A H1 RNA [Presence] in Lower respiratory specimen by NAA with probe detection
36660307	Influenza virus A H3 RNA [Presence] in Lower respiratory specimen by NAA with probe detection
21493425	Influenza virus A H7 Eurasia RNA [Presence] in Respiratory specimen by NAA with probe detection
37020197	Influenza virus A H1 RNA [Presence] in Upper respiratory specimen by NAA with probe detection
37020995	Influenza virus A RNA [Presence] in Lower respiratory specimen by NAA with non-probe detection
37021109	Influenza virus B RNA [Presence] in Lower respiratory specimen by NAA with non-probe detection
37021392	Influenza virus A H3 RNA [Presence] in Upper respiratory specimen by NAA with probe detection
40758594	Influenza virus A H1 2009 pandemic RNA [Presence] in Specimen by NAA with probe detection
40763592	Influenza virus A H1+H3+B RNA [Presence] in Specimen by NAA with probe detection
46236738	Influenza virus A H1 2009 pandemic RNA [Presence] in Nasopharynx by NAA with probe detection

concept_id	concept_name
21493334	Influenza virus A H1 2009 pandemic RNA [Presence] in Nasopharynx by NAA with non-probe detection
36660200	Influenza virus A H1 2009 pandemic RNA [Presence] in Lower respiratory specimen by NAA with probe detection
40757373	Influenza virus identified in Isolate
40757375	Influenza virus identified in Specimen
3001507	Influenza virus A identified in Specimen by Bioassay
3018941	Influenza virus identified in Sputum by Organism specific culture
3023193	Influenza virus identified in Throat by Organism specific culture
3023788	Influenza virus identified in Specimen by Organism specific culture
3033040	Influenza virus identified in Specimen by Shell vial culture
3049508	Influenza virus A and B identified in Specimen by Bioassay
3022226	Influenza virus identified in Sputum tracheal aspirate by Organism specific culture
36303956	Influenza virus identified in Lower respiratory specimen by Organism specific culture
37021091	Influenza virus identified in Upper respiratory specimen by Organism specific culture
21494796	Influenza virus A and B identified in Nasopharynx by Shell vial culture
36661375	Influenza virus A and B and SARS-CoV-2 (COVID-19) identified in Respiratory specimen by NAA with probe detection
3028969	Influenza virus A Ag [Identifier] in Isolate
43054943	Influenza virus A neuraminidase segment sequence identifier
43055601	Influenza virus A hemagglutinin segment sequence identifier
40757374	Influenza virus RNA [Identifier] in Specimen by Probe
43054944	Influenza virus A matrix protein segment sequence identifier
3033001	Influenza virus B RNA [Identifier] in Isolate by Sequencing
3029905	Influenza virus A polymerase RNA [Identifier] in Isolate by Sequencing
3041200	Influenza virus A hemagglutinin cDNA [Identifier] in Specimen by Sequencing
3031630	Influenza virus A hemagglutinin type RNA [Identifier] in Isolate by Sequencing
3036018	Influenza virus A subtype [Identifier] in Specimen by Immune diffusion (ID)
40763863	Influenza virus A and B Ag [Identifier] in Specimen by Immunofluorescence
43054996	Influenza virus A and B Ag [Identifier] in Nose by Immunofluorescence
3020346	Influenza virus A subtype [Identifier] in Specimen by NAA with probe detection
43054990	Influenza virus A and B Ag [Identifier] in Specimen by Rapid immunoassay
43054997	Influenza virus A and B Ag [Identifier] in Nose by Rapid immunoassay
3042355	Influenza virus A hemagglutinin cDNA [Identifier] in Specimen by NAA with probe detection
3044524	Influenza virus A neuraminidase cDNA [Identifier] in Specimen by NAA with probe detection
40758263	Influenza virus A hemagglutinin cDNA [Identifier] in Isolate by NAA with probe detection
40758264	Influenza virus A neuraminidase RNA [Identifier] in Isolate by NAA with probe detection
44816682	Influenza virus B lineage RNA [Identifier] in Specimen by NAA with probe detection

concept_id	concept_name
3033066	Influenza virus A and B RNA [Identifier] in Isolate by NAA with probe detection
3048504	Influenza virus A and B RNA [Identifier] in Specimen by NAA with probe detection
1175638	Influenza virus A subtype [Identifier] in Lower respiratory specimen by NAA with probe detection
37020237	Influenza virus A subtype [Identifier] in Upper respiratory specimen by NAA with probe detection
40758592	Influenza virus A swine origin RNA [Identifier] in Specimen by NAA with probe detection
40762514	Influenza virus A hemagglutinin type RNA [Identifier] in Specimen by NAA with probe detection
40762515	Influenza virus A hemagglutinin type RNA [Identifier] in Isolate by NAA with probe detection
42528606	Influenza virus A and B and H1 2009 pandemic RNA [Identifier] in Upper respiratory specimen by NAA with probe detection
3039888	Influenza virus B RNA [#/volume] (viral load) in Specimen by NAA with probe detection
3042219	Influenza virus A RNA [#/volume] (viral load) in Specimen by NAA with probe detection
3046850	Influenza virus A RNA [Units/volume] (viral load) in Specimen by NAA with probe detection
3044170	Influenza virus A H6 RNA [Units/volume] (viral load) in Specimen by NAA with probe detection
3046387	Influenza virus A H7 RNA [Units/volume] (viral load) in Specimen by NAA with probe detection
3046999	Influenza virus A H5 RNA [Units/volume] (viral load) in Specimen by NAA with probe detection
40759145	Influenza virus A N1 RNA [Units/volume] (viral load) in Specimen by NAA with probe detection
3029698	Influenza virus.neuraminidase inhibitor resistance [Susceptibility] Qualitative
3030160	Influenza virus.neuraminidase inhibitor resistance [Susceptibility] by Genotype method
3029894	Influenza virus A.neuraminidase inhibitor resistance [Susceptibility] Qualitative by Phenotype method
40761006	Influenza virus A+B.neuraminidase inhibitor resistance [Susceptibility] in Specimen by Genotype method
40761004	Influenza virus A H1.neuraminidase inhibitor resistance [Susceptibility] in Specimen by Genotype method
40761005	Influenza virus A 2009 H1N1v.neuraminidase inhibitor resistance [Susceptibility] in Specimen by Genotype method
40763862	Influenza virus A neuraminidase RNA [Type] in Specimen by Sequencing
1001915	Influenza virus A NP gene [Nucleotide sequence] in Isolate by Sequencing
1001930	Influenza virus A PB2 gene [Nucleotide sequence] in Isolate by Sequencing
1001933	Influenza virus A PA gene [Nucleotide sequence] in Isolate by Sequencing
1002337	Influenza virus A PB1 gene [Nucleotide sequence] in Isolate by Sequencing
1002397	Influenza virus A NS1 gene [Nucleotide sequence] in Isolate by Sequencing

