Study Report P2-C1-011

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

20/03/2024

Version 2.2

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DOCUMENT HISTORY

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Countries of study	Estonia, France, Germany, Spain, and United Kingdom.

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LIST OF ABBREVIATIONS

Acronyms/terms	Description
CDM	Common Data Model
CDW BORDEAUX	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 DESCRIPTION OF STUDY TEAM

Study team Role	Names	Organisation
Principal Investigator(s)/ Clinical Epidemiologists	Johnmary Arinze	Erasmus MC
	Katia Verhamme	Erasmus MC
Data analysts	Maarten van Kessel	Erasmus MC
Data Partner*	**Names**	**Organization**
Local Study Coordinator/Data Analyst	Antonella Delmestri	University of Oxford – CPRD
	James Brash	IQVIA DA Germany
	Guillaume Verdy	CDW BORDEAUX France
	Romain Griffier	CDW BORDEAUX France
	Raivo Kolde	University of Tartu - EBB
	Marek Oja	University of Tartu - EBB
	Juan Manuel Ramirez	IMASIS Spain
	Miguel-Angel Mayer	IMASIS Spain
	Angela Leis	IMASIS Spain
	Talita Duarte Salles	IDIAPJGol – SIDIAP
	Laura Pérez Crespo	IDIAPJGol – SIDIAP

*Data partners' role is only to execute code at their data source, review and approve their results. These people do not have an investigator role. Data analysts/programmers do not have an investigator role and thus declaration of interests (DOI) for these people is not needed.

2 DATA SOURCES

This study was 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 (CDW BORDEAUX), 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

Detailed information on data sources is described below:

Country	Name of Database	Health Care setting (e.g. primary care, specialist care, hospital care)	Type of Data (EHR, claims, registries)	Number of active subjects	End of calendar period covered
France	CDW BORDEAUX	Secondary care (in and outpatients)	EHR	2.1 million	05/05/2023
UK	CPRD GOLD	Primary care	EHR	3 million	20/03/2023
Estonia	EBB	Biobank	Claims	0.2 million	20/03/2023
Germany	IQVIA DA Germany	Primary care and outpatient specialist care	EHR	8.5 million	13/03/2023
Spain	IMASIS	Secondary care (in and outpatient)	EHR	0.6 million	22/03/2023
Spain	SIDIAP	Primary care	EHR	8.3 million	20/03/2023

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, DA = Disease Analyzer, IMASIS = Institut Municipal Assistencia Sanitaria Information System, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, EHR = Electronic Heath record.

3 ABSTRACT (STAND-ALONE SUMMARY OF THE STUDY REPORT)

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. Accurate information about RSV burden in high-risk groups is essential for decision-making to support the continuous assessment of their benefit/risk profile.

The study findings complement the work carried out by European initiatives such as IMI 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 once the vaccines are deployed and along their lifecycle. RSV vaccines effectiveness studies are 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 hospitalization rates and mortality rates related to Respiratory Syncytial Virus (RSV) infection and the co-infection frequencies 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 hospitalised due to 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 with RSV-related hospitalisation, 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 with recorded diagnosis of 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 recorded diagnosis of RSV infection.

Population

Population-level descriptive epidemiology: This analysis included all individuals in the respective databases from 2013 to 2022 (or the latest available date if earlier).

Patient-level characterization: This analysis included all patients with recorded diagnosis of RSV infection between 2013 and 2022 (or the latest available date if earlier).

Variables

Drug of interest: Not applicable

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

Outcomes of interest: Study outcomes included 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 (CDW BORDEAUX), 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 was 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 were as follows: 6,100 (EBB), 6,700 (CDW BORDEAUX), 9,100 (IQVIA DA Germany), and 9,800 (IMASIS).

Data analysis

Descriptive analysis of data was 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 was estimated among patients hospitalised due to with RSV infection (Objective 3).

The statistical analyses were 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) were calculated using the Kaplan-Meier (KM) method and survival was calculated using data on time at risk of RSV-related death, defined as within 30 days of RSV infection. Results were 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 estimated all-cause 30-day mortality rates following RSV infection. The statistical analysis was 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) was calculated between the date of in-patient care/ hospital stay and the date of hospital discharge in patients with RSV infection. This included summary statistics such as the median, interquartile range (p25 and p75), maximum, and minimum days of hospitalisation. Results were stratified by age, calendar year and database.

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

Results

Overall, 52,289,267 individuals were identified from six European databases: namely, IQVIA DA Germany (n=32,302,018, 61.78%), CPRD GOLD (n=9,836,797, 18.81%), SIDIAP (n=7,506,032, 14.35%), CDW Bordeaux (n=1,852,310, 3.54%), IMASIS (n=582,963, 1.11%), and EBB (n=209,147, 0.40%).

Approximately 0.1% (n=44,467) of the study participants had RSV infection, with major contributions from SIDIAP (n=23,194, 52.16%) and IQVIA DA Germany (n=16,612, 37.36%). Other databases each contributed less than 10% of the patient population: CDW Bordeaux (n=2,799, 6.29%), IMASIS (n=995, 2.24%), CPRD GOLD (n=609, 1.37%), and EBB (n=258, 0.58%). RSV infection was most prevalent in infants and older adults (≥ 60 years), with a similar trend among patients with laboratory confirmed RSV infection. The most frequently identified viral respiratory pathogens in patients with RSV infection were influenza virus (1.5% – 8.2%), adenovirus (0.8% – 4.2%), and SARS-CoV-2 (0.5% – 2.9%).

In the general population, the incidence rate of RSV-related hospitalisation was 35.44 (95% CI, 34.96 - 35.92) per 100,000 person-years (PY), with the highest incidence rates observed in infants (< 1 year) (2,730.25 per 100,000 PY, 95% CI, 2,681.25 – 2,779.90), toddlers and preschoolers (1 to 5 years) (153.41 per 100,000 PY, 95% CI, 148.78 – 158.15), and older adults (≥ 60 years) (28.09 per 100,000 PY, 95% CI, 27.23 – 28.97). A rising trend in hospitalization rates was observed throughout the study period, from 18.16 per 100,000 PY in 2013 to 70.68 per 100,000 PY in 2022.

In hospital settings (IMASIS and CDW Bordeaux), the incidence of RSV-related hospitalisation ranged from 182 to 274 cases per 100,000 patients hospitalised with disproportionate burden in infants aged below one year (2,159 – 2,352 per 100,000 patients), children aged 1 to 5 years (398 – 906 per 100,000 patients), and adults aged ≥ 60 years (95 – 295 per 100,000 patients). The rate was much lower for other age groups, with an increasing trend in the annual rates during the study period, from 79 – 44 per 100,000 patients in 2013 to 391 – 452 per 100,000 patients in 2022. The prevalence of RSV-related ICU admission varied from 1.07% in IMASIS to 37.35% in CDW Bordeaux. Age-specific prevalence rates were generally comparable, with infants below 1 year (39%), and adults aged ≥ 60 years (36%) requiring more ICU admission compared to the other age groups. An upward trend in the annual ICU admission rates were observed, almost tripling from 14% in 2013 to 38% in 2022. Most RSV hospitalisations lasted 1-2 days, but infants and older adults needed longer stays (2-4 and 1-5 days, respectively). The median length of stay remained stable over time, from 1-4 days in 2013 to 2 days in 2022.

Out of 26,988 patients with recorded diagnosis of RSV infection, 1% died within 30 days following diagnosis. The 30-day mortality rate of RSV infection varied notably by country and age. RSV mortality rate was slightly higher in Spain (13.1 – 18.1 per 1,000 patients) than in France (11.8 per 1,000 patients). Age-specific RSV mortality rates were discernibly high in adults (≥ 18 years), with fewer or no cases of deaths reported in children across the databases. The mortality rate varied from 50.3 per 1,000 patients in Estonia, which included only the adult population (≥ 18 years), to 18.1 per 100,000 patients in Spain which includes all age groups.

Discussion

This study confirms that RSV infection is a highly prevalent respiratory pathogen that poses a significant public health burden, particularly among infants and older adults. These vulnerable populations are disproportionately affected by RSV infection, experiencing a higher incidence of hospitalization, longer hospital stay, intensive care unit admission, and mortality.

Vulnerability of Infants and Older Adults

The susceptibility of infants and older adults to severe RSV infection stems from several factors. Infants, particularly those under six months of age, have immature immune systems, making them more susceptible to RSV's pathogenic effects. Additionally, infants lack the protective antibodies developed through previous RSV infections, which can help older children and adults combat the virus more effectively. In older adults, the decline in immune function and the presence of underlying health conditions, such as chronic lung disease or cardiovascular diseases, increase their vulnerability to RSV infection. These factors impair the body's ability to mount an effective immune response and clear the virus, leading to a higher risk of complications.

Co-infections with Other Respiratory Viruses

RSV infection often occurs in conjunction with other respiratory viruses, such as influenza virus, adenovirus, and SARS-CoV-2. These co-infections can further exacerbate the severity of RSV infection, leading to more severe illness, hospitalization, and increased mortality risk. Influenza virus, with its ability to cause respiratory inflammation and impair lung function, can intensify the symptoms and complications of RSV infection,

particularly in infants and older adults. Similarly, adenovirus, known for its association with bronchiolitis and pneumonia, can synergistically increase the severity of RSV infection. The co-occurrence of RSV with SARS-CoV-2, the virus responsible for COVID-19, poses a particularly concerning situation, as both viruses can target the respiratory tract and exacerbate each other's effects. This dual infection can lead to more severe disease manifestations, increased hospitalization rates, and higher mortality risks.

Severity of RSV Infection in Infants and Older Adults

While RSV infection appears to be more severe in infants compared to older adults, the mortality risk is significantly higher among older adults. Infants, particularly those under six months of age, are more susceptible to bronchiolitis, a lower respiratory tract infection that can cause breathing difficulties and oxygen deprivation. However, mortality rates in this age group are relatively low, with most infants recovering without major complications. In contrast, older adults face a substantially higher mortality risk from RSV infection. The weakened immune systems and underlying health conditions of this population make them more susceptible to severe complications, such as pneumonia, which can lead to respiratory failure and death.

Implications for Prevention and Management

The disproportionately high burden of RSV infection on infants and older adults emphasizes the need for targeted prevention and management strategies. For infants, early exposure to RSV through maternal antibodies or vaccination may help protect them from severe disease. Additionally, improving hand hygiene practices and reducing exposure to environmental factors that facilitate RSV transmission can help lower the risk of infection. In older adults, vaccination against influenza and pneumococcal bacteria can reduce the risk of co-infections, which can worsen RSV infection. Additionally, early diagnosis and prompt treatment of RSV infection in older adults, especially those with underlying health conditions, can help prevent complications and mortality.

Conclusion

In conclusion, infants and older adults are disproportionately affected by RSV infection, with a substantial burden of RSV-related hospitalisation in children aged 5 years and below, and high mortality rate in older adults. The study highlights the importance of age-specific considerations in understanding the epidemiology and clinical outcomes of RSV infection, providing insights for healthcare planning and intervention strategies, especially among vulnerable populations, to mitigate the impact of RSV infection on public health.

4 LIST OF ABBREVIATIONS

Acronyms/terms	Description
CDM	Common Data Model
CDW BORDEAUX	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

5 AMENDMENTS AND UPDATES

Number	Date	Section of study report	Amendment or update	Reason
1	15/02/2024	All	Update	Stratified analyses results were included/ updated.
2.	27/02/2024	All	Update	Minor textual changes.

6 MILESTONES

STUDY SPECIFIC DELIVERABLE	TIMELINE (planned)	TIMELINES (actual)
Draft Study Protocol	9th November 2023	
Final Study Protocol	4th December 2023	
Creation of Analytical code	5th January 2024	
Execution of Analytical Code on the data	12th January 2024	17th January 2024
Interim Study Report (if applicable)	Not applicable	
Draft Study Report	26th January 2024	
Final Study Report	15th February 2024	
Draft Manuscript (if agreed on)		
Final Manuscript (if agreed on)		

7 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 provide essential complementary evidence to monitor the effectiveness of RSV vaccines during deployment and throughout their lifecycle.

8 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

Research question

What are the age-specific hospitalization rates and mortality rates related to Respiratory Syncytial Virus (RSV) infection and the co-infection frequencies 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 hospitalised due to 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 with RSV-related hospitalisation, 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 with recorded diagnosis of RSV infection, stratified by year and age groups, between January 1, 2013, and December 31, 2022.

Table 1. 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 with recorded diagnosis of 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). Patient-level characterization: All individuals with recorded diagnosis of RSV infection between 2013 and 2022.
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 started when participants fulfil inclusion criteria (i.e., present in the database between 1st of January 2013 and 31st of December 2022). Patient-level characterization: Follow-up started from the date of RSV diagnosis during the study period. End of follow-up was defined as the earliest of loss to follow-up, end of data availability, death, or end of study period (31st December 2022), whatever came first.

Setting:	Inpatient and outpatient setting using data from the following 6 data sources: CDW BORDEAUX (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

9 RESEARCH METHODS

9.1 Study Type and Study Design

This study was conducted using routinely collected health data from 6 databases. The study comprised two consecutive parts:

- Population-level cohort study: To 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: 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 with recorded diagnosis of RSV infection.

Table 2. 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)

9.2 Study Setting and Data Sources

This study was 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 (CDW BORDEAUX), 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 include 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 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) was examined in population-based databases (CPRD, EBB, SIDIAP, and IQVIA Germany), and in hospital-based databases (CDW BORDEAUX and IMASIS) using a different denominator population (all patients hospitalised during the study period). Likewise, the incidence of RSV-related hospitalisation (Objective 1) was confined to population-based databases with linkage to secondary care (SIDIAP and EBB) and in hospital-based databases (CDW BORDEAUX 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) was restricted to secondary care databases (CDW BORDEAUX and IMASIS), and population-based databases with good linkage to secondary care (SIDIAP). Also, the prevalence of RSV-related ICU admission (Objective 3) was limited to secondary care databases (CDW BORDEAUX and IMASIS). In terms of RSV-related mortality (Objective 5), it was reported in all included databases except for the IQVIA DA Germany database, which lacks information regarding the date of death. **Table 3a** outlines specific study objectives that were investigated within specific databases.

