PROTOCOL

Study Title:	Respiriamo - Italian hospital surveillance for Lower Respiratory Tract Infections
Acronym:	RESPIRIAMO
Study Code:	INC_RESP_003
Experimental design:	Multicenter Observational study
Protocol version:	3.0
Date:	13 October 2022
Funder:	Sanofi Pasteur (a Société Anonyme organized and existing under the laws of the French Republic, having its registered head office at 14, espace Henri Vallée, 69007 LYON, FRANCE)
Sponsor:	INCiPiT (Italian Network For Paediatric Clinical Trials)
Scientific Coordinator:	Dr. Elena Bozzola Paediatric Infectivologist at the IRCCS Bambino Gesù Children's Hospital (OPBG); National Secretary and Councillor of the Board of the Italian Paediatric Society (SIP)

TABLE 1: Clinical Sites involved

Scientific Coordinator: Dr. Elena Bozzola (The Italian Pediatric Society – SIP)						
ID NB	**CITY**	**REGION**	**HOSPITAL SITE**	**PRINCIPAL INVESTIGATOR**	**EMAIL**	**AFFILIATION**
1	Rome	Lazio	DPUO (Department of Paediatrics), Bambino Gesù Children's Hospital	Dr. Annachiara Vittucci	annachiara.vittucci@opbg.net	INCiPiT *(Italian Network for Paediatric Clinical Trials)*
2	Milan	Lombardy	Paediatric and Paediatric First Aid Department, "Vittore Buzzi" Children's Hospital	Dr. Enza D'Auria	enza.dauria@unimi.it	SIP
3	Parma	Emilia-Romagna	UOC Paediatric Clinic of the Pietro Barilla Hospital, "Azienda Ospedaliera-Universitaria di Parma"	Prof. Susanna Esposito	susannamariaroberta.esposito@unipr.it	INCiPiT *(Italian Network for Paediatric Clinical Trials)*
4	Pisa	Tuscany	UO Paediatric Clinic, "Azienda Ospedaliera-Universitaria di Pisa"	Prof. Diego Peroni	diego.peroni@unipi.it	SIP
5	Palermo	Sicily	Department of Health Promotion, Maternal-Childhood, Internal and Specialized Medicine of Excellence, "G. D'Alessandro ", University of Palermo	Prof. Giovanni Corsello	giovanni.corsello@unipa.it	SIP
6	Naples	Campania	"Torre del Greco Hospital", ASL Napoli 3 SUD	Dr.ssa Antonietta Giannattasio	antonella.giannattasio@virgilio.it	SIP
7	Turin	Piedmont	SCDU Neonatology, "Azienda Ospedaliera OIRM – Sant'Anna"	Dr. Alessandra Coscia	alessandra.coscia@unito.it	SIP
8	Genoa	Liguria	UOC for Paeditric Emergency, Paediatric Hospital "Istituto Giannina Gaslini"	Dr. Emanuela Piccotti	emanuelapiccotti@gaslini.org	INCiPiT *(Italian Network for Paediatric Clinical Trials)*
9	Padoa	Veneto	UOC of Neonatal Pathology, "Azienda Ospedaliera Universitaria di Padova"	Prof. Eugenio Baraldi	eugenio.baraldi@unipd.it	INCiPiT *(Italian Network for Paediatric Clinical Trials)*
10	Brescia	Lombardy	Department of Paediatrics of the "Spedali Civili di Brescia"	Prof. Raffaele Badolato	raffaele.badolato@unibs.it	INCiPiT *(Italian Network for Paediatric Clinical Trials)*
11	Florence	Tuscany	Department of Medical Paediatrics A of the "Azienda Ospedaliero-Universitaria Meyer"	Dr. Sandra Trapani	sandra.trapani@unifi.it	INCiPiT *(Italian Network for Paediatric Clinical Trials)*
12	Rome	Lazio	Department of Paediatrics and Child Neuropsychiatry "Azienda Policlinico Umberto I"	Prof. Raffaella Nenna	raffaella.nenna@uniroma1.it	SIP

PROTOCOL APPROVAL SIGNATURE PAGE

- I, the undersigned, confirm that the following protocol has been agreed and accepted, that the trial will be conducted in compliance with the approved protocol and will adhere to the principles of the European Clinical Trials Regulation no. 536/2014 and local laws pertaining clinical trials conduction and management, as well as GCP and GPP guidelines, the Sponsor's SOPs, and any other applicable regulatory/ethical requirements.
- I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.
- I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given.
- I ensure that any discrepancies and serious breaches of GCPs from the trial as planned in this protocol will be appropriately justified and managed.

Sponsor:
Signature: ..... Date: ...../...../.....
Name (*capital letters*): .....
Title: .....

Scientific Coordinator:
Signature: ..... Date: ...../...../.....
Name (*capital letters*): .....

Principal Investigator:
Signature: ..... Date: ...../...../.....
Name (*capital letters*): .....

Table of Contents

Acronyms

Abbreviation	Expansion
AE	Adverse Event
AIFA	Agenzia Italiana del Farmaco
ALCOAC	Attributable, Legible, Contemporaneous, Original, Accurate, Complete
CHD	Congenital Heart Disease
CIOMS	Council for International Organizations of Medical Sciences
CLD	Chronic Lung Disease
COA	Clinical Outcome Assessments
COVID-19	Coronavirus Disease 2019
CRA	Clinical Research Associate
DMr	Data Manager
EC	Ethics Committee
eCRF	electronic Case Report Form
ED	Emergency Department
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GCP	Guideline for Good Clinical Practice
GDPR	General Data Protection Regulation
GEP	Good Epidemiological Practice
GP	General Practitioner
GPP	Good Pharmacoepidemiology Practice
HIV	Human Immunodeficiency Virus
ICD	International Classification of Diseases
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
ILI	Influenza-Like-Illness
INCiPiT	Italian Network for Paediatric Clinical Trials
IRCCS	Istituto di Ricovero e Cura a Carattere Scientifico
ISF	Investigator Site File
ISPE	International Society for Pharmacoepidemiology
ISS	Istituto Superiore di Sanità – National Institute of Health
ISTAT	Istituto Nazionale di Statistica – National Institute of Statistics
KID	Kids' Inpatient Database
LRTC	Lower Respiratory Tract Complication
LRTI	Low Respiratory Trait Infection

mAb	monoclonal Antibody
ME	Margin of Error
MIS-C	Multisystem Inflammatory Syndrome in Children
NEDS	Nationwide Emergency Department Sample
NIS	Network Information Service
PCR	Polymerase Chain Reaction
PI	Principal Investigator
RNA	Ribonucleic Acid
RSO	Registro Studi Osservazionali
RSV	Respiratory Syncytial Virus
OPBG	Bambino Gesù Children's Hospital
PICU	Paediatric Intensive Care Unit
PLS	Pediatra di Libera Scelta - General Paediatrician
SAP	Statistical Analysis Plan
SARI	Severe Acute Respiratory Infection
SARS-COV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SIP	Società Italiana di Pediatria - Italian Paediatric Society
SOP	Standard Operating Procedure
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
UO	Unità Operativa – Operational Unit
UOC	Unità Operativa Complessa – Complex Operational Unit
URTI	Upper Respiratory Tract Infection
wGA	Week Gestational Age