concept_id	concept_name
36203376	Influenza virus A whole genome [Nucleotide sequence] in Isolate by Sequencing
36304442	Influenza virus A NA gene [Nucleotide sequence] in Isolate by Sequencing
36305961	Influenza virus A HA gene [Nucleotide sequence] in Isolate by Sequencing
36306048	Influenza virus A M gene [Nucleotide sequence] in Isolate by Sequencing

Influenza Viruses (SNOMED)

concept_id	concept_name
46269741	Bronchiolitis caused by influenza virus
4248810	Healthcare associated influenza disease
4266367	Influenza
764960	Influenza A virus inconclusive
764964	Influenza A virus subtype H1 2009 pandemic strain inconclusive
764962	Influenza A virus subtype H1 inconclusive
764967	Influenza A virus subtype H5 asian strain inconclusive
765125	Influenza A virus subtype H5 inconclusive
36676221	Influenza caused by Influenza A virus subtype H3N2
37016926	Influenza caused by Influenza A virus subtype H5
36676233	Influenza caused by Influenza A virus subtype H5N1
36714570	Influenza caused by pandemic influenza virus
36714388	Influenza caused by seasonal influenza virus
40483537	Influenza due to Influenza A virus
40484544	Influenza due to Influenza A virus subtype H1N1
42872723	Influenza due to Influenza A virus subtype H7
45768913	Influenza due to Influenza A virus subtype H7N9
42872724	Influenza due to Influenza A virus subtype H9
765607	Influenza due to Influenza A virus with upper respiratory signs
4080680	Influenza due to Influenza B virus
4304374	Influenza due to Influenza C virus
37394477	Influenza due to pandemic influenza virus
37394478	Influenza due to seasonal influenza virus
37394476	Influenza due to zoonotic influenza virus
4112664	Influenza with laryngitis
4110512	Influenza with pharyngitis
37394479	Influenza with pneumonia due to seasonal influenza virus
4183609	Influenzal acute upper respiratory infection
4186568	Influenzal bronchopneumonia
256723	Pneumonia and influenza
36676238	Pneumonia caused by Influenza A virus
46270121	Pneumonia due to H1N1 influenza

concept_id	concept_name
46270318	Pneumonia due to influenza
763011	Pneumonia due to Influenza A virus
763012	Pneumonia due to Influenza A virus subtype H1N1
46270122	Upper respiratory tract infection due to H1N1 influenza
46273463	Upper respiratory tract infection due to Influenza
46270491	Upper respiratory tract infection due to Influenza A

SARS-CoV-2 (LOINC)

concept_id	concept_name
586516	SARS-CoV-2 (COVID-19) [Presence] in Specimen by Organism specific culture
36661377	SARS-CoV-2 (COVID-19) RNA [Presence] in Respiratory specimen by Sequencing
715261	SARS-CoV-2 (COVID-19) RNA [Presence] in Saliva (oral fluid) by Sequencing
723477	SARS-CoV-2 (COVID-19) Ag [Presence] in Respiratory specimen by Rapid immunoassay
36031213	SARS-CoV-2 (COVID-19) S gene [Presence] in Respiratory specimen by Sequencing
36032419	SARS-CoV-2 (COVID-19) Ag [Presence] in Upper respiratory specimen by Immunoassay
586526	SARS-CoV-2 (COVID-19) RNA [Presence] in Nasopharynx by NAA with probe detection
706170	SARS-CoV-2 (COVID-19) RNA [Presence] in Specimen by NAA with probe detection
757677	SARS-CoV-2 (COVID-19) RNA [Presence] in Nose by NAA with probe detection
757686	SARS-CoV-2 (COVID-19) IgA+IgM [Presence] in Serum or Plasma by Immunoassay
36031944	SARS-CoV-2 (COVID-19) specific TCRB gene rearrangements [Presence] in Blood by Sequencing
36033641	SARS-CoV-2 (COVID-19) Ag [Presence] in Upper respiratory specimen by Rapid immunoassay
706163	SARS-CoV-2 (COVID-19) RNA [Presence] in Respiratory specimen by NAA with probe detection
706173	SARS-CoV-2 (COVID-19) RdRp gene [Presence] in Specimen by NAA with probe detection
706175	SARS-CoV-2 (COVID-19) N gene [Presence] in Specimen by NAA with probe detection
715272	SARS-CoV-2 (COVID-19) N gene [Presence] in Nasopharynx by NAA with probe detection
723466	SARS-CoV-2 (COVID-19) S gene [Presence] in Specimen by NAA with probe detection
723476	SARS-CoV-2 (COVID-19) RNA [Presence] in Nasopharynx by NAA with non-probe detection
757678	SARS-CoV-2 (COVID-19) N gene [Presence] in Nose by NAA with probe detection
757685	SARS-CoV+SARS-CoV-2 (COVID-19) Ag [Presence] in Respiratory specimen by Rapid immunoassay
36033656	SARS-CoV-2 (COVID-19) RNA [Presence] in Oropharyngeal wash by NAA with probe detection
36033665	SARS-CoV-2 (COVID-19) S gene mutation [Presence] in Specimen by Molecular genetics method
1617191	SARS-CoV-2 (COVID-19) ORF1b region [Presence] in Respiratory specimen by NAA with probe detection