Table 3a. 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 with recorded diagnosis of RSV infection
CDW BORDEAUX	F*	F	F	F#	F
CPRD GOLD	NF	NF	NF	F	F
EBB	F	NF	NF	F	F
IQVIA DA Germany	NF	NF	NF	F	NF
IMASIS	F*	F	F	F#	F
SIDIAP	F	NF	NF	NF	F

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 with recorded diagnosis of RSV infection
F = Feasible; 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 **Table 3b**.

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 3b. 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	CDW BORDEAUX	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	05/05/2023
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	20/03/2023
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	0.2 million	20/03/2023
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	13/03/2023
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	22/03/2023
Spain	SIDIAP	Covers primary care settings for RSV-related hospitalisation, co-infection, and mortality rates.	Primary care	EHR	8.3 million	20/03/2023

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, DA = Disease Analyzer, IMASIS = Institut Municipal Assistencia Sanitaria Information System, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (, EHR = Electronic Heath record.

Bordeaux University Hospital (CDW BORDEAUX), 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]

9.3 Study Period

The study period was from 1st of January 2013 until the earliest of 31st December 2022 or the respective data lock for the last database update (see **Table 3b** for more details) to capture changes in healthcare use / testing for respiratory infections due to the COVID-19 pandemic.

9.4 Follow-up

For population-level descriptive epidemiology, follow up started when patients fulfilled inclusion criteria i.e., present in the database between 1st of January 2013 and 31st of December 2022. End of follow-up was defined as the earliest of loss to follow-up, end of data availability, death, or end of study period (31st December 2022), whichever came first.

For patient-level characterization, follow-up started 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 4**.

Table 4. 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 during the study period	Study entry date	Multiple	Incident	[30 days]	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 days]	IP and OP	n/a	n/a	RSV diagnosis	n/a	n/a

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

9.5 Study Population with in and exclusion criteria

For population-level descriptive epidemiology (Objectives 1 and 4), the study population included all individuals in the respective databases between 2013 and 2022 (or the most recent available date if earlier).

For patient-level characterization (Objectives 2, 3, and 5), the study population included all patients with recorded diagnosis of RSV infection between 2013 and 2022 (or the most recent available date if earlier).

Table 5. 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
RSV infection	Patients with recorded diagnosis of RSV infection during the study period.	After	[-∞,0]	IP and OP	SNOMED	primary and secondary diagnosis code	All individuals within selected databases	n/a	n/a

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

9.6 Variables

9.6.1 Exposure

n/a

9.6.2. Outcome

This study examined the following four primary outcomes of interest.

- **RSV-related hospitalisation**

RSV-related hospitalisation was 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 were 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-related hospitalisation, as defined above, and the date of hospital discharge.

- **RSV-related ICU admission**

The RSV-related ICU admission rate was calculated as the percentage of hospitalized patients with recorded RSV infection who were admitted to the 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, was 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 diagnosis RSV infection (as defined in Table 5).

RSV-related Mortality

Overall survival in patients with recorded diagnosis of RSV infection (as defined in Table 5) was calculated within 30 days of diagnosis, based on the registered date of death.

Table 6. 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 detail 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.

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

The study covariates for stratification included:

Calendar year

Age at study entry:

- Elderly/ Older Adults: 60 years and above
- Adults: 18 to 59 years
- Children: 6 to 17 years
- Toddlers and Preschoolers: Children aged 1 to 5 years
- Infants: Children under 1 year

Sex: male or female.

9.7 Study size

No sample size has been calculated for this study as our primary objective was 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 (CDW BORDEAUX), 9,100 (IQVIA DA Germany), and 9,800 (IMASIS).

9.8 Data transformation

Analyses were conducted separately for each database. Before study initiation, test runs of the analytics were performed on a subset of the data sources and on a simulated set of patients and quality control checks were performed. After all the tests were passed (see section 11 Quality Control), the final package was released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally executed the analytics against the OMOP-CDM in R Studio and reviewed and approved the - by default - aggregated results.

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

9.9 Statistical Methods

This section describes the details of the analysis approach and rationale for the choice of analysis, with reference to the Complete Catalogue of Data Analysis which describes the type of analysis in function of the study type.

Table 7. 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

9.9.1 Patient privacy protection

Cell suppression was implemented in accordance with database protocols to safeguard individuals' privacy. Instances where cell counts were less than 5 were effectively concealed.

9.9.2 Statistical model specification and assumptions of the analytical approach considered

R-packages: We employed various R packages to conduct a comprehensive analysis:

Population-level Estimation: For estimating the incidence of RSV-related hospitalization and the prevalence of RSV co-infection with other respiratory pathogens, we utilized the "*IncidencePrevalence*" R package [27].

Patient-level Characterization: The "*PatientProfile*" package was used to estimate the duration of RSV-related hospitalization. Additionally, it was instrumental in determining the prevalence of RSV-related ICU admission.

30-day Survival Probability Estimation: The "*CohortSurvival*" R package was employed to estimate the 30-day survival probability. This calculation was based on the time from the date of RSV infection diagnosis to death from any cause. The proportion of patients who died within 30 days following the diagnosis of RSV infection was reported, and survival curves were estimated using the Kaplan-Meier (KM) method. Individuals lost to follow-up were accounted for by censoring them at the time of the loss of follow-up.

Cohort Characterization: The results of *CohortDiagnostics* were used to describe the characteristics of the participants included in the study and the respective aspects of the data analyses.

Calendar time: Calendar time was based on the calendar year of the index date.

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

- Elderly/ Older Adults: 60 years and above
- Adults: 18 to 59 years
- Children: 6 to 17 years
- Toddlers and Preschoolers: Children aged 1 to 5 years
- Infants: Children under 1 year

Sex: Results were presented by sex were applicable.

Prevalence calculations: The prevalence of RSV co-infections was 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 were calculated. Results were stratified by calendar year, age categories, and database.

The prevalence of RSV-related ICU admission was calculated as the percentage of hospitalized patients with recorded RSV infection who were admitted to the ICU. That is, the number of patients with RSV-related ICU admission divided by the population being hospitalised during that same period due to RSV infection. Binomial 95% confidence intervals were calculated. Results were stratified by calendar year, age categories, and database.

Incidence calculations: Annual incidence rates of RSV-related hospitalisation was 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 entered the denominator population then contributed 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 became eligible to contribute time for another or subsequent event of hospitalisation. If they did not have RSV-related hospitalisation, they contributed time at risk up to the end of follow-up. Incidence rates were reported together with 95% Poisson confidence intervals.

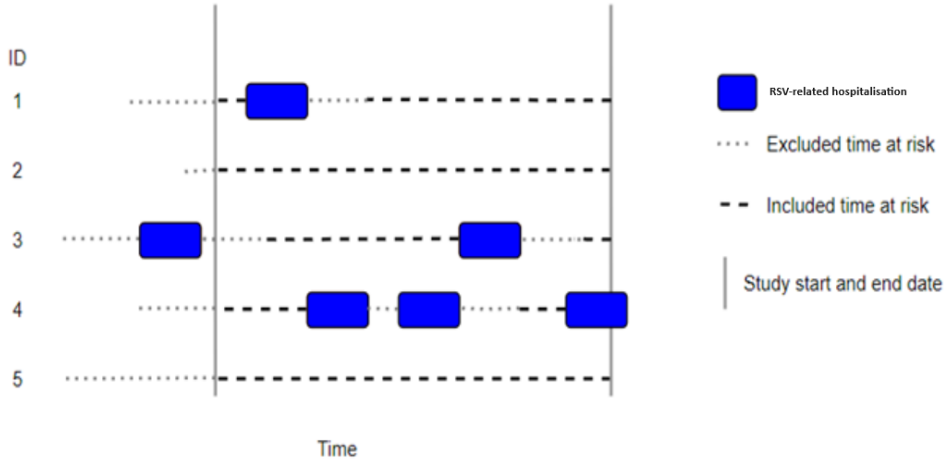

Figure 1: example of incidence rate estimation

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

Duration of RSV-related hospitalisation: Duration of RSV-related hospitalisation was 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 were calculated. Results were stratified by calendar year, age categories, and database.

9.9.3 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 provided the median follow-up time by database. Differences in follow-up time were accounted for in the incidence rate and mortality rate analyses, as the denominator consisted of person-years.

In light of the observational nature of this study, which was conducted within a dynamic population, it was 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. Since we used different databases from various countries, data completeness might be affected by differences in how well specific clinical information is captured within the respective databases.

9.9.4 Sensitivity Analysis

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 were repeated, whenever possible, restricted exclusively to laboratory-confirmed cases of RSV infection. To ensure comprehensive ascertainment of cases, we included:

(i) cases with positive confirmatory laboratory test results, or
(ii) cases with diagnostic (SNOMED) codes and evidence of RSV laboratory tests, irrespective of the availability of detailed test results.

9.10 Evidence synthesis

Results from analyses described in section 9.9 were presented separately for each database and no meta-analysis of results was conducted.

9.11 Deviations from the protocol

None.

10 DATA MANAGEMENT

10.1 Data management

All databases were mapped to the OMOP common data model. This enabled the use of standardised analytics and tools across the network since the structure of the data and the terminology system was harmonised. The OMOP CDM was developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and was 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 was written in R. Each data partner executed the study code against their database containing patient-level data and then returned the results set which only contained aggregated data. The results from each of the contributing data sites were then combined in tables and figures for the study report.

10.2 Data storage and protection

For this study, participants from various EU member states processed personal data from individuals 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 were run, which generated 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 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.

11 QUALITY CONTROL

General database quality control

Several 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 ran 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 and other parameters of interet, a systematic search of possible codes for inclusion were identified using *CodelistGenerator* R package (https://github.com/darwin-eu/CodelistGenerator) and reviewed by a medical doctor. This software allows the user to define a search strategy and using this then queries 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) was conducted to assess the use of different codes across the databases contributing to the study and identify any codes potentially omitted in error. This allowed 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 was based on three R packages namely the *IncidencePrevalence*, the *CohortSurvival*, and the *PatientProfile* Packages. These packages included numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R package was made publicly available via GitHub.

12 RESULTS

The results of this study can be accessed through a web application, the "shiny app," available at https://data-dev.darwin-eu.org/RSVStudyDiagnostics/

12.1 Demographic Characteristics of the Study Cohorts

The study population included 52,289,267 participants from six databases. IQVIA DA Germany contributed the largest number of participants (n=32,302,018, 61.78%), followed by CPRD GOLD (n=9,836,797, 18.81%), and SIDIAP (n=7,506,032, 14.35%). CDW Bordeaux (n=1,852,310, 3.54%), IMASIS (n=582,963, 1.11%), and EBB (n=209,147, 0.40%) together constitute approximately 5% of the study population.

12.1.1 Demographic characteristics of patients with recorded diagnosis of RSV infection

Table 8 describes the demographic characteristics of patients with recorded diagnosis of RSV infection during the study period, per database.

The study identified 44,467 individuals with recorded RSV infection across the six participating databases from 2013 to 2022. Most of the patient population (52.16%) were from SIDIAP (n=23,194), followed by IQVIA DA Germany (n=16,612, 37.36%). Other databases, including IMASIS (n=995, 2.24%), CPRD GOLD (n=609, 1.37%), and EBB (n=258, 0.58%), each contributed less than 5% of the patient population, except for CDW Bordeaux (n=2,799), which accounted for 6.29% of the patients with RSV infection.

The infant population (below one year) emerged as the most prevalent age group, constituting more than two-thirds of the patient population of individuals with recorded RSV infection in CDW Bordeaux (n=2,237, 79.92%) and SIDIAP (n=15,775, 68.01%), and well represented in CPRD GOLD (n=390, 64.04%), IQVIA DA Germany (n=10,386, 56.00%), and IMASIS (n=450, 45.23%). Also, older adults (aged 60 years and over) were the second most prevalent age group in most databases, including IMASIS (n=318, 31.96%), CPRD GOLD (n=110, 18.06%), SIDIAP (n=4,125, 17.78%), and CDW Bordeaux (n=255, 9.11%), except for IQVIA DA Germany (n=413, 2.49%), where they constitute the minority age group.

The gender distribution of the patients with recorded RSV infection was largely consistent across the databases, with a notably higher proportion of males in IQVIA DA Germany (55.1%), CPRD GOLD (53.4%), CDW Bordeaux (53.3%), and SIDIAP (52.4%). Conversely, a higher proportion of females was observed in EBB (71.3%), while IMASIS showed a slightly higher proportion of females (53.2%).

Table 8. Demographic characteristics of patients with recorded diagnosis of RSV infection during the study period, per database.

	CPRD GOLD UK	CDW Bordeaux France	EBB Estonia	IMASIS Spain	IQVIA DA Germany	SIDIAP Spain
Database population	17,216,081	2,203,469	209,457	1,066,675	41,974,403	8,553,325
Number of study participants	9,836,797	1,852,310	209,147	582,963	32,302,018	7,506,032
Number of patients with RSV infection	609	2,799	258	995	16,612	23,194
Age group (years), n (%)						
• < 1	390 (64.04)	2,237 (79.92)	NA	450 (45.23)	10,386 (56.00)	15,775 (68.01)
• 1 to 5	45 (7.39)	140 (5.00)	NA	71 (7.14)	3,903 (23.54)	2,035 (8.77)
• 6 to 17	10 (1.64)	44 (1.57)	NA	9 (0.90)	895 (4.81)	247 (1.06)
• 18 to 59	54 (8.87)	123 (4.39)	129 (50.00)	147 (14.77)	1,015 (6.12)	1,012 (4.36)
• ≥ 60	110 (18.06)	255 (9.11)	129 (50.00)	318 (31.96)	413 (2.49)	4,125 (17.78)
Sex, %						
• Female	46.6	46.7	71.3	53.2	44.8	47.6
• Male	53.4	53.3	28.7	46.8	55.1	52.4
• Missing					0.1	

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, DA = Disease Analyzer, IMASIS = Institut Municipal Assistencia Sanitaria Information System, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària. Hospital databases are indicated in yellow.