1. Synopsis

Short Title	RESPIRIAMO
Long Title of Trial	Respiriamo - Italian hospital surveillance for Lower Respiratory Tract Infections
Protocol Version	3.0
Protocol Version Date	13 October 2022
INCiPiT #	INC_RESP_003
EudraCT #	*Not applicable*
Synopsis Version	3.0
Version Date	13 October 2022
Study Design	This is a no-profit, multicenter retrospective and prospective observational study, which aims to conduct a hospital-based surveillance for Low Respiratory Trait Infections (LRTIs) in Emergency Departments, wards and Intensive Care Units of twelve main paediatric hospitals and/or Paediatric Departments located in General Hospitals, in Italy, and covering metropolitan areas of different national Regions. The study will include a prospective surveillance phase and a retrospective surveillance phase. The profile of the patients included in both phases will be the same.
Setting	At least twelve major Paediatric Hospitals and Paediatric Departments located in General Hospitals, in Italy. The Sponsor of the study, INCiPiT (the Italian Network for Paediatric Clinical Trials), is a no profit legally defined Consortium composed by the main Italian children's hospitals, the largest Departments of Paediatrics as well as national and international Paediatric Therapeutic Networks coordinated by Italian Institutions. The mission of INCiPiT is to foster and support the planning, conduct and completion of all types of clinical studies conducted in Italy in the paediatric population. The Institutions, which are involved in the present study, are part of the Consortium, as direct members of the network or indirectly involved being within one of the official members, i.e. the SIP (Società Italiana di Pediatria- the Italian Paediatric Society).
Study population	Infants 0-<2 years of life, hospitalized for LRTI for less than 72 hours will be evaluated for their eligibility in the study.
Primary Objective	The primary objective of this study is to estimate the burden of LRTI hospitalizations attributable to RSV in Infants aged 0-<2 years of age, in Italy; this includes resulting clinical complications (if any), economic impact related to the management of the child's illness and utilization of the relevant healthcare resources. The objective will be reached acting within the framework of Paediatric Hospitals and Paediatric Departments located in General Hospitals, in Italy and therefore also promoting an operative and clinical networking.

Secondary Objectives	• Estimating LRTI hospitalizations attributable to other pathogens comprehensively of SARS-COV-2 • To conduct a retrospective surveillance of LRTI hospitalizations attributable to RSV and to other pathogens in children aged 0-<2 years of age.
Primary endpoints	• The proportion of hospitalizations and ED visits and/or any kind of accesses through PICU and direct accesses through Paediatric Wards due to LRTI and to RSV, overall and by infant, hospital, and disease characteristics in infants < 2 years of age • The incidence of LRTI hospitalizations in infants 0-<2 years of age attributable to RSV (number of infants aged <2 years with LRTI-RSV per year, divided the estimated number of infants aged < 2years in the area served by the selected hospitals) • To determine and measure the healthcare resources utilization associated with LRTI and LRTI- RSV hospitalizations and ED visits and/or any kind of accesses through PICU and direct accesses through Paediatric Wards (as statistically defined by national recognized parameters) overall and by infant, hospital, and disease characteristics, within one month following LRTI hospitalization • To determine the proportion and costs of hospitalizations or ED visit and/or any kind of accesses through PICU and direct accesses through Paediatric Wards by indicators of healthcare resources utilization.
Secondary endpoints	• The proportion of LRTI hospitalizations in infants 0-<2 years of age attributable to other pathogens non-RSV • The incidence of LRTI hospitalizations in infants 0-<2 years of age attributable to other pathogens non-RSV • The proportion of co-infections with RSV in LRTI hospitalizations in infants 0-<2 years of age • To describe and compare the circulation of respiratory pathogens during the RSV season and in the context of COVID-19 (details of the metrics which will be used will be defined in the study specific Statistical Ananlysis Plan) • To describe clinical complications within one month following LRTI hospitalizations (details of the metrics which will be used will be defined in the study specific Statistical Ananlysis Plan) • To describe the demographic and medical background of LRTI cases (risk factors, comorbidities) • To describe the length of stay and the antibiotic use of LRTI cases (details of the metrics which will be used will be defined in the study specific Statistical Analysis Plan).
Exploratory endpoints	• To describe the impact that the standardization of the tests done locally for the pathogens identification would have on the comparability and uniformity of their identification, in terms of completeness of the pathogens panels, of qualitative detection and differentiation of nucleic acids. The accurate definition of the etiology of a respiratory infection is leading to the appropriate treatment and management of the patient, with specific implications on the health system resources management.

<table>
<tr><td></td><td>

- According to the information collected as for the primary and secondary endpoints, it is intended to explore the feasibility of the construction of a dedicated Paediatric Disease Registry targeting LRTI, other than the epidemiological network represented by the recent initiative taken by the ISS (Istituto Superiore di Sanità - National Institute of Health) called InfluNet. InfluNet surveillance is the “national influenza epidemiological and virological surveillance system”. InfluNet is coordinated by ISS, with the support of the Ministry of Health. The Network uses the contribution of General Practitioners (GPs) and General Paediatricians (Pediatri di Libera Scelta - PLS) therefore not including in the loop the information coming from the management of paediatric cases done in Paediatric dedicated Clinical Institutions and/or in the Paediatric Departments of General Hospitals.

  The assessment will be done upon the evaluation of the consistency and uniformity of the data collected in each of the clinical sites involved in the study. Based on the data collected as per standard of care, efforts will be made to define a unique panel of data in order to be inserted in the eCRF of the study. The Paediatric Registry would be conceived to collect and categorize the clinical information needed to improve the management of the unmet medical need (prophylactically and therapeutically) in children with LRTI infection.