1617427	SARS-CoV-2 (COVID-19) ORF1a region [Presence] in Respiratory specimen by NAA with probe detection
706160	SARS-CoV-2 (COVID-19) RdRp gene [Presence] in Respiratory specimen by NAA with probe detection
706161	SARS-CoV-2 (COVID-19) N gene [Presence] in Respiratory specimen by NAA with probe detection
715260	SARS-CoV-2 (COVID-19) RNA [Presence] in Saliva (oral fluid) by NAA with probe detection
723463	SARS-CoV-2 (COVID-19) RNA [Presence] in Serum or Plasma by NAA with probe detection
723465	SARS-CoV-2 (COVID-19) S gene [Presence] in Respiratory specimen by NAA with probe detection
36031238	SARS-CoV-2 (COVID-19) RNA [Presence] in Respiratory specimen by NAA with non-probe detection
36033644	SARS-CoV-2 (COVID-19) N gene [Presence] in Nose by NAA with non-probe detection
36033655	SARS-CoV-2 (COVID-19) RNA [Presence] in Specimen from Donor by NAA with probe detection
36033658	SARS-CoV-2 (COVID-19) E gene [Presence] in Respiratory specimen by NAA with probe detection
36033662	SARS-CoV-2 (COVID-19) S gene codon N501= [Presence] in Specimen by Molecular genetics method
36033663	SARS-CoV-2 (COVID-19) S gene codon N501Y [Presence] in Specimen by Molecular genetics method
1616454	SARS-CoV-2 (COVID-19) ORF1a region [Presence] in Saliva (oral fluid) by NAA with probe detection
1616841	SARS-CoV-2 (COVID-19) ORF1b region [Presence] in Saliva (oral fluid) by NAA with probe detection
586519	SARS-CoV-2 (COVID-19) S gene [Presence] in Serum or Plasma by NAA with probe detection
586520	SARS-CoV-2 (COVID-19) N gene [Presence] in Serum or Plasma by NAA with probe detection
36661378	SARS-CoV-2 (COVID-19) N gene [Presence] in Saliva (oral fluid) by NAA with probe detection
36031453	SARS-CoV-2 (COVID-19) RdRp gene [Presence] in Upper respiratory specimen by NAA with probe detection
36031506	SARS-CoV-2 (COVID-19) ORF1ab region [Presence] in Saliva (oral fluid) by NAA with probe detection
36031652	SARS-CoV-2 (COVID-19) RdRp gene [Presence] in Lower respiratory specimen by NAA with probe detection
36032174	SARS-CoV-2 (COVID-19) RdRp gene [Presence] in Saliva (oral fluid) by NAA with probe detection
36033642	SARS-CoV-2 (COVID-19) Nsp2 gene [Presence] in Upper respiratory specimen by NAA with probe detection

36033645	SARS-CoV-2 (COVID-19) M gene [Presence] in Upper respiratory specimen by NAA with probe detection
36033660	SARS-CoV-2 (COVID-19) S gene [Presence] in Saliva (oral fluid) by NAA with probe detection
706154	SARS-CoV-2 (COVID-19) N gene [Presence] in Specimen by Nucleic acid amplification using CDC primer-probe set N2
706156	SARS-CoV-2 (COVID-19) N gene [Presence] in Specimen by Nucleic acid amplification using CDC primer-probe set N1
586524	SARS-CoV-2 (COVID-19) N gene [Presence] in Respiratory specimen by Nucleic acid amplification using CDC primer-probe set N1
586525	SARS-CoV-2 (COVID-19) N gene [Presence] in Respiratory specimen by Nucleic acid amplification using CDC primer-probe set N2
36032258	SARS-CoV-2 (COVID-19) N gene [Presence] in Saliva (oral fluid) by Nucleic acid amplification using CDC primer-probe set N1
36033646	SARS-CoV-2 (COVID-19) N gene [Presence] in Saliva (oral fluid) by Nucleic acid amplification using CDC primer-probe set N2
36661375	Influenza virus A and B and SARS-CoV-2 (COVID-19) identified in Respiratory specimen by NAA with probe detection
36033652	SARS-CoV-2 (COVID-19) lineage [Identifier] in Specimen by Molecular genetics method
1988376	SARS-CoV-2 (COVID-19) RdRp gene mutation detected [Identifier] in Specimen by Molecular genetics method
36033664	SARS-CoV-2 (COVID-19) S gene mutation detected [Identifier] in Specimen by Molecular genetics method
1989163	SARS-CoV-2 (COVID-19) lineage [Type] in Specimen by Sequencing
36033667	SARS-CoV-2 (COVID-19) variant [Type] in Specimen by Sequencing
36033651	SARS-CoV-2 (COVID-19) sequencing and identification panel - Specimen by Molecular genetics method
586517	SARS-CoV-2 (COVID-19) whole genome [Nucleotide sequence] in Isolate or Specimen by Sequencing
715262	SARS-CoV-2 (COVID-19) RNA [Log #/volume] (viral load) in Specimen by NAA with probe detection
36661370	SARS-CoV-2 (COVID-19) N gene [#/volume] (viral load) in Respiratory specimen by NAA with probe detection
36661371	SARS-CoV-2 (COVID-19) N gene [Log #/volume] (viral load) in Respiratory specimen by NAA with probe detection
36033640	SARS-CoV-2 (COVID-19) ORF1ab region [Units/volume] (viral load) in Upper respiratory specimen by NAA with probe detection