12.1.2 Demographic characteristics of patients with laboratory-confirmed RSV infection

Table 9 describes the demographic characteristics of patients with laboratory-confirmed RSV infection during the study period, per database.

Among the three databases with laboratory data on RSV infection, approximately two-fifths (37.44%) of the recorded RSV infection cases in the study (4,052 cases) were confirmed by laboratory investigations. This accounted for 71.32% of cases in EBB (n=258), 56.18% in IMASIS (n=559), and 27.65% in CDW Bordeaux (n=774). The age distribution of patients with laboratory-confirmed RSV infection was largely consistent with that of the overall RSV infection patient population. Specifically, infants (below one year old) were the most prevalent age group in databases with laboratory data on RSV infection, including CDW Bordeaux (n=526, 67.96%) and IMASIS (n=235, 42.04%). Additionally, older adults (aged 60 years and over) were the second most prevalent age group in patients with laboratory-confirmed RSV infection, comprising 30.23% of cases in IMASIS (n=169) and 13.18% in CDW Bordeaux (n=102). Notably, older adults (aged 60 years and over) accounted for more than half of laboratory-confirmed RSV cases in EBB (n=100, 54.35%), a database that included only adults (aged 18 years and above).

EBB and IMASIS databases had higher proportions of female patients with RSV infection (68.5% and 52.8% respectively) compared to CDW Bordeaux, which showed comparable gender distribution (50.3%).

Table 9. Demographic characteristics of patients with laboratory-confirmed RSV infection during the study period, per database.

	CPRD GOLD UK	CDW Bordeaux France	EBB Estonia	IMASIS Spain	IQVIA DA Germany	SIDIAP Spain
Number of patients with RSV infection, n	609	2,799	258	995	16,612	23,194
Number of patients with lab-confirmed RSV infection, n (%)	NA	774 (27.65)	184 (71.32)	559 (56.18)	NA	NA
Age group (years), n (%)						
• < 1	NA	526 (67.96)	NA	235 (42.04)	NA	NA
• 1 to 5	NA	57 (7.36)	NA	33 (5.90)	NA	NA
• 6 to 17	NA	25 (3.23)	NA	<5 (NA)	NA	NA
• 18 to 59	NA	64 (8.27)	84 (45.65)	118 (21.11)	NA	NA
• ≥ 60	NA	102 (13.18)	100 (54.35)	169 (30.23)	NA	NA
Sex, %						
• Female	NA	50.3	68.5	52.8	NA	NA
• Male	NA	49.7	31.5	47.2	NA	NA

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, DA = Disease Analyzer, IMASIS = Institut Municipal Assistencia Sanitaria Information System, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària. Hospital databases are indicated in yellow. NA = Not applicable as laboratory data on RSV infection are not available or obscured for counts less than 5.

12.2 Prevalence of RSV Co-infection with other Viral Respiratory Pathogens

12.2.1 Prevalence of RSV co-infection with other viral respiratory pathogens in the general population

Table 10 shows the prevalence of RSV co-infection with other viral respiratory pathogens in the general population during the study period, per database.

The prevalence of RSV co-infection - defined as presence of codes or positive laboratory test result of predefined respiratory viruses in the 7 days before, on, or 7 days after the index date - was investigated in a large cohort of 49,853,994 individuals across four major databases: IQVIA DA Germany (n=32,302,018, 64.79%), CPRD GOLD (n=9,836,797, 19.73%), SIDIAP (n=7,506,032, 15.05%), and EBB (n=209,147, 0.42%). Out of the ten predefined respiratory viruses, six were identified in at least one participating database, namely influenza virus, adenovirus, SARS-CoV-2, rhinovirus, parainfluenza virus, and metapneumovirus.

RSV co-infection with influenza virus was the most prevalent pattern identified in all the participating databases, with the highest prevalence (per 100,000 persons) observed in EBB (6.69, 95% CI, 3.99 – 11.24) and SIDIAP (6.47, 95% CI, 5.92 – 7.08), followed by IQVIA DA Germany (4.19, 95% CI, 3.98 – 4.42). In contrast, CPRD GOLD reported the lowest prevalence at 0.09 (95% CI, 0.05 – 0.17) per 100,000 persons. RSV co-infection with adenovirus was the second most prevalent RSV co-infection in SIDIAP and IQVIA DA Germany, with prevalence of 2.90 (95% CI, 2.54 – 3.31) and 2.48 (95% CI, 2.31 – 2.66) per 100,000 persons, respectively. RSV co-infection with SARS-Cov-2 was also common in the study population, with a prevalence of 3.00 (95% CI, 2.63 – 3.42) per 100,000 persons in SIDIAP, and 0.25 (95% CI, 0.20 – 0.31) per 100,000 persons in IQVIA DA Germany.

Lower prevalences of RSV co-infection with rhinovirus, parainfluenza virus, and metapneumovirus were observed in at least two databases. The prevalence of RSV-rhinovirus co-infection (per 100,000 persons) was 0.77 (95% CI, 0.60 – 1.00) in SIDIAP, 0.08 (95% CI, 0.05 – 0.12) in IQVIA DA Germany, and 0.06 (95% CI, 0.03 – 0.13) in CPRD GOLD. RSV-parainfluenza co-infection prevalence (per 100,000 persons) ranged from 0.17 (95% CI: 0.13 – 0.22) in IQVIA DA Germany to 0.25 (95% CI: 0.16 – 0.40) in SIDIAP. Lastly, the prevalence of RSV-metapneumovirus co-infection ranged from 0.07 (95% CI: 0.04 – 0.10) per 100,000 persons in IQVIA DA Germany to 0.33 (95% CI: 0.23 – 0.49) per 100,000 persons in SIDIAP.

Table 10. Prevalence of RSV co-infection with other respiratory pathogens in the general population during the study period, per database.

	CPRD GOLD UK		EBB Estonia		IQVIA DA Germany		SIDIAP Spain	
Number of participants, n	9,836,797		209,147		32,302,018		7,506,032	
Number of patients with RSV infection, n	609		258		16,612		23,194	
Number (N), Prevalence of RSV co-infection per 100,000 persons, (95% CI)	N	Estimate	N	Estimate	N	Estimate	N	Estimate
• RSV-SARS-Cov-2	NA	NA	NA	NA	80	0.25 (0.20 – 0.31)	225	3.00 (2.63 – 3.42)
• RSV-Metapneumovirus	0	NA	NA	NA	22	0.07 (0.04 – 0.10)	25	0.33 (0.23 – 0.49)
• RSV-Parainfluenza virus	NA	NA	NA	NA	54	0.17 (0.13 – 0.22)	19	0.25 (0.16 – 0.40)
• RSV-Influenza virus	9	0.09 (0.05 – 0.17)	14	6.69 (3.99 – 11.24)	1,355	4.19 (3.98 – 4.42)	486	6.47 (5.92 – 7.08)
• RSV-Rhinovirus	6	0.06 (0.03 – 0.13)	NA	NA	26	0.08 (0.05 – 0.12)	58	0.77 (0.60 – 1.00)
• RSV-Bocavirus	0	NA	0	NA	0	NA	0	NA
• RSV-Adenovirus	NA	NA	NA	NA	801	2.48 (2.31 – 2.66)	218	2.90 (2.54 – 3.31)
• RSV-Parechovirus	0	NA	0	NA	0	NA	0	NA
• RSV-Coxsackievirus	0	NA	0	NA	NA	NA	0	NA
• RSV-Echovirus	0	NA	0	NA	NA	NA	0	NA

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, DA = Disease Analyzer, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària. NA – Not available or suppressed due to privacy concerns (count < 5).

12.2.2 Co-infection of viral respiratory pathogens in patients with RSV infection

Table 11. Co-infection of viral respiratory pathogens in patients with RSV infection during the study period, per database.

	CPRD GOLD UK	CDW Bordeaux	EBB Estonia	IMASIS Spain	IQVIA DA Germany	SIDIAP Spain
Number of patients with RSV infection, n	609	2,799	258	995	16,612	23,194
Prevalence of co-infection, n (%)						
• RSV-SARS-Cov-2	NA	NA	NA	29 (2.9)	80 (0.5)	225 (1.0)
• RSV-Metapneumovirus	0	25 (0.9)	NA	NA	22 (0.1)	25 (0.1)
• RSV-Parainfluenza virus	NA	12 (0.4)	NA	5 (0.5)	54 (0.3)	19 (0.1)
• RSV-Influenza virus	9 (1.5)	71 (2.5)	14 (5.4)	34 (3.4)	1,355 (8.2)	486 (2.1)
• RSV-Rhinovirus	6 (1.0)	42 (1.5)	NA	43 (4.3)	26 (0.2)	58 (0.3)
• RSV-Bocavirus	0	0	0	16 (1.6)	0	0
• RSV-Adenovirus	NA	21 (0.8)	NA	22 (2.2)	801 (4.8)	218 (0.9)
• RSV-Parechovirus	0	0	0	0	0	0
• RSV-Coxsackievirus	0	0	0	0	NA	0
• RSV-Echovirus	0	0	0	0	NA	0

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, DA = Disease Analyzer, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària. NA – Not available or suppressed due to privacy concerns (count < 5). Hospital databases are indicated in yellow.

The investigation into co-infections of viral respiratory pathogens among patients with recorded RSV infection was conducted within a large cohort of 44,467 individuals across six participating databases. The distribution of patients in each database was as follows: SIDIAP (n=23,194, 52.16%), IQVIA DA Germany (n=16,612, 37.36%), CDW Bordeaux (n=2,799), IMASIS (n=995, 2.24%), CPRD GOLD (n=609, 1.37%), and EBB (n=258, 0.58%).

Across all databases, the proportion of RSV patients with at least one co-infection involving influenza virus, adenovirus, SARS-CoV-2, rhinovirus, parainfluenza virus, metapneumovirus, or bocavirus showed substantial variability, ranging from 0.1% to 8.2%. The most frequently identified viral respiratory pathogen in patients with RSV infection was influenza virus (1.5% – 8.2%), followed by adenovirus (0.8% – 4.8%), and SARS-CoV-2 (0.5% – 2.9%). Additionally, RSV co-infection with rhinovirus (0.2% – 4.3%), parainfluenza virus (0.1% – 0.5%), metapneumovirus (0.1% – 0.9%), and bocavirus (1.6%) were also observed, albeit with much lower prevalences.

IMASIS recorded the highest RSV co-infections with rhinovirus (4.3%), SARS-CoV-2 (2.9%), bocavirus (1.6%), and parainfluenza virus (0.5%). Additionally, it had relatively high prevalence of co-infection with influenza virus (3.4%) and adenovirus (2.2%).

IQVIA DA Germany had the highest prevalence of co-infections with influenza (8.2%) and adenovirus (4.8%) co-infections, but lower prevalences of other co-infections, including SARS-CoV-2 (0.5%), parainfluenza virus (0.3%), rhinovirus (0.2%), and metapneumovirus (0.1%).

In CPRD GOLD, 1.5% of patients with RSV had a co-infection with influenza virus, and 1.0% had a co-infection with rhinovirus. In CDW Bordeaux, diverse co-infections were observed, including 2.5% with influenza virus, 1.5% with rhinovirus, 0.9% with metapneumovirus, 0.8% with adenovirus, and 0.4% with parainfluenza virus. EBB recorded the second-highest rate of RSV co-infection with influenza virus at 5.4%.

In SIDIAP, RSV co-infections were sparse for metapneumovirus (0.1%), parainfluenza virus (0.1%), rhinovirus (0.3%), adenovirus (0.9%), and SARS-CoV-2 (1.0%), except for influenza virus, which had a rate of 2.1%.

12.3 Outcome Rates of RSV Infection

12.3.1 Incidence rate of RSV-related hospitalisation in the general population

Table 12a depicts the incidence rate of RSV-related hospitalisation in the general population during the study period by age groups, per database.

During the study period (2013 – 2022), 20,892 cases of RSV-related hospitalisation were observed among 7,506,032 individuals (children and adults) in SIDIAP with 58,953,564 person-years of follow-up, resulting in an incidence rate of 35.44 (95% CI, 34.96 - 35.92) per 100,000 person-years (PY). The highest incidence of RSV-related hospitalization was observed in infants (≤ 1 year), with a rate of 2,730.25 (95% CI: 2,681.25-2,779.90) per 100,000 PY. Toddlers and preschoolers (1-5 years) also recorded a notable incidence rate at 153.41 (95% CI, 148.78 – 158.15) per 100,000 PY. Older adults (≥ 60 years) had a relatively high incidence rate at 28.09 (95% CI, 27.23 - 28.97) per 100,000 PY, while individuals aged 6 to 17 years had a lower rate at 2.68 (95% CI, 2.32 - 3.09) per 100,000 PY. The lowest incidence was observed among those aged 18 to 59 years, with a rate of 2.06 (95% CI, 1.91 - 2.22) per 100,000 PY.

EBB, which exclusively included adults, reported a lower overall incidence rate of RSV-related hospitalization compared to SIDIAP. Specifically, EBB reported 102 cases of RSV-related hospitalization among 209,147 adults over 1,866,654 person-years of follow-up, representing an incidence rate of 5.46 (95% CI, 4.46 – 6.63) per 100,000 PY. In this adult population, older adults (≥ 60 years) had the highest incidence rate at 17.00 (95% CI, 13.25 - 21.50) per 100,000 PY, whereas younger/middle-aged adults (18 to 59 years) had a lower rate at 2.25 (95% CI, 1.54 - 3.18) per 100,000 PY.

Table 12b details the annual incidence rates of RSV-related hospitalisation in the general population during the study period, per database.