</td></tr>
<tr><td>Inclusion Criteria (for both retrospective and prospective phases of the study)</td><td>

Infants will be enrolled in the study if the following inclusion criteria are satisfied:

1. Signed and dated written informed consent obtained from the parent(s)/legal representative(s) of the subject.
2. infants of 0-<2 years
3. Hospitalization for LRTI (as defined in the table below)
4. Access to Emergency Departments, Paediatric Intensive Care Units (PICU) and/or direct access to Paediatric Wards with signs and symptoms of LRTI (as defined in the table below), confirmed during the subsequent hospitalization

Group A (one or more)	Group B (one or more)
○ Fever >38 °C	○ Wheezing
○ Cough	○ Crackles or Rales
○ Nasal congestion	○ Diminished breath sounds
○ Rhinorrhea/ Coryza	○ Shortness of breath, rapid or shallow breathing
○ Sore throat	○ Hypoxemia (O_2 saturation below 92%)

Table 2: infants less than 24 months of age with at least one symptom of Group A and one symptom of Group B as well as need for hospitalization

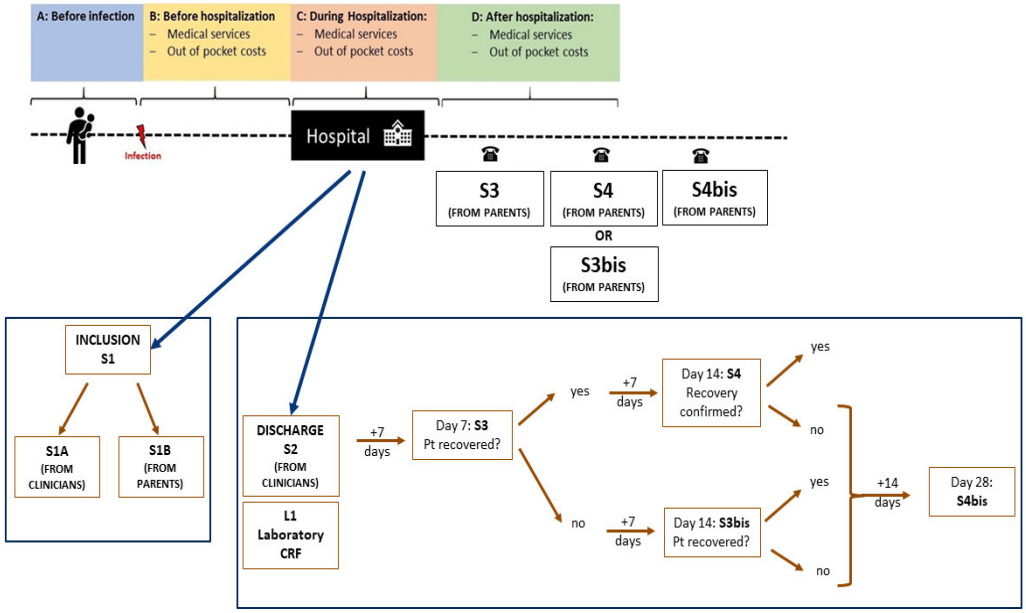
</td></tr>
<tr><td>Exclusion Criteria (for both retrospective and prospective phases of the study)</td><td>

Infants having symptoms/conditions reported hereinafter will not be included in the study:

1. Hospitalized for >72 hours prior to LRTI
2. Newborn Infants, <72 hours of life
3. Presenting with non-infectious cause for symptoms
4. Already included in the study, because of a previous hospitalization

</td></tr>
<tr><td>Number of Participants for the prospective surveillance phase</td><td>Considering an estimated Prevalence of 36% and a Prevalence Confidence interval of 0.31-0.41, the estimated sample size for the prospective surveillance phase should be of 355 infants with RSV and RSV-like infections (for details please refer to section 8.11.1 of the protocol).</td></tr>
</table>

Number of Participants for the retrospective surveillance phase	Six Italian provinces of interest (Rome, Milan, Turin, Genoa, Parma, Florence) have been identified as being representative of the distribution of the Paediatric population and therefore data filtered by age and province have been extracted from the ISTAT website [ISTAT 2021], in order to calculate the population basin relevant to the 6 selected hospitals that are or have been part of the INCiPiT Consortium (Italian Network for Paediatric Clinical Trials) and that will participate in the study. Data updated to 1st Jan 2021 were extracted. The hospitals' capacity to catch paediatric hospitalization cases with respect to the population basin has been estimated in a range from 40% to 90%, depending on the presence of other major hospitals in the province of interest. Data for the population by age, for the estimated catchment of each hospital±10%, and for the incidence rate were used to build an average incidence rate/average catchment scenario, a lower incidence rate/lower catchment scenario, and a higher incidence rate/higher catchment scenario for the expected RSV-hospitalization cases to be observed by the 6 considered hospitals. According to the average scenario, the selected hospitals should observe a total of 687 RSV-associated hospitalizations in infants <2years of age every year (lower incidence rate/lower catchment scenario: 555 children; higher incidence rate/ higher catchment scenario 843 children). Due to the variability that might occur between seasons, substantial differences are expected between seasons. Giving the above, the retrospective surveillance phase of the present study will collect data for 1665 patients, i.e. considering for each season a total of 555 children and therefore targeting the lower incidence rate as above calculated. If, according to the variability expected in between the seasons, the incidence rate will show to be higher, the collection of data will be continued making reference to the subsequent slots of incidence as above defined. To be noted that this is identified as a secondary objective.
Total Duration of the study	It is expected to collect the data relevant to the retrospective surveillance phase of the study in up to 12 months, starting from the activation of each clinical site involved. It is expected to collect data for the prospective surveillance phase of the study for 3-4 months starting from the activation of the clinical sites, which might be extended, depending on LRTI admission rates that will be observed throughout 2022 The collection will start only when the clinical site will be initiated. For the second study season (from beginning of 2023) the timeframe will be determined according to the results of the first season. The duration will be of a minimum of 8 months Timeframe between database cleaning/freezing and finalization of the Clinical Study Report will last up to 2 months. Therefore, the total duration of the study will be of at least 24 months.
Study Flow-Chart and Schedule of Assessments	An overview of study procedures is given in Figure 1. The study procedures were conceived to capture direct and indirect costs, and medical services utilized (Figure 1, top panel).

	 *Figure 1 - Overview of study phases and of study specific procedures related to each phase*
Funder	Sanofi Pasteur (a *Société Anonyme* organized and existing under the laws of the French Republic, having its registered head office at 14, espace Henri Vallée, 69007 LYON, FRANCE)
Sponsor	INCiPiT (Italian Network for Paediatric Clinical Trials)
Scientific Coordinator	Dr. Elena Bozzola Paediatric Infectivologist at the IRCCS Bambino Gesù Children's Hospital (OPBG); National Secretary and Councillor of the Board of the Italian Paediatric Society (SIP)

2. Background and Rationale

Respiratory Syncytial Virus (RSV) is considered the most important cause of acute Lower Respiratory Tract Infection (LRTI) in infants and young children [Shi 2017]. RSV is a negative-stranded ribonucleic acid (RNA) virus belonging to the recently defined Pneumoviridae family. Two subtypes of RSV (i.e. subtypes A and B) have been identified, generally co-circulating simultaneously, with one subtype predominating in a single season, alternating annually, with regional variations [Ciarlitto 2019, Nam 2019].