SARS-CoV-2 (SNOMED)

concept_id	concept_name
37311061	COVID-19

Parainfluenza Viruses (LOINC)

concept_id	concept_name
37019589	Parainfluenza virus 1 RNA [Presence] in Respiratory specimen by NAA with probe detection
37019613	Parainfluenza virus 2 RNA [Presence] in Respiratory specimen by NAA with probe detection
37021465	Parainfluenza virus 3 RNA [Presence] in Respiratory specimen by NAA with probe detection
3000425	Parainfluenza virus Ag [Presence] in Specimen
3005880	Parainfluenza virus 3 Ag [Presence] in Specimen
3009629	Parainfluenza virus 1 Ag [Presence] in Throat
3010464	Parainfluenza virus 1 Ag [Presence] in Specimen
3016196	Parainfluenza virus 2 Ag [Presence] in Throat
3021578	Parainfluenza virus 2 Ag [Presence] in Specimen
3022602	Parainfluenza virus 3 Ag [Presence] in Throat
40763479	Parainfluenza virus 4 Ag [Presence] in Specimen
3002962	Parainfluenza virus Ag [Presence] in Specimen by Immunofluorescence
3009449	Parainfluenza virus 3 Ag [Presence] in Specimen by Immunofluorescence
3011598	Parainfluenza virus 2 Ag [Presence] in Throat by Immunofluorescence
3012334	Parainfluenza virus 3 Ag [Presence] in Throat by Immunofluorescence
3019247	Parainfluenza virus 1 Ag [Presence] in Specimen by Immunofluorescence
3022517	Parainfluenza virus 1 Ag [Presence] in Throat by Immunofluorescence
3026121	Parainfluenza virus 2 Ag [Presence] in Specimen by Immunofluorescence
3027146	Parainfluenza virus 1+2+3 Ag [Presence] in Specimen
3039228	Parainfluenza virus 4 Ag [Presence] in Specimen by Immunofluorescence
3050787	Parainfluenza virus 1 Ag [Presence] in Nose by Immunofluorescence
3051190	Parainfluenza virus 1 Ag [Presence] in Nasopharynx by Immunofluorescence
40770410	Parainfluenza virus 1 Ag [Presence] in Isolate by Immunofluorescence
40770411	Parainfluenza virus 2 Ag [Presence] in Isolate by Immunofluorescence
40770412	Parainfluenza virus 3 Ag [Presence] in Isolate by Immunofluorescence
40770413	Parainfluenza virus 4 Ag [Presence] in Isolate by Immunofluorescence
46236092	Parainfluenza virus 2 Ag [Presence] in Nasopharynx by Immunofluorescence
46236093	Parainfluenza virus 3 Ag [Presence] in Nasopharynx by Immunofluorescence
3000560	Canine parainfluenza virus 2 Ag [Presence] in Tissue by Immunofluorescence
3011433	Bovine parainfluenza virus 3 Ag [Presence] in Tissue by Immunofluorescence
40758227	Parainfluenza virus 1 [Presence] in Specimen by Organism specific culture
40758228	Parainfluenza virus 2 [Presence] in Specimen by Organism specific culture
40758229	Parainfluenza virus 3 [Presence] in Specimen by Organism specific culture
46236086	Parainfluenza virus 1 Ag [Presence] in Bronchoalveolar lavage by Immunofluorescence