In EBB, the annual RSV-related hospitalization incidence rate remained relatively stable, ranging from 6.72 (95% CI, 3.67–11.27) to 7.80 (95% CI, 4.46–12.66) per 100,000 PY between 2016 and 2021. SIDIAP exhibited a gradual increase in RSV-related hospitalization rates (per 100,000 PY) throughout the study period. Rates rose from 18.16 (95% CI, 17.09-19.28) in 2013 to a peak of 49.78 (95% CI, 48.00-51.61) in 2019, followed by a decrease to 22.81 (95% CI, 21.61-24.05) in 2020. Notably, a higher rate was observed again in 2022 (70.68, 95% CI, 68.56-72.85).

The sensitivity analyses involving laboratory-confirmed cases of RSV infection in EBB (**Table 13a and 13b)** revealed estimates and trends in RSV-related hospitalization that closely mirrored those observed among adults with a broader definition of RSV infection.

Specifically, 98 cases of laboratory-confirmed RSV-related hospitalization were identified during 1,866,675 person-years of observation, resulting in an incidence rate of 5.25 (95% CI, 4.26 - 6.40) per 100,000 PY. Similarly, the highest incidence rate was again observed among older adults, with a rate of 16.52 (95% CI, 12.82 – 20.94) per 100,000 PY, while individuals aged 18-59 years experienced a significantly lower incidence rate of 2.11 (95% CI, 1.43 – 3.02) per 100,000 PY.

Also, substantial peaks in the incidence rate of laboratory-confirmed RSV-related hospitalization were discernible in 2018 (10.63, 95% CI, 6.66 – 16.09) and 2020 (9.68, 95% CI, 5.91 – 14.96), surpassing both the overall rate and rates observed in the subsequent years.

Table 12a. Incidence rate of RSV-related hospitalisation in the general population during the study period, per age group and database.

	No. of patients with RSV infection, n (%)	No. of RSV-related hospitalisation	Person-years (PY)	Incidence rate per 100,000 PY (95% CI)
EBB, Estonia	**258**	**102**	**1,866,654**	**5.46 (4.46 – 6.63)**
• < 1 year	NA	NA	NA	NA
• 1 to 5 years	NA	NA	NA	NA
• 6 to 17 years	NA	NA	NA	NA
• 18 to 59 years	129 (50.00)	32	1,419,120	2.25 (1.54 – 3.18)
• ≥ 60 years	129 (50.00)	70	411,740	17.00 (13.25 – 21.50)
SIDIAP, Spain	**23,194**	**20,892**	**58,953,564**	**35.44 (34.96 – 35.92)**
• < 1 year	15,775 (68.01)	11,825	433,112	2,730.25 (2,681.25 – 2,779.90)
• 1 to 5 years	2,035 (8.77)	4,149	2,704,553	153.41 (148.78 – 158.15)
• 6 to 17 years	247 (1.06)	195	7,264,239	2.68 (2.32 – 3.09)
• 18 to 59 years	1,012 (4.36)	706	34,250,815	2.06 (1.91 – 2.22)
• ≥ 60 years	4,125 (17.78)	4,017	14,300,844	28.09 (27.23 – 28.97)

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, DA = Disease Analyzer, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària. NA – Not available or suppressed due to privacy concerns (count < 5).

Table 12b. Annual incidence rates of RSV-related hospitalisation in the general population during the study period, per database.

Database	No. of RSV-related hospitalisation	Person-years (PY)	Incidence rate per 100,000 PY (95% CI)
EBB, Estonia	**102**	**1,866,654**	**5.46 (4.46 – 6.63)**
• 2013	0	208,842	NA
• 2014	NA	208,490	NA
• 2015	NA	208,162	NA
• 2016	14	208,361	6.72 (3.67 – 11.27)
• 2017	10	207,414	4.82 (2.31 – 8.87)
• 2018	22	207,039	10.63 (6.66 – 16.09)
• 2019	14	206,557	6.78 (3.71 – 11.37)
• 2020	20	206,532	9.68 (5.92 – 14.96)
• 2021	16	205,257	7.80 (4.46 – 12.66)
• 2022	NA	NA	NA
SIDIAP, Spain	**20,892**	**58,953,564**	**35.44 (34.96 – 35.92)**
• 2013	1,071	5,898,767	18.16 (17.09 – 19.28)
• 2014	1,259	5,878,860	21.42 (20.25 – 22.63)
• 2015	1,650	5,832,475	28.29 (26.94 – 29.69)
• 2016	2,043	5,849,345	34.93 (33.43 – 36.48)
• 2017	2,089	5,848,873	35.72 (34.20 – 37.28)
• 2018	2,229	5,876,503	37.93 (36.37 – 39.54)
• 2019	2,946	5,917,793	49.78 (48.00 – 51.61)
• 2020	1,360	5,962,381	22.81 (21.61 – 24.05)

Database	No. of RSV-related hospitalisation	Person-years (PY)	Incidence rate per 100,000 PY (95% CI)
• 2021	2,040	5,939,385	34.35 (32.87 – 35.87)
• 2022	4,205	5,949,180	70.68 (68.56 – 72.85)

CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, DA = Disease Analyzer, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària. NA – Not available or suppressed due to privacy concerns (count < 5).

Table 13a. Incidence rate of lab-confirmed RSV-related hospitalisation in the adult population during the study period by age group.

	No. of patients with lab-confirmed RSV infection n (%)	No. of lab-confirmed RSV-related hospitalisation	Person-years (PY)	Incidence rate per 100,000 PY (95% CI)
EBB, Estonia	**184**	**98**	**1,866,675**	**5.25 (4.26 – 6.40)**
• < 1 year	NA	NA	NA	NA
• 1 to 5 years	NA	NA	NA	NA
• 6 to 17 years	NA	NA	NA	NA
• 18 to 59 years	84	30	1,419,133	2.11 (1.43 – 3.02)
• ≥ 60 years	100	68	411,747	16.52 (12.82 – 20.94)

EBB = Estonian Biobank. NA – Not available or suppressed due to privacy concerns (count < 5)

Table 13b. Annual incidence rate of lab-confirmed RSV-related hospitalisation in the adult population during the study period.

Database	No. of lab-confirmed RSV-related hospitalisation	Person-years (PY)	Incidence rate per 100,000 PY (95% CI)
EBB, Estonia	**98**	**1,866,675**	**5.25 (4.26 – 6.40)**
• 2013	0	208,842	NA
• 2014	NA	208,490	NA
• 2015	NA	208,163	NA
• 2016	12	208,361	5.76 (2.98 – 10.06)
• 2017	10	207,417	4.82 (2.31 – 8.87)
• 2018	22	207,041	10.63 (6.66 – 16.09)
• 2019	14	206,560	6.78 (3.71 – 11.37)
• 2020	20	206,535	9.68 (5.91 – 14.96)
• 2021	15	205,260	7.31 (4.09 – 12.05)
• 2022	NA	NA	NA

EBB = Estonian Biobank. NA – Not available or suppressed due to privacy concerns (count < 5).

12.3.2 Incidence of RSV-related hospitalisation in hospital settings

Table 14a. Incidence of RSV-related hospitalisation in hospital settings during the study period, per age group and database.

Database	No. of patients with RSV-related hospitalisation	Total no. of persons hospitalised	Incidence per 100,000 hospitalised persons (95% CI)
CDW Bordeaux, France	**2,736**	**997,644**	**274 (264 – 285)**
• < 1 year	2,054	95,142	2,159 (2,068 – 2,253)
• 1 to 5 years	298	74,790	398 (356 – 446)
• 6 to 17 years	39	106,868	36 (27 – 50)
• 18 to 59 years	106	468,417	23 (19 – 27)
• ≥ 60 years	239	252,427	95 (83 – 108)
IMASIS, Spain	**936**	**513,112**	**182 (171 – 195)**
• < 1 year	363	15,434	2,352 (2,124 – 2603)
• 1 to 5 years	159	17,554	906 (776 – 1,057)
• 6 to 17 years	<5	32,108	12 (5 – 32)
• 18 to 59 years	102	343,664	30 (24 – 36)
• ≥ 60 years	308	104,352	295 (264 – 330)

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System

Table 14a presents a comprehensive overview of the incidence of RSV-related hospitalization across different age groups within both the CDW Bordeaux, France, and Estonian Biobank databases. In hospital settings, a minority of patients, comprising 0.24% (n=3,672) of the total 1,510,774 hospitalized individuals during the study period, had a record of RSV infection. Among 997,658 hospitalized patients in CDW Bordeaux, 2,736 cases of RSV infection were recorded, indicating an incidence of 274 (95% CI, 264 - 285) cases of RSV-related hospitalisation per 100,000 hospitalized patients. Of 513,112 hospitalized patients in IMASIS, 936 had recorded RSV infection, suggesting an incidence of 182 (95% CI, 171 - 195) cases of RSV-related hospitalisation per 100,000 hospitalized patients.

In CDW Bordeaux, the highest incidence of RSV-related hospitalization per 100,000 hospitalized persons was notably observed in infants (2,159, 95% CI, 2,068 – 2,253) and those aged 1 to 5 years (398, 95% CI, 356 – 446). Older adults (≥ 60 years) had a relatively high incidence (95, 95% CI, 83 - 108), while individuals aged 6 to 17 years had a lower incidence (36, 95% CI, 27 - 50). The lowest incidence was recorded among those aged 18 to 59 years (23, 95% CI, 19 - 27).

In IMASIS, a comparable age-dependent pattern was observed with highest rates reported in infants below 1 year (2,352, 95% CI, 2,124 – 2,603) and children aged 1 – 5 years (906, 95% CI, 776 – 1,057). Older adults (≥ 60 years) had a relatively high incidence (295, 95% CI, 264 – 330), while individuals aged 18 to 59 years had a lower rate (30, 95% CI, 24 – 36). The lowest incidence was recorded among those aged 6 to 17 years (12, 95% CI, 5 – 32).

Approximately one-third (33%, n=1,228) of patients with recorded diagnosis of RSV infection in hospital settings (n=3,672) had their diagnosis confirmed via laboratory testing (**Table 14b**). In CDW Bordeaux, 730 cases of laboratory confirmed RSV infection were reported among 997,658 hospitalized patients, resulting in an incidence rate of 73 (95% CI, 68-79) cases per 100,000 hospitalized patients. In IMASIS, 498 cases of RSV infection were reported among 513,116 hospitalized patients, representing an incidence rate of 97 (95% CI, 89 - 106) cases per 100,000 hospitalized patients.

The age-specific incidence of laboratory-confirmed RSV-related hospitalization (per 100,000 hospitalized persons) in CDW Bordeaux mirrored the trends observed in broadly defined cases. Notably, infants (487, 95% CI, 444 – 533), toddlers/preschoolers (147, 95% CI, 122 – 177), and older adults (33, 95% CI, 27 – 41) accounted for the highest number of cases of laboratory-confirmed RSV-related hospitalization among hospitalized persons. In contrast, the lowest incidence was observed among those aged 6 to 17 years (22, 95% CI, 14 – 32) as well as among those aged 18 to 59 years (11, 95% CI, 8 – 14).

In IMASIS, the highest incidence of laboratory-confirmed RSV-related hospitalization (per 100,000 hospitalized persons) occurred in infants below 1 year (1,244, 95% CI, 1,081 – 1,431), followed by children aged 1 – 5 years (444, 95% CI, 356 – 554), and adults aged ≥ 60 years (148, 95% CI, 126 – 173). Lowest rates were recorded in adults aged 18 – 59 years (21, 95% CI, 17 – 27), and in children aged 6 – 17 years (3, 95% CI, 1 – 18).

Table 14b. Incidence of laboratory-confirmed RSV-related hospitalisation in hospital settings during the study period, per age group and database.

Database	No. of patients with lab-confirmed RSV-related hospitalisation	Total no. of persons hospitalised	Incidence per 100,000 hospitalised persons (95% CI)
CDW Bordeaux, France	**730**	**997,644**	**73 (68 – 79)**
• < 1 year	463	95,142	487 (444 – 533)
• 1 to 5 years	110	74,790	147 (122 – 177)
• 6 to 17 years	23	106,868	22 (14 – 32)
• 18 to 59 years	51	468,417	11 (8 – 14)
• ≥ 60 years	83	252,427	33 (27 – 41)
IMASIS, Spain	**498**	**513,112**	**97 (89 – 106)**
• < 1 year	192	15,434	1,244 (1,081 – 1,431)
• 1 to 5 years	78	17,554	444 (356 – 554)
• 6 to 17 years	<5	32,108	3 (1 – 18)
• 18 to 59 years	73	343,664	21 (17 – 27)
• ≥ 60 years	154	104,352	148 (126 – 173)

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System.

Table 14c presents the annual incidence of RSV-related hospitalization during the study period, categorized by database (CDW Bordeaux, France, and IMASIS, Spain). The table includes the number of patients with RSV-related hospitalization, the total number of persons hospitalized, and the incidence per 100,000 hospitalized persons with corresponding 95% confidence intervals (95% CI) for each year.

Within CDW Bordeaux, a sharp increase in RSV-related hospitalization incidence per 100,000 hospitalized persons was observed between 2013 (79, 95% CI, 66 – 94) and 2014 (121, 95% CI, 108 – 136). Subsequently, the rates stabilized from 2015 (203, 95% CI, 187 – 220) to 2020 (196, 95% CI, 183 – 211), with substantial peaks in 2021 (326, 95% CI, 309 – 345) and 2022 (452, 95% CI, 431 – 475).

In the IMASIS database, there was a consistent increase in the incidence of RSV-related hospitalization per 100,000 hospitalized persons from 2013 (44, 95% CI, 32 – 59) to 2021 (187, 95% CI, 167 – 209), with 2022 reaching the highest incidence at 391 (95% CI, 362 – 423) per 100,000 hospitalized persons.

In summary, a discernible pattern emerged from the overall trend within the hospital databases, indicating a progressive rise in the incidence of RSV-related hospitalization over the study years.

Table 14c. Annual incidence of RSV-related hospitalisation during the study period, per database.