RSV is highly contagious and causes respiratory tract infections in people of all ages [Borchers 2013]. In most patients the pathogen causes a self-limiting, upper respiratory tract infection (URTI) with "common cold"-like symptoms [Zhou 2021].

However, RSV infection can result in LRTI or Lower Respiratory Tract Complications (LRTC), compromising respiration, leading to hospitalization (with an estimate of 55/100,000 person-year in the US), and causing considerable morbidity and mortality especially in infants [Zhou 2021, Shi 2017]: in fact, RSV is recognized as a major cause of hospitalization and death in young children worldwide [Shi 2017, Rudan 2008, Navarro 2021].

The RSV season occurs during winter months in regions with temperate climates, with hospitalization rates peaking from December-March in premature children in the northern hemisphere [Anderson 2017].

Infants born prematurely or close to the RSV season and/or suffering from bronchopulmonary dysplasia or congenital heart disease have the highest risk of developing severe RSV-related acute LRTI [Feltes 2017].

Approximately 50-70% of infants are infected with RSV during the first year of life, and almost 100% are infected with RSV by 2 years of age. The risk of severe LRTI is highest in infants under 6 months of age, with 2.0% on average being hospitalized for RSV-associated LRTI, most of them without additional risk factors: 45% of all hospital admissions and in-hospital deaths for RSV-LRTI occur in infants <6 months of age [Boyce 2000; Deshpande 2003; García 2010; Hall 2009; Holman 2004; Iwane 2004; Paramore 2004; Rietveld 2004; Shi 2017; Stein 2017; Vicente 2003]. Furthermore, RSV is associated with high hospitalization costs in children, mainly if younger than 3 months of age (Bozzola, 2021). RSV infections in infants of 6-15 months of age can still lead to LRTIs requiring medical attention [Fisher 1997]. About 61 to 77% of acute bronchiolitis episodes in infants <2 years have been reported as being RSV-related [Diez-Domingo 2014] and for this reason, this population can be considered at risk for severe RSV-related disease.

RSV-LRTI hospitalization rate was estimated to be 64 per 1000 among premature infants <1 year, compared to 19 per 1000 in general <1 year population [Stein 2017]. Among the other risk factors, asthma, hospitalization before the RSV infection, no breastfeeding, history of atopy, siblings, and crowding, were associated with an increased risk of hospitalization for RSV infection in children independent of gestational age, while young maternal age, maternal asthma, single parenthood, maternal smoking, being born small for gestational age, Caesarian section, male gender, and day care were associated with an increased risk of hospitalization for RSV infection in term children

[Shi 2015, Haerskjold 2016]. Human immunodeficiency virus (HIV) was reported to increase the risk of hospitalization for RSV in children by 2.5- to 5- fold [Cohen 2015; Madhi 2006; Shi 2015]. RSV subtype and genotype could interact with these risk factors, as both RSV-B subtype and the less virulent RSV genotypes (ON1 and BA) have been reported to preferentially cause bronchiolitis in infants with a possible genetic predisposition toward asthma and atopy [Midulla 2019, Ciarlitto 2019].
Reinfection with RSV is common in all age groups: it usually presents clinically as an URTI, while occasionally leading to severe disease in immunocompromised subjects or in the elderly [Graham 2011, Simoes 1999; Krilov 2011].

A recent meta-analysis estimated inpatient management costs with follow-up in European countries to be €18,607 per patient; in addition, direct nonmedical costs (mainly food and transportation) to be responsible for 2.3%–3.8% of the total management cost per patient, and indirect costs (productivity losses) representing 5.8%–31.6% of the total management cost [Zhang 2020]; however, currently few studies explored the clinical and socioeconomic burden of disease of RSV infections in young children in primary care setting [van Summeren 2021]. The level of distress and anxiety of the parent/caregiver due to severe RSV infection remains probably underestimated [Leidy 2005].
Despite the large medical and economic burden, treatment of RSV disease is largely symptomatic and supportive care, consisting of supplemental oxygen therapy, nutrition, fluids, and, in some cases, mechanical ventilation in hospitalized patients [Empey 2010, Wainwright 2010, Murray, 2014]. Only 2 antiviral agents have been approved for the or treatment of RSV infection in paediatric populations: antiviral ribavirin is approved in selected countries for RSV treatment of severe hospitalized cases, due to uncertainties regarding its efficacy, complexity in administration (aerosol), safety concerns (potential genotoxic effects) and high cost [AAP 2006, Boe 2001, Virazole SPC], while RSV-specific monoclonal antibody (mAb) palivizumab is indicated for prophylaxis of RSV infection in infants at higher risk for severe RSV disease [Synagis EPAR Summary].
Overall, the unmet medical need (prophylactically and therapeutically) is substantial in both children and adults with RSV infection, whether hospitalized or outpatients.
Currently, no vaccine for RSV is available, but new candidate RSV vaccines and mAbs are in late-stage clinical trials [Griffin 2020, Mejias 2020, Schwarz 2021]. Accurate estimates of the burden of RSV will be crucial to better assess the overall impact RSV prevention and/or treatment may have on the society [van Summeren 2021].

Since its appearance in 2019, the SARS-CoV-2 has affected over 231 million persons and caused more than 4.7 million deaths [Who 2021]. An Italian seroprevalence study has shown a substantial increase in blood anti-SARS-CoV-2 antibodies from 1% of July 2020 to 9.5% of January 2021 in children and adolescents of Friuli Venezia-Giulia [Comar 2021]. The mortality rate is associated with age, gender and comorbidity [De Crescenzo 2021], and even if nearly half of young COVID-19 cases were asymptomatic, 7% (95%, CI: 0% - 30%) required intensive-care-unit

admission according to a recent meta-analysis [Bhuiyan 2021]. Emerging data suggest higher SARS-CoV-2 infection susceptibility in patients with asthma or renal malformation [Mehta 2020], and the possibility to develop a Kawasaki-like syndrome which has been termed as multisystem inflammatory syndrome in children (MIS-C) [Bhuiyan 2021, Dembiński 2021]. These findings are important given that infants and young children <5 years old are already at higher risk of severe RSV or influenza infection manifestations [Bhuiyan 2021]. Also, although SARS-CoV-2 infection being less dangerous in paediatric population, the indirect consequences of COVID-19 pandemic have severely affected children and adolescents in terms of physical, intellectual, and emotional development [Dembiński 2021].

Since the season 2019/2020, in Italy epidemiological and virological surveillance for RSV is made within Influnet, a system that surveils influenza-like-illness (ILI) cases, and since the season 2020/2021 has been further integrated with CovidNet in order to monitor also SARS-COV-2 [Influnet 2021].
However, to date there is no national system for the surveillance of paediatric hospitalization due to severe acute respiratory infections (SARI) causing LRTI. Evidence available regarding LRTI in Italy are limited to few studies, which have no systematic laboratory confirmation, limited timeframe of retrospective observation and limited geographic coverage to single city or single Region [Kuhdari 2018, Calderaro 2021, Barbati 2020].