46236087	Parainfluenza virus 2 Ag [Presence] in Bronchoalveolar lavage by Immunofluorescence
46236088	Parainfluenza virus 3 Ag [Presence] in Bronchoalveolar lavage by Immunofluorescence
36031350	Bovine parainfluenza virus 3 [Presence] in Specimen by Organism specific culture
36304216	Parainfluenza virus 1 Ag [Presence] in Lower respiratory specimen by Immunofluorescence
36304243	Parainfluenza virus 2 Ag [Presence] in Lower respiratory specimen by Immunofluorescence
36305893	Parainfluenza virus 3 Ag [Presence] in Lower respiratory specimen by Immunofluorescence
40764126	Parainfluenza virus RNA [Presence] in Specimen by NAA with probe detection
3006262	Parainfluenza virus 3 RNA [Presence] in Specimen by NAA with probe detection
3012158	Parainfluenza virus 2 RNA [Presence] in Specimen by NAA with probe detection
3025634	Parainfluenza virus 1 RNA [Presence] in Specimen by NAA with probe detection
3038297	Parainfluenza virus 4 RNA [Presence] in Specimen by NAA with probe detection
40763324	Parainfluenza virus 1 RNA [Presence] in Isolate by NAA with probe detection
40763470	Parainfluenza virus 4 RNA [Presence] in Isolate by NAA with probe detection
40763471	Parainfluenza virus 3 RNA [Presence] in Isolate by NAA with probe detection
40763472	Parainfluenza virus 2 RNA [Presence] in Isolate by NAA with probe detection
40770419	Parainfluenza virus 4a RNA [Presence] in Specimen by NAA with probe detection
40770420	Parainfluenza virus 4b RNA [Presence] in Specimen by NAA with probe detection
46235763	Parainfluenza virus 1 RNA [Presence] in Nasopharynx by NAA with probe detection
46235764	Parainfluenza virus 2 RNA [Presence] in Nasopharynx by NAA with probe detection
46235765	Parainfluenza virus 3 RNA [Presence] in Nasopharynx by NAA with probe detection
46235766	Parainfluenza virus 4 RNA [Presence] in Nasopharynx by NAA with probe detection
21493337	Parainfluenza virus 1 RNA [Presence] in Nasopharynx by NAA with non-probe detection
21493338	Parainfluenza virus 2 RNA [Presence] in Nasopharynx by NAA with non-probe detection
21493339	Parainfluenza virus 3 RNA [Presence] in Nasopharynx by NAA with non-probe detection
21493340	Parainfluenza virus 4 RNA [Presence] in Nasopharynx by NAA with non-probe detection
21493379	Parainfluenza virus 1 F gene [Presence] in Nasopharynx by NAA with probe detection
21493380	Parainfluenza virus 2 L gene [Presence] in Nasopharynx by NAA with probe detection
21493381	Parainfluenza virus 3 NP gene [Presence] in Nasopharynx by NAA with probe detection
21493382	Parainfluenza virus 4 P gene [Presence] in Nasopharynx by NAA with probe detection
36303698	Porcine parainfluenza virus 1 RNA [Presence] in Specimen by NAA with probe detection
36304620	Parainfluenza virus RNA [Presence] in Lower respiratory specimen by NAA with probe detection
37019554	Parainfluenza virus RNA [Presence] in Upper respiratory specimen by NAA with probe detection
37020335	Parainfluenza virus 4 RNA [Presence] in Respiratory specimen by NAA with probe detection
36303784	Parainfluenza virus 3 RNA [Presence] in Lower respiratory specimen by NAA with probe detection
36304298	Parainfluenza virus 4 RNA [Presence] in Lower respiratory specimen by NAA with probe detection

36304319	Parainfluenza virus 2 RNA [Presence] in Lower respiratory specimen by NAA with probe detection
36305681	Parainfluenza virus 1 RNA [Presence] in Lower respiratory specimen by NAA with probe detection
37019976	Parainfluenza virus 3 RNA [Presence] in Upper respiratory specimen by NAA with probe detection
37019984	Parainfluenza virus 4 RNA [Presence] in Upper respiratory specimen by NAA with probe detection
37020005	Parainfluenza virus RNA [Presence] in Lower respiratory specimen by NAA with non-probe detection
37020881	Parainfluenza virus 1 RNA [Presence] in Upper respiratory specimen by NAA with probe detection
37021346	Parainfluenza virus 2 RNA [Presence] in Upper respiratory specimen by NAA with probe detection
40763309	Parainfluenza virus 1+2+3 RNA [Presence] in Specimen by NAA with probe detection
1616435	Parainfluenza virus 1+2+3+4 RNA [Presence] in Specimen by NAA with probe detection
36659829	Parainfluenza virus 3 RNA [Presence] in Lower respiratory specimen by NAA with non-probe detection
36660052	Parainfluenza virus 2 RNA [Presence] in Lower respiratory specimen by NAA with non-probe detection
36660164	Parainfluenza virus 1 RNA [Presence] in Lower respiratory specimen by NAA with non-probe detection
36660474	Parainfluenza virus 4 RNA [Presence] in Lower respiratory specimen by NAA with non-probe detection
36304614	Parainfluenza virus 1+2+3+4 RNA [Presence] in Nasopharynx by NAA with non-probe detection
37019678	Parainfluenza virus 1+2+3+4 RNA [Presence] in Lower respiratory specimen by NAA with probe detection
37020326	Parainfluenza virus 1+2+3+4 RNA [Presence] in Upper respiratory specimen by NAA with probe detection
3012406	Parainfluenza virus identified in Nose by Organism specific culture
3041784	Parainfluenza virus identified in Specimen by Organism specific culture
1175382	Parainfluenza virus identified in Upper respiratory specimen by Organism specific culture
1175802	Parainfluenza virus identified in Lower respiratory specimen by Organism specific culture
3045012	Parainfluenza virus Ag [Identifier] in Specimen by Immunofluorescence
36303630	Porcine parainfluenza virus 1 F gene [Nucleotide sequence] in Isolate by Sequencing
36305529	Porcine parainfluenza virus 1 HN gene [Nucleotide sequence] in Isolate by Sequencing
3041077	Parainfluenza virus 2 RNA [#/volume] (viral load) in Specimen by NAA with probe detection
3041665	Parainfluenza virus 3 RNA [#/volume] (viral load) in Specimen by NAA with probe detection

3041991	Parainfluenza virus 1 RNA [#/volume] (viral load) in Specimen by NAA with probe detection
1175987	Porcine parainfluenza virus 1 RNA [#/volume] (viral load) in Specimen by NAA with probe detection

Parainfluenza Viruses (SNOMED)