Database	No. of patients with RSV-related hospitalisation	Total no. of persons hospitalised	Incidence per 100,000 hospitalised persons (95% CI)
CDW Bordeaux, France			
• 2013	123	155855	79 (66 – 94)
• 2014	291	239638	121 (108 – 136)
• 2015	604	297844	203 (187 – 220)
• 2016	688	344209	200 (186 – 215)
• 2017	760	380012	200 (186 – 215)
• 2018	769	404021	190 (177 – 204)
• 2019	871	417467	209 (195 – 223)
• 2020	791	402548	196 (183 – 211)
• 2021	1273	389923	326 (309 – 345)
• 2022	1631	360693	452 (431 – 475)
IMASIS, Spain			
• 2013	40	91819	44 (32 – 59)
• 2014	66	124584	53 (42 – 67)
• 2015	100	146889	68 (56 – 83)
• 2016	146	157624	93 (79 – 109)
• 2017	173	166402	104 (90 – 121)
• 2018	215	174526	123 (108 – 141)
• 2019	304	176319	172 (154 – 193)
• 2020	289	161768	179 (159 – 200)
• 2021	308	164657	187 (167 – 209)
• 2022	627	160231	391 (362 – 423)

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System.

Consistent patterns emerged in the annual incidence of laboratory-confirmed RSV-related hospitalization throughout the study period, as detailed in **Table 14d**. In CDW Bordeaux, the available data suggests

relatively stable rates from 2019 to 2021, with a peak incidence of 177 per 100,000 hospitalized persons in 2022 (95% CI, 164 – 192). IMASIS data revealed a continuous upward trend over the study duration, culminating in a peak incidence of 212 per 100,000 hospitalized persons in 2022 (95% CI, 190 – 235).

Table 14d. Annual incidence of laboratory-confirmed RSV-related hospitalisation during the study period, per database.

Database	No. of patients with lab-confirmed RSV-related hospitalisation	Total no. of persons hospitalised	Incidence per 100,000 hospitalised persons (95% CI)
CDW Bordeaux, France			
• 2013	NA	155855	NA
• 2014	NA	239638	NA
• 2015	NA	297844	NA
• 2016	NA	344209	NA
• 2017	NA	380012	NA
• 2018	NA	404021	NA
• 2019	118	417467	28 (24 – 34)
• 2020	178	402548	44 (38 – 51)
• 2021	145	389923	37 (32 – 44)
• 2022	640	360693	177 (164 – 192)
IMASIS, Spain			
• 2013	30	91819	33 (23 – 47)
• 2014	57	124584	46 (35 – 59)
• 2015	87	146889	59 (48 – 73)
• 2016	130	157624	82 (69 – 98)
• 2017	154	166402	93 (79 – 108)
• 2018	172	174526	99 (85 – 114)
• 2019	166	176319	94 (81 – 110)
• 2020	137	161768	85 (72 – 100)
• 2021	117	164657	71 (59 – 85)
• 2022	339	160231	212 (190 – 235)

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System. NA – Not available or suppressed due to privacy concerns (count < 5).

12.3.3 Prevalence of RSV-related ICU admissions

Table 15a outlines the prevalence of ICU admissions among patients with RSV infection during the study period, per database.

Among 2,736 patients with RSV-related hospitalisation in CDW Bordeaux, 1,022 required admissions to the intensive care unit (ICU), indicating an RSV-related ICU admission prevalence of 37.35% (95% CI, 35.56% – 39.18%). Age-stratified analysis revealed moderate variations in ICU admission rates. The highest prevalence was observed in infants <1 year old (803 ICU admissions/2,054 hospitalizations; 39.09%, 95% CI, 37.00-41.22), followed by the ≥ 60 years group (87 ICU admissions/239 hospitalizations; 36.40%, 95% CI, 30.56-42.67), and 18-59 years group (37 ICU admissions/106 hospitalizations; 34.91%, 95% CI, 26.50-44.36). Slightly lower prevalences were observed in the 1-5 years group (79 ICU admissions/298 hospitalizations; 26.51%, 95% CI, 21.82-31.80), and 6-17 years group (14 ICU admissions/39 hospitalizations; 35.90%, 95% CI, 22.74-51.58).

In IMASIS, 10 out of 936 patients with RSV-related hospitalisation were admitted to the ICU, resulting in an RSV-related ICU admission prevalence of 1.07% (95% CI, 0.58% – 1.96%). Due to data limitations, further age-stratified analysis was not feasible. However, for the 18-59 year age group, where data was sufficient, 6 ICU admissions occurred out of 102 hospitalizations, resulting a prevalence of 5.88% (95% CI, 2.72% - 12.24%).

Table 15a. Prevalence of RSV-related ICU admissions during the study period, per age group and database.

Database	No. of patients with RSV-related ICU admission, n	No. of patients with RSV-related hospitalisation, n	Prevalence of RSV-related ICU admissions (%), (95% CI)
CDW Bordeaux, France	**1,022**	**2,736**	**37.35 (35.56 – 39.18)**
• < 1 year	803	2,054	39.09 (37.00 – 41.22)
• 1 to 5 years	79	298	26.51 (21.82 – 31.80)
• 6 to 17 years	14	39	35.90 (22.74 – 51.58)
• 18 to 59 years	37	106	34.91 (26.50 – 44.36)
• ≥ 60 years	87	239	36.40 (30.56 – 42.67)
IMASIS, Spain	**10**	**936**	**1.07 (0.58 – 1.96)**
• < 1 year	0	363	NA
• 1 to 5 years	0	159	NA
• 6 to 17 years	0	<5	NA
• 18 to 59 years	6	102	5.88 (2.72 – 12.24)
• ≥ 60 years	<5	308	NA

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System. NA – Not available or suppressed due to privacy concerns (count < 5).

As shown in **Table 15b** below, the results of the sensitivity analysis, restricted to lab-confirmed RSV cases, closely mirrored the findings observed in the primary analysis that included RSV diagnostic codes. There were discernible age-specific differences in ICU admission rates. Among 730 patients with RSV-related hospitalisation in CDW Bordeaux, 298 required ICU admission, reflecting an RSV-related ICU admission prevalence of 40.82% (95% CI, 37.31% – 44.43%). The highest prevalence was observed in infants <1 year old (217 ICU admissions/463 hospitalizations; 46.87%, 95% CI, 42.36 – 51.42), followed by the ≥60 years group

(33 ICU admissions/83 hospitalizations; 39.76%, 95% CI, 29.91 – 50.52). Moderately lower prevalences were seen in the 1-5 years group (26 ICU admissions/110 hospitalizations; 23.64%, 95% CI, 16.67 – 32.38), 6-17 years group (6 ICU admissions/23 hospitalizations; 26.09%, 95% CI, 12.55 – 46.47), and 18-59 years group (16 ICU admissions/51 hospitalizations; 31.37%, 95% CI, 20.33 – 45.03).

Among 498 patients with RSV-related hospitalisation in IMASIS, 6 had ICU admission, resulting in an RSV-related ICU admission prevalence of 1.20% (95% CI, 0.55% – 2.60%).

Table 15b. Prevalence of laboratory-confirmed RSV-related ICU admissions during the study period, per age group and database.

Database	No. of patients with lab-confirmed RSV-related ICU admission, n	No. of patients with lab-confirmed RSV-related hospitalisation, n	Prevalence of lab-confirmed RSV-related ICU admissions (%), (95% CI)
CDW Bordeaux, France	**298**	**730**	**40.82 (37.31 – 44.43)**
• < 1 year	217	463	46.87 (42.36 – 51.42)
• 1 to 5 years	26	110	23.64 (16.67 – 32.38)
• 6 to 17 years	6	23	26.09 (12.55 – 46.47)
• 18 to 59 years	16	51	31.37 (20.33 – 45.03)
• ≥ 60 years	33	83	39.76 (29.91 – 50.52)
IMASIS, Spain	**6**	**498**	**1.20 (0.55 – 2.60)**
• < 1 year	0	192	NA
• 1 to 5 years	0	78	NA
• 6 to 17 years	<5	<5	NA
• 18 to 59 years	<5	73	NA
• ≥ 60 years	NA	154	NA

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System. NA – Not available or suppressed due to privacy concerns (count < 5).

Table 15c presents data on the annual prevalence of RSV-related ICU admissions in CDW Bordeaux, France, over a ten-year period. A marked and upward trend in the prevalence of RSV-related ICU admissions was observed in CDW Bordeaux between 2013 and 2022, almost tripling from 13.82% in 2013 to 38.44% in 2022. Notably, 2019 and 2020 had the highest prevalence, both exceeding 40%, indicating a substantial burden during these years. Due to limited data, the annual prevalence of RSV-related ICU admissions in IMASIS was not described.

The results of the sensitivity analysis, restricted to lab-confirmed RSV cases (**Table 15d**) align closely with the primary analysis that included broader RSV diagnostic codes. Notably, 2019 and 2020 exhibited the highest annual prevalence of RSV-related ICU admissions in CDW Bordeaux, with rates of 61.86% (95% CI: 52.86 - 70.12) and 52.47% (95% CI: 44.93 - 59.46), respectively. Both figures surpassed the prevalence observed in 2021 (49.66%, 95% CI: 41.63 - 57.70) and 2022 (38.59%, 95% CI: 34.90 - 42.42

Table 15c. Annual prevalence of RSV-related ICU admissions during the study period, per database.

Database	No. of patients with RSV-related ICU admission, n	No. of patients with RSV-related hospitalisation, n	Prevalence of RSV-related ICU admissions (%), (95% CI)
CDW Bordeaux, France			
• 2013	17	123	13.82 (8.80 – 21.02)
• 2014	45	291	15.46 (11.76 – 20.07)
• 2015	111	604	18.38 (15.49 – 21.66)
• 2016	146	688	21.22 (18.33 – 24.43)
• 2017	221	760	29.08 (25.96 – 32.41)
• 2018	266	769	34.59 (31.31 – 38.02)
• 2019	352	871	40.41 (37.20 – 43.71)
• 2020	318	791	40.20 (36.84 – 43.66)
• 2021	475	1,273	37.31 (34.70 – 40.00)
• 2022	627	1,631	38.44 (36.11 – 40.83)
IMASIS, Spain			
• 2013	NA	40	NA
• 2014	NA	66	NA
• 2015	NA	100	NA
• 2016	NA	146	NA
• 2017	NA	173	NA
• 2018	NA	215	NA
• 2019	NA	304	NA
• 2020	NA	289	NA
• 2021	NA	308	NA
• 2022	NA	627	NA

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System. NA – Not available or suppressed due to privacy concerns (count < 5).

Table 15d. Annual incidence of laboratory-confirmed RSV-related hospitalisation during the study period, per database.

Database	No. of patients with lab-confirmed RSV-related ICU admission, n	No. of patients with lab-confirmed RSV-related hospitalisation, n	Prevalence of lab-confirmed RSV-related ICU admissions (%), (95% CI)
CDW Bordeaux, France			
• 2013	NA	NA	NA
• 2014	NA	NA	NA
• 2015	NA	NA	NA
• 2016	NA	NA	NA
• 2017	NA	NA	NA
• 2018	NA	NA	NA
• 2019	73	118	61.86 (52.86 – 70.12)
• 2020	93	178	52.47 (44.93 – 59.46)
• 2021	72	145	49.66 (41.63 – 57.70)
• 2022	247	640	38.59 (34.90 – 42.42)
IMASIS, Spain			
• 2013	NA	NA	NA
• 2014	NA	NA	NA
• 2015	NA	NA	NA
• 2016	NA	NA	NA
• 2017	NA	NA	NA
• 2018	NA	NA	NA
• 2019	NA	NA	NA
• 2020	NA	NA	NA
• 2021	NA	NA	NA
• 2022	NA	NA	NA

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System. NA – Not available or suppressed due to privacy concerns (count < 5).

12.4 Duration of RSV-related hospitalisation

Table 16a outlines the duration of RSV-related hospitalisation among patients with RSV infection during the study period, per database.

The overall median duration of RSV-related hospitalisation ranged from 1 day in IMASIS to 2 days in CDW Bordeaux. Interestingly, both databases observed the longest median durations in infants under 1 year old (4 days in CDW Bordeaux, 2 days in IMASIS) and adults aged 60 and above (5 days in CDW Bordeaux, 1 day in IMASIS). While both databases show similar trends, they differ in specific lengths of stay. CDW Bordeaux generally reported longer median durations, particularly for older adults (5 days compared to 1 day in IMASIS).

In CDW Bordeaux, the highest median duration occurred in the ≥ 60 years age group (5 days), followed by the < 1 year age group (4 days), and the 18 to 59 years age group (4 days). Children aged 1 to 5 years had a comparatively shorter median duration of 1 day, while the 6 to 17 years age group primarily had short emergency room visits (median duration of 0 days).

Similarly, within IMASIS, the longest median duration of RSV-related hospitalization was observed among patients below 1 year (2 days) and those aged ≥ 60 years (1 day). The remaining age groups mostly had short emergency room visits (median duration of 0 days).

While both databases showed similar trends, they differed in specific lengths of hospital stay. CDW Bordeaux generally reported longer median durations, particularly for older adults (5 days compared to 1 day in IMASIS).

Table 16a. Duration of RSV-related hospitalisation during the study period, per age group and database.

Database	No. of patients with RSV-related hospitalisation	Duration of RSV-related hospital visits (days)		
		Median (IQR)	Minimum	Maximum
CDW Bordeaux, France	**2,736**	**2 (0 – 6)**	**0**	**811**
• < 1 yr	2,054	4 (2 – 6)	0	175
• 1 to 5 yrs	298	1 (0 – 3)	0	469
• 6 to 17 yrs	39	0 (0 – 3)	0	337
• 18 to 59 yrs	106	4 (1 – 14)	0	363
• ≥ 60 yrs	239	5 (1 – 11)	0	811
IMASIS, Spain	**936**	**1 (0 – 3)**	**0**	**191**
• < 1 yr	363	2 (1 – 3)	0	28
• 1 to 5 yrs	159	0 (0 – 1)	0	22
• 6 to 17 yrs	<5	0 (0 – 0)	0	4
• 18 to 59 yrs	102	0 (0 – 1)	0	145
• ≥ 60 yrs	308	1 (0 – 5)	0	191

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System. Note that zero days of hospitalization indicate emergency room visits without an overnight stay.