3. Study design and Setting

This is a no-profit, multicenter retrospective and prospective observational study, which aims to conduct a hospital-based surveillance for LRTIs in Emergency Department, wards, and Intensive Care Units of at least twelve major Paediatric Hospitals and/or Paediatric Departments located in General Hospitals, in Italy, and covering metropolitan areas of different national Regions.

The study will include a prospective surveillance phase (a primary collection of data available as per clinical practice) and a retrospective surveillance phase (a secondary use of data already available as per clinical practice).

The Sponsor of the study, INCiPiT (the Italian Network for Paediatric Clinical Trials), is a no profit legally defined Consortium composed by the main Italian children's hospitals, the largest Departments of Paediatrics as well as national and international Paediatric Therapeutic Networks coordinated by Italian Institutions. The mission of INCiPiT is to foster and support the planning, conduct and completion of all types of clinical studies conducted in Italy in the paediatric population. The Institutions which are involved in the present study are part of the Consortium, as direct members of the network or indirectly involved being within one of the official members, i.e. the SIP (Società Italiana di Pediatria - the Italian Paediatric Society).

3.1 Prospective surveillance

Prospective surveillance of LRTI will be conducted across two RSV seasons.

Data collection for the first RSV season will be conducted for 3-4 months starting from the activation of the clinical sites, which might be extended depending on LRTI admission rates that will be observed throughout 2022.
An interim analysis will be conducted when 50% of the patient population of the prospective surveillance phase will be included in the study. As this is an observational study no comparative analyzes are expected. Descriptive analyses will be performed on data collected to gain an understanding of their qualitative and quantitative nature and on the characteristics of the patients enrolled. The results of this analysis will determine if surveillance should continue through the subsequent period of seasonality (for additional details please refer to paragraph 8.11.1). The purpose of this interim analysis is to provide to the Investigators the opportunity to perform necessary adjustments or provide them with operational indications to elevate data quality.

For the second study season (from the beginning of 2023) the timeframe will be determined according to the results of the first season. Surveillance is to be carried out seven days a week, including every child meeting inclusion/exclusion criteria identified during the study period.

3.2 Retrospective surveillance

Retrospective surveillance of LRTI will be conducted including the 3 following seasons

- 2018/2019
- 2019/2020
- 2020/2021

in order to collect data from pre/during/post-COVID pandemic seasons and to compare these results with the active prospective surveillance starting from 2022 season.

3.3 Total duration of the study

It is expected to collect the data relevant to the retrospective surveillance phase of the study in up to 12 months, starting from the activation of each clinical site involved.

It is expected to collect data for the prospective surveillance phase of the study for initial 3-4 months starting from the activation of the clinical sites, which might be extended, depending on LRTI admission rates that will be observed throughout 2022.
The collection will start only when the clinical site will be initiated.
For the second study season (from beginning of 2023) the timeframe will be determined according to the results of the first season. Nevertheless, duration will be of a minimum of 8 months.

Timeframe between database cleaning/freezing and finalization of the Clinical Study Report will last up to 2 months.

Therefore, the total duration of the study will be of at least 24 months.

4. Study population

Study setting includes emergency department, wards, and intensive care of the selected study sites.
Study sites are (at least) twelve main Paediatric Hospitals and Paediatric Departments located in General Hospitals in Italy, covering metropolitan areas for different national Regions and supplying paediatric healthcare for the population of their respective Region. The clinical sites proposed for the participation to the present study are listed in Table 1 ("Clinical Sites involved").

5. Objectives

5.1 Primary Objective

The primary objective of this study is to estimate the burden of LRTI hospitalizations attributable to RSV in Infants aged 0-<2 years of age, in Italy; this includes resulting complications, economic impact, and healthcare resources utilization. The objective will be reached acting within the framework of Paediatric Hospitals and Paediatric Departments located in General Hospitals, in Italy and therefore promoting an operative and clinical networking.

5.2 Secondary objectives

- Estimating LRTI hospitalizations attributable to other pathogens comprehensively of SARS-COV-2
- To conduct a retrospective surveillance of LRTI hospitalizations attributable to RSV and to other pathogens in children aged 0-<2 years of age.

6. Endpoints

6.1 Primary endpoints

- The proportion of hospitalizations and ED visits and/or any kind of accesses through PICU and direct accesses through Paediatric Wards due to LRTI and to RSV, overall and by infant, hospital, and disease characteristics in infants < 2 years of age
- The incidence of LRTI hospitalizations in infants 0-<2 years of age attributable to RSV (number of infants aged <2 years with LRTI-RSV per year, divided the estimated number of infants aged < 2years in the area served by the selected hospitals)
- To determine and measure the healthcare resources utilization associated with LRTI and LRTI- RSV hospitalizations and ED visits and/or any kind of accesses through PICU and direct accesses through Paediatric Wards (as statistically defined by national recognized parameters) overall and by infant, hospital, and disease characteristics, within one month following LRTI hospitalization
- To determine the proportion and costs of hospitalizations or ED visit and/or any kind of accesses through PICU and direct accesses through Paediatric Wards by indicators of healthcare resources utilization.

6.2 Secondary endpoints

- The proportion of LRTI hospitalizations in infants 0-<2 years of age attributable to other pathogens non-RSV
- The incidence of LRTI hospitalizations in infants 0-<2 years of age attributable to other pathogens non-RSV
- The proportion of co-infections with RSV in LRTI hospitalizations in infants 0-<2 years of age
- To describe and compare the circulation of respiratory pathogens during the RSV season and in the context of COVID-19 (details of the metrics which will be used will be defined in the study specific Statistical Analysis Plan)
- To describe clinical complications within one month following LRTI hospitalizations (details of the metrics which will be used will be defined in the study specific Statistical Analysis Plan)
- To describe the demographic and medical background of LRTI cases (risk factors, comorbidities)
- To describe the length of stay and the antibiotic use of LRTI cases (details of the metrics which will be used will be defined in the study specific Statistical Analysis Plan).