4008269	Parainfluenza
439857	Parainfluenza virus pneumonia
4030792	Parainfluenza virus laryngotracheitis
4099911	Parainfluenza virus bronchitis
4146838	Parainfluenza virus laryngotracheobronchitis
4193918	Parainfluenza virus pharyngitis
4244268	Parainfluenza virus rhinopharyngitis
4274802	Parainfluenza virus bronchopneumonia
4312196	Parainfluenza virus laryngitis
4112359	Acute parainfluenza virus bronchitis
4256895	Healthcare associated parainfluenza virus disease
4147524	Infection due to Human parainfluenza virus 3
4248511	Infection due to Human parainfluenza virus 1
4288743	Infection due to Human parainfluenza virus 4
4289924	Infection due to Human parainfluenza virus 2

Adenoviruses (LOINC)

concept_id	concept_name
1002061	Adenovirus A+B+C+D+E DNA [Presence] in Respiratory specimen by NAA with probe detection
3003330	Adenovirus Ag [Presence] in Specimen
3005534	Adenovirus Ag [Presence] in Throat
3035162	Adenovirus Ag [Presence] in Nasopharynx
3043318	Adenovirus Ag [Presence] in Nose
3009001	Equine adenovirus Ag [Presence] in Lung
3020161	Adenovirus Ag [Presence] in Conjunctival specimen
3001155	Adenovirus rRNA [Presence] in Tissue by Probe
3008787	Adenovirus Ag [Presence] in Throat by Immunofluorescence
3011647	Adenovirus Ag [Presence] in Specimen by Immunoassay
3015977	Adenovirus Ag [Presence] in Throat by Immunoassay
3016799	Adenovirus Ag [Presence] in Tissue by Immunoassay
3016845	Adenovirus Ag [Presence] in Specimen by Immunofluorescence
3020619	Adenovirus rRNA [Presence] in Specimen by Probe
3034121	Adenovirus Ag [Presence] in Tissue by Immunofluorescence
3043539	Adenovirus Ag [Presence] in Trachea by Immunofluorescence
3044357	Adenovirus Ag [Presence] in Nasopharynx by Immunofluorescence
3046184	Adenovirus Ag [Presence] in Nose by Immunofluorescence
36304958	Adenovirus Ag [Presence] in Nasopharynx by Immunoassay
3010009	Canine adenovirus Ag [Presence] in Tissue by Immunofluorescence
3015897	Equine adenovirus Ag [Presence] in Lung by Immunofluorescence
3021131	Porcine adenovirus Ag [Presence] in Tissue by Immunofluorescence
3037768	Adenovirus Ag [Presence] in Conjunctival specimen by Immunoassay
3038070	Adenovirus Ag [Presence] in Conjunctival specimen by Immunofluorescence
3046648	Adenovirus Ag [Presence] in Bronchial specimen by Immunofluorescence
40758225	Adenovirus [Presence] in Specimen by Organism specific culture
46235792	Adenovirus Ag [Presence] in Bronchoalveolar lavage by Immunofluorescence
3009318	Bovine adenovirus 3 Ag [Presence] in Tissue by Immunofluorescence
3010161	Bovine adenovirus 5 Ag [Presence] in Tissue by Immunofluorescence
36303237	Adenovirus Ag [Presence] in Lower respiratory specimen by Immunofluorescence
36305905	Adenovirus Ag [Presence] in Lower respiratory specimen by Immunoassay
37021271	Adenovirus Ag [Presence] in Upper respiratory specimen by Immunoassay
3041623	Adenovirus DNA [Presence] in Specimen by NAA with probe detection
36203754	Adenovirus DNA [Presence] in Tissue by NAA with probe detection
36203755	Adenovirus DNA [Presence] in Blood by NAA with probe detection
36031829	Adenovirus RNA [Presence] in Specimen by NAA with probe detection
36303631	Adenovirus [Presence] in Upper respiratory specimen by Organism specific culture
36304215	Adenovirus DNA [Presence] in Aspirate by NAA with probe detection