Table 16b shows the duration of RSV-related hospitalisation among patients with laboratory-confirmed RSV infection during the study period, per database. In summary, the overall median duration of RSV-related hospitalization ranged from short emergency room visits (0 days) in IMASIS to 3 days in CDW Bordeaux.

Notably, the results of this sensitivity analysis mirrored trends observed in the broader category of RSV infection cases (**Table 16a**). Specifically, both databases identified the longest median durations in infants under 1 year old (4 days in CDW Bordeaux, 2 days in IMASIS) and adults aged 60 and above (4 days in CDW Bordeaux, 1 day in IMASIS).

In CDW Bordeaux, the highest median duration RSV-related hospitalisation (4 days) was recorded among infants under 1 year old, patients aged 6 to 17 years, and older adults (≥ 60 years). Adults aged 18 to 59 years had a slightly shorter median duration of 3 day, while the 1 to 5 years age group had the shortest median duration of 1 day.

In IMASIS, the longest median duration of RSV-related hospitalization was observed among patients below 1 year (2 days) and those aged ≥ 60 years (1 day). The remaining age groups mostly had short emergency room visits (median duration of 0 days).

While both databases demonstrated similar age-related trends, they differed in specific lengths of hospital stay, with CDW Bordeaux consistently reporting longer durations compared to IMASIS.

Table 16b. Duration of laboratory-confirmed RSV-related hospitalisation during the study period, per age group and database.

Database	No. of patients with lab-confirmed RSV-related hospitalisation	Duration of lab-confirmed RSV-related hospital visits (days)		
		Median (IQR)	Minimum	Maximum
CDW Bordeaux, France	**730**	**3 (1 – 7)**	**0**	**811**
• < 1 yr	463	4 (2 – 6)	0	141
• 1 to 5 yrs	110	1 (0 – 3)	0	469
• 6 to 17 yrs	23	4 (0 – 60)	0	334
• 18 to 59 yrs	51	3 (0 – 10)	0	346
• ≥ 60 yrs	83	4 (1 – 12)	0	811
IMASIS, Spain	**498**	**0 (0 – 2)**	**0**	**145**
• < 1 yr	192	2 (1 – 4)	1	23
• 1 to 5 yrs	78	0 (0 – 1)	0	15
• 6 to 17 yrs	<5	0 (0 – 0)	0	4
• 18 to 59 yrs	73	0 (0 – 1)	0	145
• ≥ 60 yrs	154	1 (0 – 4)	0	96

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System. Note that zero days of hospitalization indicate emergency room visits without an overnight stay.

Table 16c provides insights into the temporal trends of RSV-related hospitalization duration across two databases (CDW Bordeaux, France, and IMASIS, Spain) during the study period. The overall median duration

of RSV-related hospitalization remained moderately stable over the year, ranging from 1 – 4 days in 2013 to 2 days in 2022.

In CDW Bordeaux, a slight downward trend in the median duration of RSV-related hospitalization was observed between 2013 (4 days) and 2022 (2 days). The median duration was consistently reported at 3 days in 2014, 2015, 2017, 2019, and 2012. In 2016, 2018, 2020, and 2022, a median duration of 2 days was recorded. Contrastingly, the median duration of RSV-related hospitalization in IMASIS remained remarkably stable at 1 day from 2013 to 2021, except for 2022 (2 days).

Table 16c. Duration of RSV-related hospitalisation during the study period, per calendar year and database.

Database	No. of patients with RSV-related hospitalisation	Duration of RSV-related hospital visits (days)		
		Median (IQR)	Minimum	Maximum
CDW Bordeaux, France				
• 2013	123	4 (2 – 7)	0	329
• 2014	291	3 (1 – 6)	0	354
• 2015	604	3 (1 – 6)	0	175
• 2016	688	2 (0 – 6)	0	758
• 2017	760	3 (0 – 6)	0	224
• 2018	769	2 (0 – 7)	0	811
• 2019	871	3 (0 – 7)	0	337
• 2020	791	2 (0 – 6)	0	604
• 2021	1,273	3 (1 – 5)	0	361
• 2022	1,631	2 (1 – 5)	0	469
IMASIS, Spain				
• 2013	40	1 (0 – 3)	0	39
• 2014	66	1 (0 – 4)	0	96
• 2015	100	1 (0 – 2)	0	40
• 2016	146	1 (0 – 3)	0	70
• 2017	173	1 (0 – 3)	0	153
• 2018	215	1 (0 – 3)	0	58
• 2019	304	1 (0 – 4)	0	191
• 2020	289	1 (0 – 5)	0	74
• 2021	308	1 (0 – 3)	0	158
• 2022	627	2 (0 – 5)	0	90

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System. Note that zero days of hospitalization indicate emergency room visits without an overnight stay.

Table 16d provides insights into the temporal trends of RSV-related hospitalization duration in patients with laboratory confirmed RSV infection across two databases (CDW Bordeaux, France, and IMASIS, Spain) during the study period. Median hospitalization duration varied, ranging from 0 days (short emergency room visits) to 5 days across both databases.

In CDW Bordeaux, the median duration of RSV-related hospitalization fluctuated between 2 – 5 days. The longest duration of 5 days was observed in both 2014 and 2019, while the shortest duration of 2 days occurred in 2015, 2018, and 2021. In 2013, 2020, and 2022, a median duration of 4 days was reported, with durations of 3 days noted in 2016 and 2017.

Conversely, IMASIS demonstrated a more stable trend in the median duration of RSV-related hospitalization, fluctuating between 0 and 2 days. Consistently, a median duration of 1 day was observed from 2013 to 2017. Subsequent years, spanning 2018 to 2020, had short emergency room visits with a median duration of 0 days. Notably, a median duration of 1 day was observed in 2021, and this increased to 2 days in 2022.

Table 16d. Duration of laboratory-confirmed RSV-related hospitalisation during the study period, per calendar year and database.

Database	No. of patients with lab-confirmed RSV-related hospitalisation	Duration of lab-confirmed RSV-related hospital visits (days)		
		Median (IQR)	Minimum	Maximum
CDW Bordeaux, France				
2013	NA	4 (1 – 7)	0	329
2014	NA	5 (1 – 18)	0	354
2015	NA	2 (0 – 8)	0	79
2016	NA	3 (1 – 10)	0	758
2017	NA	3 (1 – 6)	0	77
2018	NA	2 (1 – 8)	0	811
2019	118	5 (3 – 10)	0	203
2020	178	4 (1 – 9)	0	604
2021	145	2 (0 – 7)	0	349
2022	640	4 (2 – 7)	0	469
IMASIS, Spain				
2013	30	1 (0 – 3)	0	14
2014	57	1 (0 – 3)	0	96

Database	No. of patients with lab-confirmed RSV-related hospitalisation	Duration of lab-confirmed RSV-related hospital visits (days)		
		Median (IQR)	Minimum	Maximum
2015	87	1 (0 – 2)	0	29
2016	130	1 (0 – 4)	0	23
2017	154	1 (0 – 2)	0	23
2018	172	0 (0 – 1)	0	29
2019	166	0 (0 – 2)	0	23
2020	137	0 (0 – 3)	0	66
2021	117	1 (0 – 2)	0	32
2022	339	2 (0 – 6)	0	89

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, IMASIS = Institut Municipal Assistencia Sanitaria Information System. Note that zero days of hospitalization indicate emergency room visits without an overnight stay.

12.5 Mortality rates among patients with RSV infection

Table 17a and Figures 2 – 6 depict the mortality rates among patients with RSV infection during the study period, per timelines, age groups, and database.

The study identified 354 deaths (1.3%) among 26,988 patients within 30 days of recorded diagnosis of RSV infection.

Mortality rates within 30 days of RSV diagnosis varied across databases, with the highest rates observed in Spain, specifically 18.1 per 1,000 patients with recorded diagnosis of RSV in IMASIS and 13.1 per 1,000 patients in SIDIAP. CDW Bordeaux, France, reported a lower rate of 11.8 per 1,000 patients.

Due to privacy reasons, the number of deaths within 30 days of RSV infection in the paediatric population across the participating databases was either zero or less than five, precluding the calculation of a mortality rate in this group.

In the adult population, age-specific mortality rates were notably higher in older adults (≥ 60 years) compared to young and middle-aged adults (18 to 59 years). The 30-day mortality rate of patients with RSV infection in CDW Bordeaux was 90.2 per 1,000 patients in older adults, compared to a substantially lower rate of 48.9 per 1,000 patients in young and middle-aged adults. Similarly, the 30-day mortality rate in SIDIAP was 69.9 per 1,000 patients in older adults, compared to 12.9 per 1,000 patients in young and middle-aged adults.

In IMASIS, the 30-day mortality rate observed in older adults was 50.3 per 1,000 patients, nearly three times higher than the rates in the general population (18.1 per 100,000 patients).

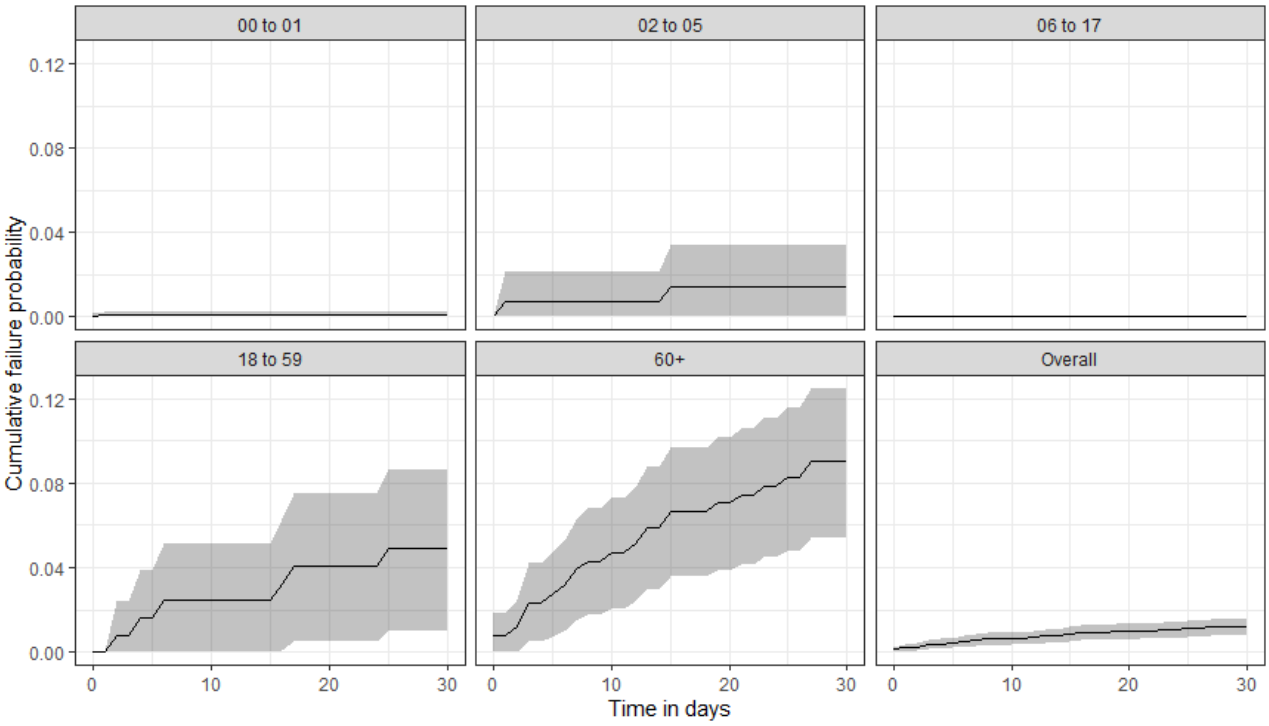

Figure 2. Cumulative Survival Probability in CDW Bordeaux

Table 17a. Mortality rates among patients with RSV infection during the study period, per timelines and database.

	CPRD GOLD UK	CDW France	EBB Estonia	IMASIS Spain	SIDIAP Spain
Number of patients with RSV infection, n	609	2,799	258	995	23,194
Number of deaths within 30 days of RSV diagnosis	<5	33	<5	18	303
• Paediatric population (< 18 years)	<5	<5	0	0	<5
• Adult population (≥ 18 years)	<5	29	<5	18	301
30-day mortality rate per 1,000 patients with RSV infection	**NA**	**11.8**	**NA**	**18.1**	**13.1**
• < 1 year	NA	NA	NA	NA	NA
• 1 to 5 years	NA	NA	NA	NA	NA
• 6 to 17 years	NA	NA	NA	NA	NA
• 18 to 59 years	NA	48.9	NA	NA	12.9
• ≥ 60 years	NA	90.2	NA	50.3	69.9

CDW France = Clinical Data Warehouse of Bordeaux University Hospital, CPRD GOLD = Clinical Practice Research Datalink GOLD, EBB = Estonian Biobank, DA = Disease Analyzer, IMASIS = Institut Municipal Assistencia Sanitaria Information System, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària.. NA: Not applicable as numbers are too low. Hospital databases are indicated in yellow.