6.3 Exploratory endpoints

- To describe the impact that the standardization of the tests done locally for the pathogens identification would have on the comparability and uniformity of their identification, in terms of completeness of the pathogens panels, of qualitative detection and differentiation of nucleic acids.
  The accurate definition of the etiology of a respiratory infection is leading to the appropriate treatment and management of the patient, with specific implications on the health system resources management.
- According to the information collected as for the primary and secondary endpoints, it is intended to explore the feasibility of the construction of a dedicated Paediatric Disease Registry targeting LRTIs, other than the epidemiological network represented by the recent initiative taken by the ISS (Istituto Superiore di Sanità - National Institute of Health) called InfluNet. InfluNet surveillance is the “national influenza epidemiological and virological surveillance system”. InfluNet is coordinated by ISS, with the support of the Ministry of Health. The Network uses the contribution of General Practitioners (GPs) and General Paediatricians (Pediatri di Libera Scelta - PLS) therefore not including in the loop the information coming from the management of paediatric cases done in Paediatric dedicated Clinical Institutions and/or in the Paediatric Departments of General Hospitals. The assessment will be done upon the evaluation of the consistency and uniformity of the data collected in each of the clinical sites involved in the study. Based on the data collected as per standard of care, efforts will be made to define a unique panel of data in order to be inserted in the eCRF of the study. The Paediatric Registry would be conceived to collect and categorize the clinical information needed to improve the management of the unmet medical need (prophylactically and therapeutically) in children with LRTI infection.

7. Eligibility criteria (applicable for both prospective and retrospective surveillance phases)

7.1 Inclusion criteria

Children will be enrolled in the study if the following inclusion criteria are satisfied:

1. Signed and dated written informed consent obtained from the parent(s)/legal representative(s) of the subject
2. Infants of 0-<2 years
3. Hospitalization for LRTI (as defined in table 2 below)
4. Access to Emergency Departments, Paediatric Intensive Care Units (PICU) and/or direct access to Paediatric Wards with signs and symptoms of LRTI (as defined in the table 2 below), confirmed during the subsequent hospitalization.

TABLE 2 - INFANTS LESS THAN 24 MONTHS OF AGE WITH AT LEAST ONE SYMPTOM OF GROUP A AND ONE SYMPTOM OF GROUP B (SEE TABLE) AS WELL AS NEED FOR HOSPITALIZATION

Group A (one or more)	Group B (one or more)
○ Fever >38 °C	○ Wheezing
○ Cough	○ Crackles or Rales
○ Nasal congestion	○ Diminished breath sounds
○ Rhinorrhea/ Coryza	○ Shortness of breath, rapid or shallow breathing
○ Sore throat	○ Hypoxemia (O2 saturation below 92%)

7.2 Exclusion criteria

1. Hospitalized for >72 hours prior to LRTI
2. Newborn infants, <72 hours of life
3. Presenting with non-infectious cause for symptoms
4. Previously included into the study

8. Study Procedures

8.1 Screening procedure (applicable for both retrospective and prospective surveillance phases of the study)

The study team will identify eligible children (qualified according to the eligibility criteria) by checking new admissions to Paediatric Wards, Emergency Departments and Paediatric Intensive Care Unit (PICU) and any other referral Unit, as per local hospitals' organization, through screening of the relevant patients' charts/medical records, for patients admitted with LRTI. The number of patients screened will be recorded in compliance with the STROBE (**ST**rengthening the **R**eporting of **Ob**servational studies in **E**pidemiology) guidelines.
In the case of the prospective surveillance phase, those procedures will be implemented during the Inclusion Visit (see Schedule of Assessments - Paragraph 8.4)

8.2 Enrollment procedure (applicable for both retrospective and prospective surveillance phases of the study)

The appointed study staff will approach parents/legal representatives for informed consent administration, in order to proceed with the confirmation of the inclusion/exclusion criteria and with the subsequent enrollment in the study. At enrolment, each patient will be identified with a unique code (patients' data will be pseudonimized in compliance with GDPR requirements). Infants will be then swabbed or the nasopharyngeal aspirate will be collected (as per clinical practice), and an eCRF will be filled out (see section 8.4 for study procedures). Only parents/legal representatives of RSV+ positive children will be asked to participate to follow-up questionnaires. Please refer to section 11.3 (Informed Consent Procedure) for additional details relevant to the consenting procedure that will be implemented for the present study.

For prospective surveillance: sequential sampling of ~355 parents/legal representatives of RSV positive hospitalized children (therefore with an estimated prevalence of 36%) will be included to fill out a questionnaire during hospitalization.
Enrollment will be distributed across study sites ensuring representativeness of each hospital/Region, with at least 32 parents/children (about 9% of total sample) to be enrolled by each clinical study site.
For the retrospective surveillance the sampling has been targeted as defined in paragraph 8.11.2

8.3 Retrospective analysis of medical records

In order to support the interpretation of study results, retrospective analyses of respiratory infections (based on ICD-9 or ICD-10 codes, see Table 3) in infants below 2 years of age (<24 months) are envisaged. Hereby, medical records (either from electronic sources or paper sources) of hospital sites will be extracted and aggregated. Results may also support interpretation of results in the context of previous respiratory seasons towards the current SARS-CoV-2 pandemic.

8.3.1 Case Identification for RSV and All-Cause Bronchiolitis

Described in Table 3, the *International Classification of Diseases, Ninth Revision and Tenth Revision, Clinical Modification (ICD-9-CM; ICD-10-CM)* codes will be used to identify RSV and all-cause bronchiolitis diagnoses. For this study, all analyses will be restricted to infants aged <2 years of age.

TABLE 3– ICD CODES FOR RSV AND ALL-CAUSE BRONCHIOLITIS

	ICD-9-CM Codes	ICD-10-CM Codes	Diagnosis
RSV	480.1	J12.1	Pneumonia due to RSV
	466.11	J21.0	Acute bronchiolitis due to RSV
	079.6	B97.4	RSV
		J20.5	Acute bronchitis due to RSV
All-cause bronchiolitis	079.6, 466.11, 466.19, 480.1	B97.4, J12.1, J21.0, J20.5, J21.1, J21.8, J21.9	RSV and unspecified bronchiolitis

8.3.2 Hospitalizations

The proportion of hospitalizations or ED visits or accesses through PICU and/or direct access to Paediatric Wards due to RSV and all-cause bronchiolitis among the total number of infants <2 years of age identified in the NIS, KID, and NEDS databases will be determined (excluding newborns). Yearly hospitalization rates may also be calculated based on the availability of data from each of the databases.