36304357	Adenovirus [Presence] in Lower respiratory specimen by Organism specific culture
37019896	Adenovirus Ag [Presence] in Upper respiratory specimen by Rapid immunoassay
37020125	Adenovirus Ag [Presence] in Lower respiratory specimen by Rapid immunoassay
40763314	Adenovirus DNA [Presence] in Isolate by NAA with probe detection
46235749	Adenovirus DNA [Presence] in Nasopharynx by NAA with probe detection
3028552	Avian adenovirus 2 Ag [Presence] in Tissue by Immune diffusion (ID)
36032114	Adenovirus DNA [Presence] in Respiratory specimen by NAA with probe detection
21493329	Adenovirus DNA [Presence] in Nasopharynx by NAA with non-probe detection
21493373	Adenovirus hexon gene [Presence] in Nasopharynx by NAA with probe detection
40765217	Adenovirus DNA [Presence] in Bronchoalveolar lavage by NAA with probe detection
43533778	Adenovirus C DNA [Presence] in Nasopharynx by NAA with probe detection
3036522	Adenovirus DNA [Presence] in Serum or Plasma by NAA with probe detection
36203953	Adenovirus B(21) DNA [Presence] in Specimen by NAA with probe detection
36203954	Adenovirus B(16) DNA [Presence] in Specimen by NAA with probe detection
36203955	Adenovirus B(11) DNA [Presence] in Specimen by NAA with probe detection
36203956	Adenovirus B(14) DNA [Presence] in Specimen by NAA with probe detection
36203957	Adenovirus B(7) DNA [Presence] in Specimen by NAA with probe detection
36203958	Adenovirus E(4) DNA [Presence] in Specimen by NAA with probe detection
36203959	Adenovirus B(3) DNA [Presence] in Specimen by NAA with probe detection
1176105	Adenovirus DNA [Presence] in Lower respiratory specimen by NAA with probe detection
36660031	Equine adenovirus 1 RNA [Presence] in Specimen by NAA with probe detection
37020093	Adenovirus DNA [Presence] in Upper respiratory specimen by NAA with probe detection
37021047	Adenovirus B+E DNA [Presence] in Specimen by NAA with probe detection
43533779	Adenovirus B+E DNA [Presence] in Nasopharynx by NAA with probe detection
37020807	Adenovirus DNA [Presence] in Lower respiratory specimen by NAA with non-probe detection
37020291	Adenovirus B+C+E DNA [Presence] in Respiratory specimen by NAA with probe detection
40764124	Adenovirus 3+4+7+21 DNA [Presence] in Specimen by NAA with probe detection
36304915	Adenovirus A+B+C+D+E+F DNA [Presence] in Nasopharynx by NAA with probe detection
3038281	Adenovirus DNA [Identifier] in Specimen by RFLP
3023687	Adenovirus type [Identifier] in Specimen by Neutralization test
3034465	Adenovirus sp identified in Specimen by Organism specific culture
3040853	Adenovirus DNA [Identifier] in Specimen by NAA with probe detection
3028979	Adenovirus DNA [#/volume] (viral load) in Blood by NAA with probe detection
3032682	Adenovirus DNA [#/volume] (viral load) in Specimen by NAA with probe detection
3033255	Adenovirus DNA [#/volume] (viral load) in Tissue by NAA with probe detection
3029254	Adenovirus DNA [#/volume] (viral load) in Bronchoalveolar lavage by NAA with probe detection
40766755	Adenovirus DNA [Log #/volume] (viral load) in Specimen by NAA with probe detection
40769381	Adenovirus DNA [#/volume] (viral load) in Body fluid by NAA with probe detection
40769382	Adenovirus DNA [Log #/volume] (viral load) in Tissue by NAA with probe detection

40769385	Adenovirus DNA [Log #/volume] (viral load) in Blood by NAA with probe detection
3032207	Adenovirus DNA [#/volume] (viral load) in Serum or Plasma by NAA with probe detection
40769380	Adenovirus DNA [Log #/volume] (viral load) in Body fluid by NAA with probe detection
40769383	Adenovirus DNA [Log #/volume] (viral load) in Serum or Plasma by NAA with probe detection
40769391	Adenovirus DNA [Log #/volume] (viral load) in Sputum or Bronchial by NAA with probe detection

Human Metapneumovirus (LOINC)

concept_id	concept_name
37020808	Human metapneumovirus RNA [Presence] in Respiratory specimen by NAA with probe detection
40763480	Human metapneumovirus Ag [Presence] in Specimen
3039848	Human metapneumovirus Ag [Presence] in Specimen by Immunofluorescence
36305650	Human metapneumovirus Ag [Presence] in Nasopharynx by Immunofluorescence
37021263	Human metapneumovirus Ag [Presence] in Upper respiratory specimen by Immunofluorescence
37021514	Human metapneumovirus Ag [Presence] in Lower respiratory specimen by Immunofluorescence
3042194	Human metapneumovirus RNA [Presence] in Specimen by NAA with probe detection
40763321	Human metapneumovirus RNA [Presence] in Isolate by NAA with probe detection
46236734	Human metapneumovirus RNA [Presence] in Nasopharynx by NAA with probe detection
21493149	Human metapneumovirus RNA [Presence] in Nasopharynx by NAA with non-probe detection
40770421	Human metapneumovirus A RNA [Presence] in Specimen by NAA with probe detection
40770422	Human metapneumovirus B RNA [Presence] in Specimen by NAA with probe detection
1176113	Human metapneumovirus RNA [Presence] in Lower respiratory specimen by NAA with probe detection
37020057	Human metapneumovirus RNA [Presence] in Upper respiratory specimen by NAA with probe detection
37020565	Human metapneumovirus RNA [Presence] in Lower respiratory specimen by NAA with non-probe detection
21493374	Human metapneumovirus A+B L+N genes [Presence] in Nasopharynx by NAA with probe detection
1175849	Human metapneumovirus identified in Lower respiratory specimen by Organism specific culture
37019600	Human metapneumovirus identified in Upper respiratory specimen by Organism specific culture
3038522	Human metapneumovirus RNA [Identifier] in Specimen by NAA with probe detection
3040511	Human metapneumovirus RNA [#/volume] (viral load) in Specimen by NAA with probe detection

Human Metapneumovirus (SNOMED)

45772094	Human metapneumovirus infection
40482061	Pneumonia due to Human metapneumovirus
40482069	Bronchiolitis due to Human metapneumovirus
46269714	Bronchopneumonia due to Human metapneumovirus

Human Bocavirus (LOINC)

concept_id	concept_name
37021321	Human bocavirus 1+2+3 DNA [Presence] in Respiratory specimen by NAA with probe detection
37021256	Human bocavirus Ag [Presence] in Lower respiratory specimen by Immunofluorescence
3049806	Human bocavirus Ag [Presence] in Specimen by Immunofluorescence
37020098	Human bocavirus Ag [Presence] in Upper respiratory specimen by Immunofluorescence
36303776	Human bocavirus DNA [Presence] in Lower respiratory specimen by NAA with probe detection
40765161	Human bocavirus DNA [Presence] in Specimen by NAA with probe detection
36204249	Human bocavirus DNA [Presence] in Tissue by NAA with probe detection
36305655	Human bocavirus DNA [Presence] in Upper respiratory specimen by NAA with probe detection