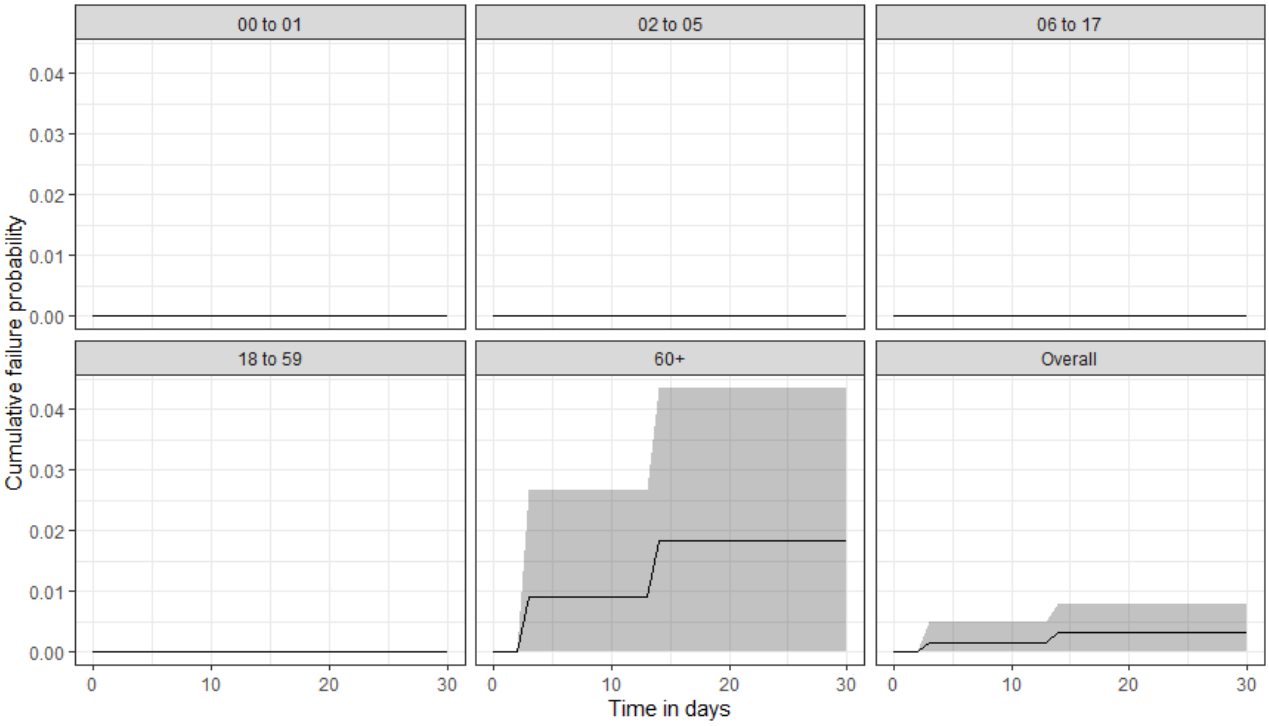

Figure 3. Cumulative Survival Probability in CPRD GOLD

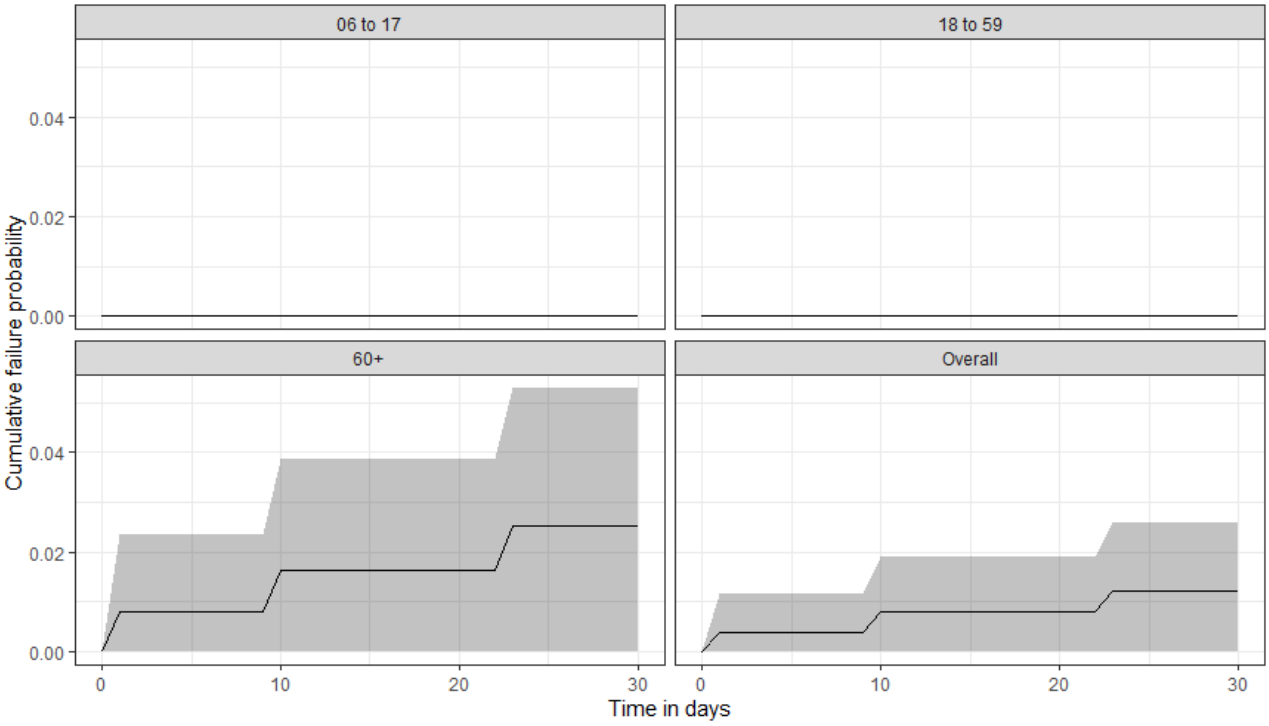

Figure 4. Cumulative Survival Probability in EBB

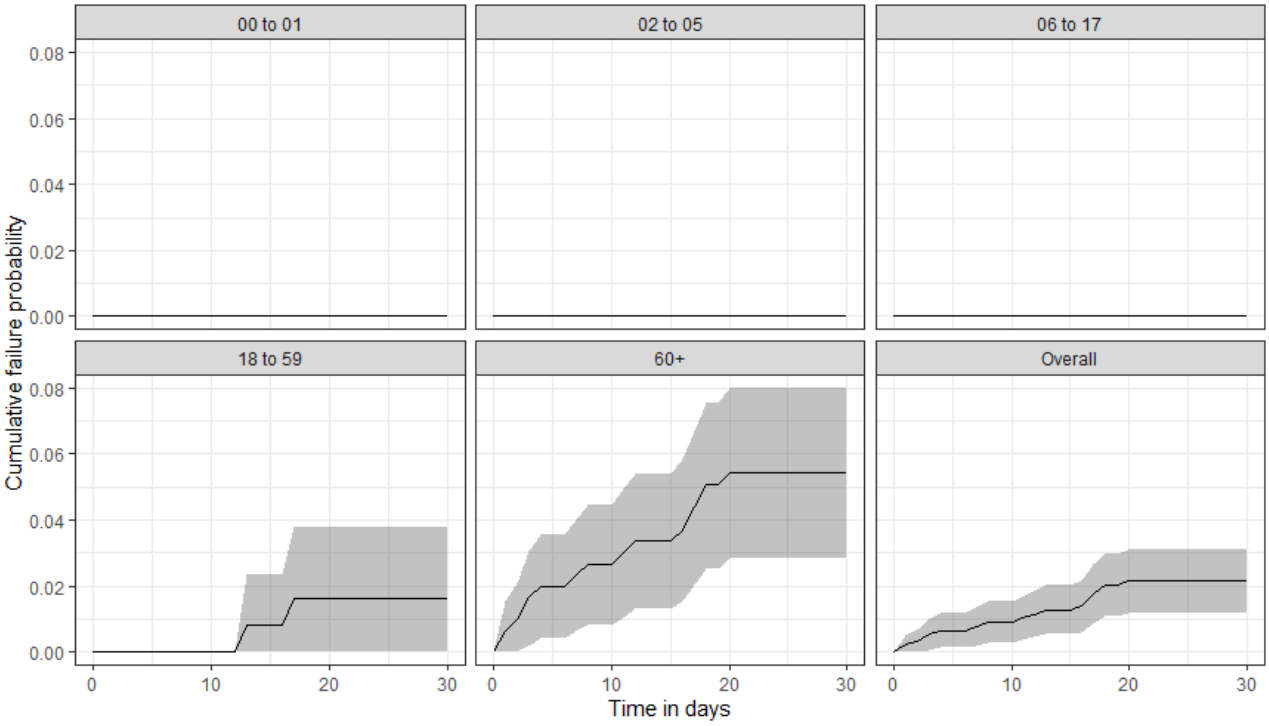

Figure 5. Cumulative Survival Probability in IMASIS

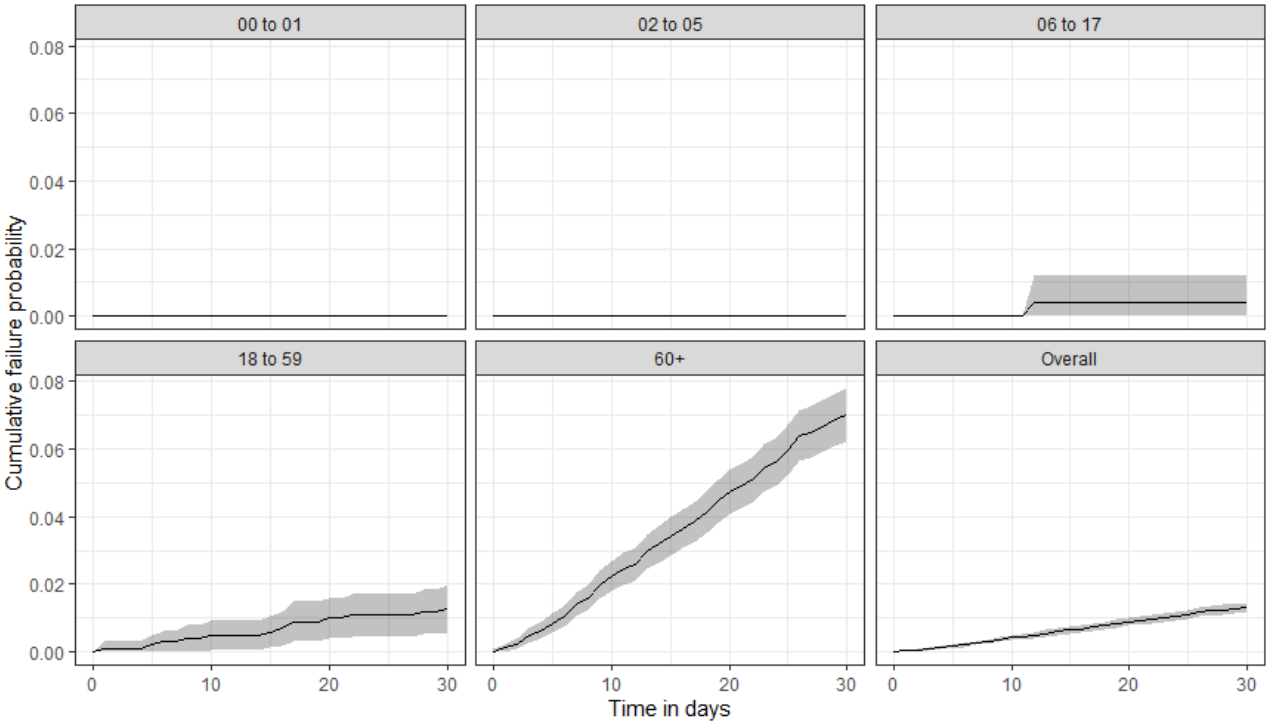

Figure 6. Cumulative Survival Probability in SIDIAP

Table 17b. Mortality rates among patients with laboratory-confirmed RSV infection during the study period, per timelines and database.

	CDW Bordeaux	EBB Estonia	IMASIS Spain
Number of patients with lab-confirmed RSV infection, n	774	184	559
Number of deaths within 30 days of RSV diagnosis	12	<5	6
• Paediatric population (< 18 years)	<5	0	0
• Adult population (≥ 18 years)	10	<5	6
30-day mortality rate per 1,000 patients with RSV infection	**15.5**	**NA**	**10.7**
• < 1 year	NA	NA	NA
• 1 to 5 years	NA	NA	NA
• 6 to 17 years	NA	NA	NA
• 18 to 59 years	78.1	NA	NA
• ≥ 60 years	49.0	NA	35.5

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, EBB = Estonian Biobank, IMASIS = Institut Municipal Assistencia Sanitaria Information System, NA: Not applicable as numbers are too low. Hospital databases are indicated in yellow.

The availability of age-specific mortality data for laboratory-confirmed RSV infection cases was limited, hindering a comprehensive analysis of rates across databases (**Table 17b**).

Based on available data, there were 12 deaths among 774 patients within 30 days of recorded diagnosis of RSV infection in CDW Bordeaux, resulting in an overall 30-day mortality rate of 15.5 per 1,000 patients. Within the adult population of this database, the mortality rate was higher in individuals aged 18 to 59 years (78.1 per 1,000 patients) compared to those aged 60 years or older (49.0 per 1,000 patients). In IMASIS, 6 deaths were reported among 559 patients with laboratory-confirmed RSV infection within 30 days of diagnosis, implying a 30-day mortality rate of 10.7 per 1,000 patients.

Noteworthily, the 30-day mortality rate (per 1,000 patients) observed in older adults (60 years or older) in both databases (49.0 for CDW Bordeaux and 35.5 for IMASIS) was significantly higher than the overall estimates in each of the databases (15.05 for CDW Bordeaux and 10.7 for IMASIS).

13 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, does not fulfil the criteria for reporting adverse events, according to module VI, VI.C.1.2.1.2 of the Good Pharmacovigilance Practices (https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf).

14 DISCUSSION

14.1 Key Results

This study investigated the epidemiology and healthcare related of burden of RSV infection in a large international cohort of over 52 million adults and children from six European databases, with over 44,000 patients with RSV infection reported over a decade. The findings highlight the significant burden of RSV infection, particularly among infants and older adults.

Cohort characterisation

The study population consisted mostly of adults across all databases, with individuals aged 18 to 59 years comprising the majority. Over two-thirds of the patient population in most databases were infants (<1 year), with older adults (≥ 60 years) being the second most prevalent age group. The gender distribution of patients with RSV infection were generally comparable except for laboratory confirmed cases which demonstrated slight female preponderance. Approximately two out of five RSV infection cases were confirmed by laboratory diagnosis and comprised mostly of infants and older adults.