To the extent possible given the data, the RSV and all-cause bronchiolitis hospitalizations and ED visits or accesses through PICU and/or direct access to Paediatric Wards will be described by the following variables:

- Age
  - All infants
  - Chronological age in month(s) (continuous)
  - Chronological age in groups: 0 to 2, 3 to 5, 6 to 8, 9 to 11 months, 12 to 23 months

- Gestational age (wGA) (based on ICD-9 and ICD-10 codes)
- Month of birth
- Gender
- Breastfeeding (no, yes/duration)
- Co-morbidities (based ICD-9 and ICD-10 codes)
  - Chronic respiratory lung disease arising in the perinatal period (CLD), higher-risk congenital heart disease (CHD), lower-risk CHD
  - Comorbidities associated with higher risk for RSV reported in Doucette et al. (2016) (e.g. Down's syndrome without congenital heart disease, HIV, immunodeficiency, cystic fibrosis with pulmonary manifestations, neuromuscular disease, other congenital and metabolic diseases)
  - Recurring hissing
  - Bronchial asthma
  - Neurodermatitis
  - Food allergies
  - Malnutrition
  - Immunocompromised state
  - No-comorbidities recorded

- Sociodemographic and siblings
- Use of medication prior admission
- Died during hospitalization
- Outcome measure
  - RSV
  - All-cause bronchiolitis

- Timeframe
  - RSV season (typically November through April)
  - Peak RSV months
  - Calendar months

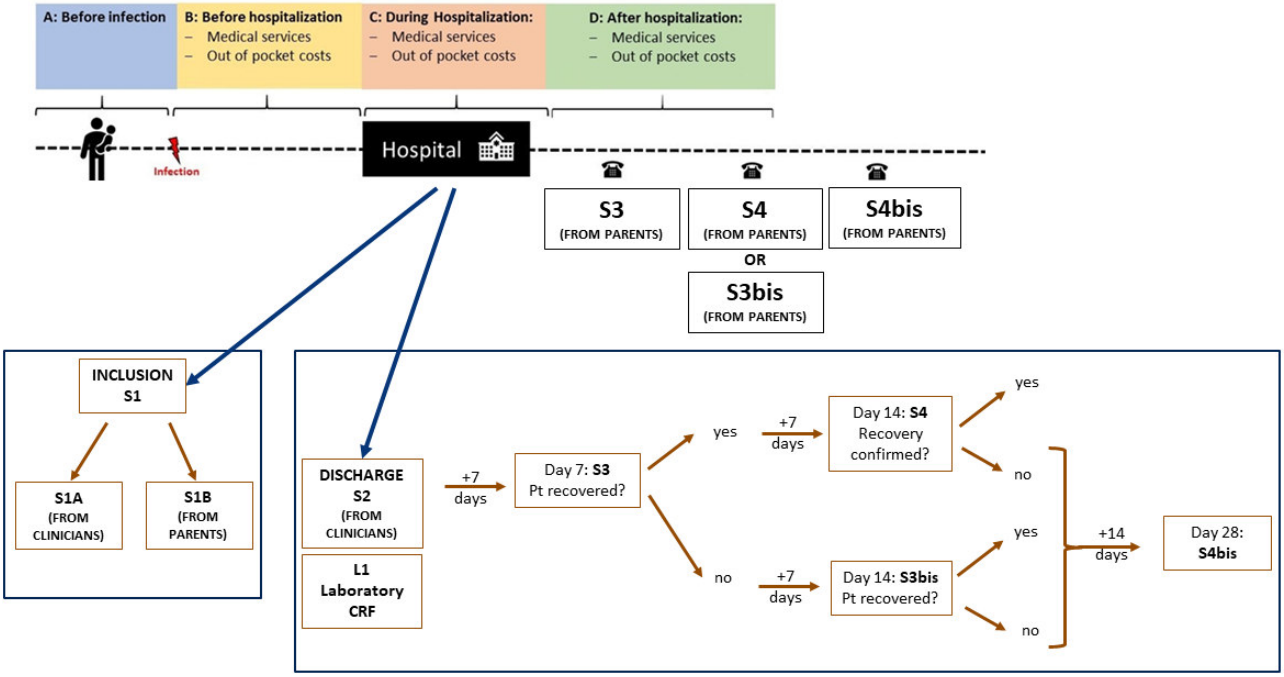
- PCR testing vs. other (if available)

8.4 Study procedures and timelines

An overview of study procedures is given in Figure 1.

The study procedures were conceived to capture direct and indirect costs, and medical services utilized (Figure 1, top panel).

Figure 1 - Overview of study phases and of study specific procedures related to each phase



Seven data collection elements (S1A, S1B, S2, S3, S3bis, S4, S4bis) are collected at five timepoints (Figure 1, central and bottom panels).

At Inclusion, eligibility assessment, informed consent, privacy form, clinical parameters, medical history (near and remote pathological history, family history) and clinical diagnosis are collected from clinicians, and rapid diagnostic testing of respiratory sample [S1A] are collected by clinicians as well as questionnaires to the parents to establish demographic information, complications, clinicial procedures, prescribed medications and estimate indirect costs, medical services before hospitalization [S1B]. Testing at point of care for every infant will include multiplex diagnostic test for RSV, Influenza and SARS-CoV-2. Only infants who tested positive for RSV using the multiplex testing method will be followed up at D14±1 and D28±1.

At Discharge, clinicians document the clinical outcome and medical services conducted [S2] and results from multiplex testing are collected.

At Follow-up I, on day 7±1 after inclusion parents are contacted by telephone, and any additional medical services, direct and indirect costs of both parents and the child are captured [S3].

At Follow up II, on day 14±1 after inclusion, there are two possibilities:

- in case the patient was fully recovered on Day 7, parents are contacted by telephone, and asked if their child has had any further incidents since Follow-up I [S4]. If not, the study ends for the participant. If yes, any additional medical services, direct and indirect costs of both parents and the child are captured, as by questions foreseen by questionnaire S3bis.

- in case the patient has not fully recovered on day 7 follow up, additional medical services, direct and indirect costs of both parents and the child for the previous 7 day are captured [S3bis]. These patients will be contacted for Follow-up III at day 28±1.

At Follow-up III, on day 28±1 after inclusion, parents are contacted by telephone, and asked if their child has had any further incidents since Follow-up II [S4bis]. If yes, any additional medical services, direct and indirect costs of both parents and the child are captured, as by questions foreseen by questionnaire S3bis. In any case, the study ends at day 28±1 after inclusion.

SCHEDULE OF ASSESSMENTS (Prospective Surveillance Phase)

VISITS	Inclusion Visit-Screening	Discharge Visit	Follow up I Visit	Follow up II Visit	Follow up III Visit
STUDY DAY AND TIME WINDOWS	**Day -3***	**Day 0**	**Day 7** (±1 day)**	**Day 14** (±1 day)**	**Day 28** (±1 day)**
QUESTIONNAIRES***	**(S1A and S1B)**	**(S2)**	**(S3)**	**(S4 or S3bis)**	**(S4bis)**
STUDY PROCEDURES					
Study informed consent/assent form, privacy form administration and signature	X				
Assessment of eligibility criteria	X				
Patient parameters collection: - Demographic data - Clinical data - Medical history - Clinical diagnosis	X				
Multiplex diagnostic testing of respiratory sample	X				
Questionnaire to be administered to parents: - Demographic data - indirect costs - medical services before hospitalization - Complications - Clinicial procedures - Prescribed medications - Blood analysis (if blood sample took at Admission visit)	X				
Clinicians document the clinical outcome and medical services conducted through Questionnaires		X			
Results from multiplex testing are collected		X			
Any additional medical services, direct and indirect costs of both parents and the child while and after the hospital staying are captured			X	X	X

through Questionnaires					

NOTES
*This is intended to be up to 72 hours. If procedures requested are completed earlier, progression to **Day 0** is allowed.
** this visit is conducted through a telephone contact. Counting of study days is intended from discharge (Day0). **S4bis** is applicable only in case **S4** results in additional untoward event
*** Assessments S1B, S2, S3, S3bis/S4 and S4bis are intended for parents/legal tutors, while assessments S1A and S2 will be delivered by clinicians.