Human Bocavirus (SNOMED)

4236592	Human Bocavirus present

Rhinoviruses (LOINC)

concept_id	concept_name
21493383	Rhinovirus 5' UTR RNA [Presence] in Nasopharynx by NAA with probe detection
3042345	Rhinovirus Ag [Identifier] in Specimen by Neutralization test
1616605	Rhinovirus+Enterovirus A+B+C RNA [Presence] in Respiratory specimen by NAA with probe detection
3039534	Rhinovirus+Enterovirus Ag [Presence] in Specimen by Immunofluorescence
37020792	Rhinovirus+Enterovirus RNA [Presence] in Lower respiratory specimen by NAA with non-probe detection
37020146	Rhinovirus+Enterovirus RNA [Presence] in Lower respiratory specimen by NAA with probe detection
21493341	Rhinovirus+Enterovirus RNA [Presence] in Nasopharynx by NAA with non-probe detection
36304423	Rhinovirus+Enterovirus RNA [Presence] in Nasopharynx by NAA with probe detection
3040684	Rhinovirus+Enterovirus RNA [Presence] in Specimen by NAA with probe detection

37019683	Rhinovirus+Enterovirus RNA [Presence] in Upper respiratory specimen by NAA with probe detection
3040406	Rhinovirus RNA [Identifier] in Specimen by NAA with probe detection
1175203	Rhinovirus RNA [Presence] in Lower respiratory specimen by NAA with probe detection
46236735	Rhinovirus RNA [Presence] in Nasopharynx by NAA with probe detection
37020003	Rhinovirus RNA [Presence] in Respiratory specimen by NAA with probe detection
3025023	Rhinovirus RNA [Presence] in Specimen by NAA with probe detection
37019747	Rhinovirus RNA [Presence] in Upper respiratory specimen by NAA with probe detection

Rhinovirus (SNOMED)

4235536	Human Bocavirus present
435186	Disease due to Rhinovirus
4112521	Acute bronchitis due to rhinovirus

Coxsackieviruses (LOINC)

40764125	Echovirus+Coxsackievirus RNA [Presence] in Specimen by NAA with probe detection

Coxsackieviruses (SNOMED)

4110483	Acute coxsackievirus bronchitis
45765949	Human coxsackievirus or human echovirus

Echoviruses (LOINC)

concept_id	concept_name
40764125	Echovirus+Coxsackievirus RNA [Presence] in Specimen by NAA with probe detection
40771044	Enterovirus and Parechovirus A RNA [Identifier] in Specimen by NAA with probe detection

Echovirus (SNOMED)

437786	Echovirus disease
442784	Human echovirus infection
4080332	Neonatal echovirus disease
4110485	Acute echovirus bronchitis
45765949	Human coxsackievirus or human echovirus

Parechoviruses (LOINC)

concept_id	concept_name
36303289	Parechovirus RNA [Presence] in Upper respiratory specimen by NAA with probe detection
37021293	Parechovirus RNA [Presence] in Lower respiratory specimen by NAA with probe detection
36304665	Parechovirus RNA [Presence] in Aspirate by NAA with probe detection
40763579	Parechovirus RNA [Presence] in Specimen by NAA with probe detection
3041258	Parechovirus A RNA [Presence] in Specimen by NAA with probe detection
36204304	Parechovirus A RNA [Presence] in Blood by NAA with probe detection

Parechoviruses (SNOMED)

concept_id	concept_name
45765956	Human parechovirus 1 or human parechovirus 2

APPENDIX II – ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title:
DARWIN EU® - Age-specific incidence rates of RSV-related disease in Europe

EU PAS Register® number: N/A
Study reference number (if applicable): N/A

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	4
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6, 7
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g., cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.2
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.8
3.4	Does the protocol specify measure(s) of association? (e.g., risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	8.2/8.5
4.2	Is the planned study population defined in terms of:				8.5
	4.2.1 Study time period	☒	☐	☐	
	4.2.2 Age and sex	☒	☐	☐	
	4.2.3 Country of origin	☒	☐	☐	
	4.2.4 Disease/indication	☒	☐	☐	
	4.2.5 Duration of follow-up	☒	☐	☐	
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	8.5

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	8.6
5.2	Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorized according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g., dose, duration)	☐	☐	☒	
5.5	Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.6
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilization, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (e.g., confounding by indication)	☐	☐	☒	

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	

Comments:

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (e.g., collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☐	☒	8.6
	9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.6
	9.1.3 Covariates and other characteristics?	☒	☐	☐	8.6
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	8.6
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.6
	9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.6
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	8.6
	9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.6

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.3 Covariates and other characteristics?	☒	☐	☐	8.6
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.8
10.2 Is study size and/or statistical precision estimated?	☐	☐	☒	8.7
10.3 Are descriptive analyses included?	☒	☐	☐	8.8
10.4 Are stratified analyses included?	☒	☐	☐	8.8
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	8.8

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.2
11.2 Are methods of quality assurance described?	☒	☐	☐	10.0
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1.1 Selection bias? 12.1.2 Information bias? 12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒ ☐ ☐	☐ ☐ ☐	☐ ☒ ☒	11
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	8.2

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	12, 13
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	9.2

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g., to regulatory authorities)?	☒	☐	☐	14
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	14

Comments:

Name of the main author of the protocol: Johnmary T. Arinze

Date: 4th December 2023

Signature: J.T. Arinze