RSV co-infections with other viral respiratory pathogens

A substantial proportion (up to 8%) of patients with recorded RSV infection had co-infections with other respiratory viruses. Influenza virus was the most common co-infection (1.5% – 8.2%), followed by adenovirus (0.8% – 4.8%) and SARS-CoV-2 (0.5% – 2.9%). Lower, but still notable, co-infection rates were observed with

rhinovirus (0.2% – 4.3%), parainfluenza virus (0.1% – 0.5%), metapneumovirus (0.1% – 0.9%), and bocavirus (1.6%).

Incidence of RSV-related hospitalisation in the general population (non-hospital settings)

The incidence rate of RSV-related hospitalisation (i.e. results from non-hospital databases) was higher in the general population (35.44 per 100,000 PY) than in the population including adult individuals aged 18 years and older (5.46 per 100,000 PY). In the general population (SIDIAP), the highest incidence rate of RSV-related hospitalisation occurred in infants (2,730.25 per 100,000 PY), which was about 18 times higher than the rates in toddlers and preschoolers (153.41 per 100,000 PY), and nearly 100 times the rates in older adults (28.09 per 100,000 PY). The lowest rates were reported among young and middle-aged adults (2.06 per 100,000 PY), and individuals aged 6 to 17 years (2.68 per 100,000 PY). Similarly, within the adult population (EBB), the rate was highest in older adults (17.00 per 100,000 PY) compared to rates in young and middle-aged adults (2.25 per 100,000 PY).

Throughout the study period, a rising trend in RSV-related hospitalization rates (per 100,000 PY) was observed in the general population (SIDIAP), with notable peaks in 2019 (49.78, 95% CI, 48.00 – 51.61) and 2022 (70.68, 95% CI, 68.56 – 72.85), and a temporary dip in 2020 (22.81, 95% CI, 21.61 – 24.05). In EBB (with only adult participants), the highest rates were observed in 2020 (9.68, 95% CI, 5.92 – 14.96), and 2018 (10.63, 95% CI, 6.66 – 16.09), with lowest rate in 2017 (4.82, 95% CI, 2.31 – 8.87).

Incidence of RSV-related hospitalisation in hospital settings

In hospital settings, 182 to 274 cases of RSV infection were reported per 100,000 patients hospitalised over a decade of observation. Most cases of RSV infection were reported among infants aged below one year (2,159 – 2,352 per 100,000 patients), children aged 1 to 5 years (398 – 906 per 100,000 patients), and adults aged ≥ 60 years (95 – 295 per 100,000 patients). The burden was much lower among Individuals aged 6 to 17 years (12 – 36 per 100,000 patients, and adults aged 18 to 59 years (23 – 30 per 100,000 patients). There was an increasing trend in the annual rates of RSV infection reported among hospitalised patients during the study period, with a pronounced peak in 2022 (391 – 452 per 100,000 patients).

Prevalence of RSV-related admission to intensive care unit (ICU)

In CDW Bordeaux, 37% of patients with recorded RSV infection during hospitalization required ICU admission. Age-specific prevalence of RSV-related ICU admission were generally comparable, with highest burden observed in infants below 1 year (39%), followed by adults aged ≥ 60 years (36%). The lowest prevalence was observed in children aged 1-5 years (27%). There was an upward trend in the annual prevalence of RSV-related ICU admission, almost tripling from 14% in 2013 to 38% in 2022. Notably, a much lower prevalence of 1% was reported in IMASIS, Spain.

Duration of RSV-related hospitalisation

Most cases of RSV-related hospitalisation were short, lasting 1 – 2 days. Infants under 1 year and adults 60 and older tended to require longer stays, with a median duration of 2-4 days and 1-5 days, respectively. Overall, the median duration of hospitalization remained stable throughout the study period, ranging from 1 – 4 days in 2013 to 2 days in 2022.

30-day mortality rate of RSV infection

Approximately 1% of the overall patient population died within 30 days of RSV infection diagnosis. The 30-day mortality rate of RSV infection was highest in Spain (13.1 – 18.1 per 1000 patients), with relatively lower rate in France (11.8 per 1,000 patients). In the adult population, age-specific mortality rates were notably higher in older adults (50.3 – 90.2 per 1000 patients) compared to young and middle-aged adults (12.9 – 48.9 per 1000 patients). Conversely, fewer number of deaths was recorded in the paediatric population, precluding the estimation of mortality rate in this age group.

14.2 Limitations of the research methods

The study was 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 hospital databases such as IMASIS and CDW Bordeaux, 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, where the study population may not fully represent of all individuals with RSV infection. 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 was conducted to 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 was missing within the hospital data, the duration of hospitalization could not be accurately calculated, introducing potential uncertainties in assessing this critical aspect of RSV-related outcomes. Nevertheless, the databases selected for this objective (IMASIS and CDW Bordeaux) (duration of hospitalisation) have the data suitable for this analysis. These limitations underscore the need for cautious interpretation of study results and the importance of considering the context in which the data were collected.

14.3 Interpretation

This large-scale, multinational, population-based and hospital-based retrospective study investigated the epidemiology of RSV infection, its co-infections, hospitalizations, ICU admissions, and mortality rates, across a diverse cohort of 52,289,267 individuals from six European databases, including Estonian EBB, CDW Bordeaux France, IQVIA DA Germany, IMASIS Spain, and SIDIAP Spain. In this real-world study, RSV infection was most prevalent infants (<1 year) and older adults (≥ 60 years), with influenza virus, adenovirus, and SARS-CoV-2 accounting for most co-infections between RSV and other respiratory viruses. The incidence rate of RSV-related hospitalisation in the general population was 35 per 100,000 person-years (PY), with infants experiencing the highest incidence, followed by toddlers, preschoolers, and older adults. A rising trend in hospitalization rates was observed throughout the study period, from 18.16 per 100,000 PY in 2013 to 70.68 per 100,000 PY in 2022. Most RSV hospitalisations lasted 1-2 days, but infants and older adults needed longer stays (2-4 and 1-5 days, respectively). ICU admission rates varied markedly, ranging from 1% in Spain to 37% in France. An upward trend in the annual ICU admission rates were observed, almost tripling from 14% in 2013 to 38% in 2022. Approximately 1% of the patients with RSV infection died within 30 days of diagnosis, particularly affecting older adults, with fewer or no deaths reported among children.

Previous study among 130,084 hospitalised patients with laboratory confirmed RSV infection in Germany showed that infants below one year are most affected (69.5%), with admission rates ranging from 2 to 11%, and median length of hospital stay of 5 (3 – 7) days.[28] Indirect estimation (based on RSV diagnostic codes) of annual incidence of RSV-associated hospitalization the German Federal Statistical Office (DeStatis) database showed an overall increasing trend, varying from 12 per 100,000 persons in 2010 to 22 per 100,000 persons in 2019.[28] The hospitalization incidence was remarkably higher among children compared to adults. In the present study, the proportion of infants with laboratory confirmed RSV infection in the hospital-based CDW Bordeaux (68.0%) is similar to the estimate in the study in Germany (69.5%).[28] However, the ICU admission rate in CDW Bordeaux, France (26 to 47%) is higher than the rate in DeStatis (2 to 11%), possibly due to the RSV infection testing disparities in in CDW Bordeaux where diagnosis of upper respiratory tract infection is primarily clinical except for severe cases that are more likely to require admission to ICU. The direct estimate of annual incidence of RSV-related hospitalisation in SIDIAP showed rising trend similar to the annual rates in DeStatis. Interestingly, the annual rates were identical in 2013 (18.2 per 100,000 PY in SIDIAP, and 18.4 per 100,000 persons in DeStatis).[28]

The present study consistently observed higher burden of RSV disease in infants below one year and adults aged 60 and older. Specifically, these age groups experienced higher rates of hospitalisation, longer hospital stay, and more ICU admission rates. Additionally, higher mortality rate was recorded in older adults aged ≥ 60 years. A study found that older adults with laboratory confirmed RSV infection suffer more severe disease, often requiring oxygen therapy, non-invasive ventilation, and ICU admission [29]. Several studies assessing the clinical outcomes of RSV infection in the general population consistently demonstrates a striking pattern: highest incidence of hospitalisation among infants, and highest mortality rate in older adults, particularly in high-income countries [30, 31]. Our findings align with this well-established trend, with our study revealing a staggering difference in the incidence rate of RSV-related hospitalization. Infants experienced rates that are remarkably 100 times higher than older adults. Moreover, while mortality among children under five was rare, the mortality rate among older adults was notably high. Nevertheless, it important that the

disproportionate burden of RSV disease in infants and older adults might be partly influenced by disparities in laboratory testing and detection rates for RSV infection.[32, 33]

Several factors might contribute to the high burden of RSV infection observed in infants and older adults. RSV infection manifests with a wide spectrum of severity, ranging from asymptomatic infection to life-threatening pneumonia, influenced by the viral strain and load as well as the host's immune response [34, 35]. Infants, especially those under six months old, are particularly vulnerable due to their immature immune systems. Their lack of protective antibodies acquired through prior RSV infections further enhances their susceptibility to the virus's pathogenic effects [36]. In older adults, the decline in immune function and the presence of underlying health conditions, such as chronic lung disease or cardiovascular diseases, significantly increase their susceptibility to RSV infection [35, 37]. These factors impair the body's ability to mount an effective immune response and clear the virus, leading to a higher risk of severe complications.

Consistent with our findings, a study investigating the co-detection of RSV with other respiratory viruses also highlighted RSV co-infection with influenza virus, adenovirus, and SARS-CoV-2 among the top ten reported viral co-infections [38]. RSV and other viruses can exacerbate the severity of RSV infection, leading to more severe illness, hospitalization, and increased mortality risk [29, 39].

The high burden of RSV infection on infants and older adults emphasizes the need for targeted prevention and management strategies. For infants, early exposure to RSV through maternal antibodies or vaccination may help protect them from severe disease [40]. Additionally, improving hand hygiene practices and reducing exposure to environmental factors that facilitate RSV transmission can help lower the risk of infection [41]. In older adults, vaccination against RSV can reduce disease severity, and vaccination against influenza and pneumococcal bacteria can reduce the risk of co-infections, which can worsen RSV infection [42]. Additionally, early diagnosis and prompt treatment of RSV infection in older adults, especially those with underlying health conditions, can help prevent complications and mortality.

The present study observed a rising trend in RSV-associated hospitalization and ICU admission rates throughout the study period. This aligns with a recent report by the European Centre for Disease Prevention and Control, which indicates intensified RSV circulation and increasing transmission rates across all population groups in Europe[43]. The observed upward trend also coincides with a growing burden of severe acute respiratory infections (SARI) caused by RSV[43]. While this might partly be attributed to increased awareness and laboratory testing for RSV infection, these findings underscore the significant public health impact of the virus, which likely remains underreported. Appropriate and timely public health measures need to be implemented to address this rising trend.

Several studies have reported changes in the global hospitalization burden of RSV infection during the COVID-19 pandemic[44]. Our study supports these findings, as we observed alterations in the temporal trends of annual RSV-related hospitalization rates. Specifically, there was a consistent drop in these rates between 2020 and 2021, followed by a rebound in 2022. This pattern suggests potential impacts from the COVID-19 pandemic, likely including disruptions in healthcare services and altered patient behaviours.

In conclusion, infants and older adults are disproportionately affected by RSV infection, with a substantial burden RSV-related hospitalisation in children aged 5 years and below, and high mortality rate in older adults.

The study highlights the importance of age-specific considerations in understanding the epidemiology and clinical outcomes of RSV infection, providing insights for healthcare planning and intervention strategies, especially among vulnerable populations, to mitigate the impact of RSV infection on public health.

14.4 Generalisability

While our study comprised data from 6 European Countries and covers a wide range of settings (hospital in-patient setting, outpatient specialist settings and primary care databases), findings from this study are not to be generalised to other countries or databases but only reflect the situation in the specific region and setting covered by the respective database.

14.5 Other information

NA.

15 CONCLUSION

The burden of RSV disease shows increasing trend, and disproportionately high in infants below 1 year and adults aged ≥ 60 years who experience higher rates of hospitalisation, longer hospital stay, and more ICU admission rates. Additionally, higher mortality rate was recorded in older adults aged ≥ 60 years. Importantly, the extent to which each database captured study outcomes may vary, potentially impacting our findings. Overall, the study highlights the importance of age-specific considerations in understanding the epidemiology and clinical outcomes of RSV infection, providing insights for healthcare planning and intervention strategies. The findings of this study reinforce the importance of RSV vaccination and other preventive measures, particularly among the high risk population.

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17 ANNEXES

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

concept_id	concept_name
3005444	Respiratory syncytial virus Ag [Presence] in Specimen by Immunofluorescence
3021508	Respiratory syncytial virus Ag [Presence] in Throat
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

concept_id	concept_name
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

concept_id	concept_name
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
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

concept_id	concept_name
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
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

concept_id	concept_name
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
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

concept_id	concept_name
46236738	Influenza virus A H1 2009 pandemic RNA [Presence] in Nasopharynx by NAA with probe detection
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

concept_id	concept_name
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
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

concept_id	concept_name
1002337	Influenza virus A PB1 gene [Nucleotide sequence] in Isolate by Sequencing
1002397	Influenza virus A NS1 gene [Nucleotide sequence] in Isolate by Sequencing
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

concept_id	concept_name
36676238	Pneumonia caused by Influenza A virus
46270121	Pneumonia due to H1N1 influenza
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

concept_id	concept_name
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

concept_id	concept_name
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

concept_id	concept_name
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

concept_id	concept_name
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

concept_id	concept_name
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)

concept_id	Concept_name
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

concept_id	concept_name
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

concept_id	concept_name
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)

concept_id	concept_name
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)

concept_id	concept_name
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

concept_id	concept_name
37019747	Rhinovirus RNA [Presence] in Upper respiratory specimen by NAA with probe detection

Rhinovirus (SNOMED)

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

Coxsackieviruses (LOINC)

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

Coxsackieviruses (SNOMED)

concept_id	concept_name
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)

concept_id	concept_name
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