8.5 Data collection (applicable for both retrospective and prospective surveillance phases of the study)

Clinical parameters will be collected from medical charts. Data points include (Table 4):

TABLE 4 – CLINICAL PARAMETERS TO BE COLLECTED FROM MEDICAL CHARTS

Demographic data	Medical History	Course of infection, before and after hospitalization	Treatment course in Hospital	Socioeconomic aspects
i. age ii. date of birth iii. gender iv. area of residency by postal code	i. Prematurity ii. Birth weight iii. Breastfeeding iv. Family medical history: asthma, atopy, eczema and other v. Patients medical conditions* vi. Previous resp. infections vii. Previous hospitalizations viii. Administration of Palivizumab	i. Symptoms ii. Medication before hospitalization iii. Initial clinical diagnosis	i. Medical procedures ii. Analyses of clinical samples iii. Medication	i. Days out of work ii. Out of pocket expenses

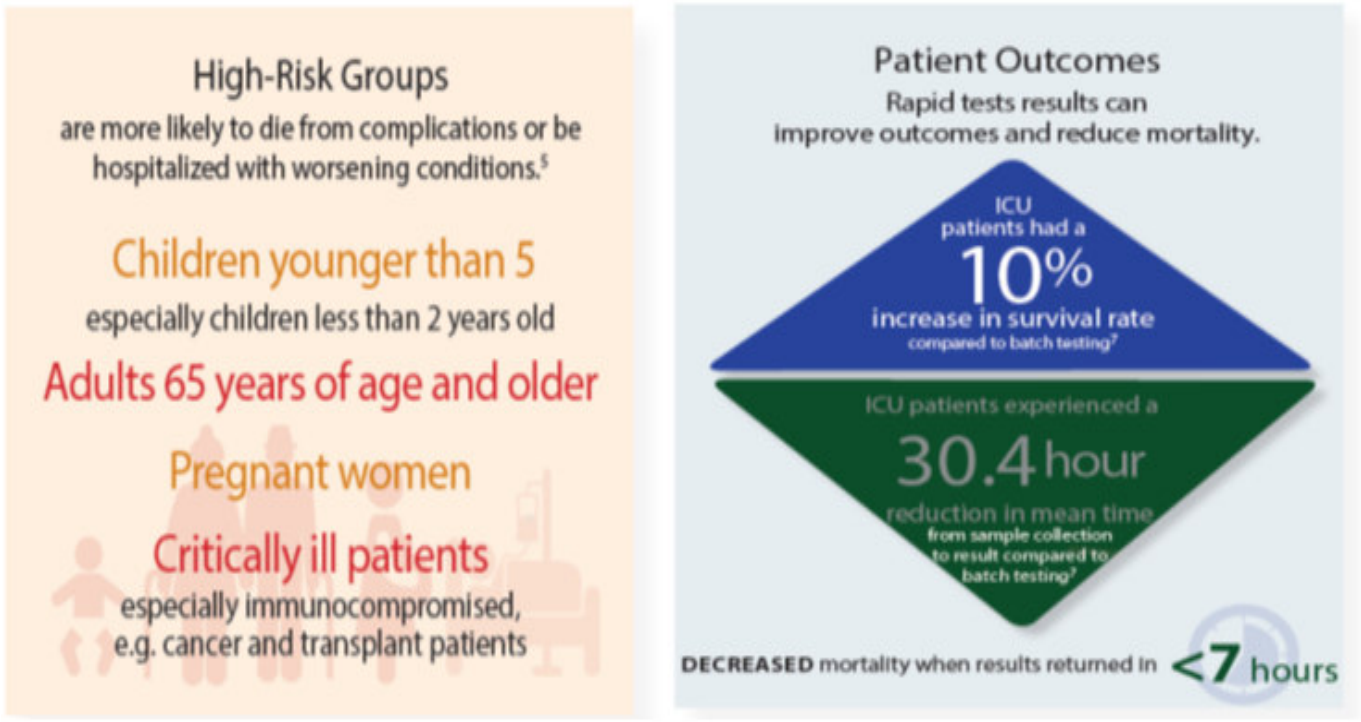
*as described in paragraph 8.3.2.

8.6 Pathogen identification and specimen collection

The clinical presentation of known respiratory pathogens is very similar, complicating diagnosis and appropriate therapy selection. Traditional diagnostic methods can be slow and miss the cause of infection.
Sample-to-answer multiplex molecular respiratory tests provide rapid, accurate, and comprehensive results to improve patient outcomes and reduce the cost-of-care (see Figure 2).
This is the reason why such tests are now the basis of the standard of care diagnostic approach for patients presenting symptoms of acute Lower Respiratory Tract Infection (LRTI), especially in the case of infants and young children.
For the purposes of the present study the identification of the pathogens will be done by the local laboratory of each of the sites involved using a multiplexed nucleic acid diagnostic test intended for the simultaneous qualitative detection and differentiation of nucleic acids from multiple respiratory viral and bacterial organisms

The analysis will be conducted on the nose and/or throat swab or nasopharyngeal aspirate which is collected, as per standard of care.
In light of one of the exploratory endpoints, the Sponsor will assess through a customized feasibility process which type of method is used locally to identify the pathogens and, given the assumption that such identification is now a days done using a multiplex method, will verify the comparability of the methodology used by each of the clinical sites involved in the present study in terms of sensitivity and in terms of completeness of the panel of pathogens which are targeted for identification.
To pursue standardization, the Sponsor might also take the decision to distribute a unique KIT to be used for identification, without interfering with the local practice but providing a unique instrument for diagnosis.

Figure 2 - Sample-to-answer multiplex molecular respiratory tests brochure.



8.7 Questionnaires to parent legal/guardian

In order to document complications, indirect costs of infant and caregivers, structured questionnaires will be administered to parents/caregivers in presence and/or via telephone by the designated site personnel at Inclusion (Day -3), Day 7±1, Day 14±1, and Day 28±1 post hospital discharge.

8.8 Data sources

Primary data collection will be performed from subjects' clinical information at enrolment and during the prospective follow-up period. Data will be also collected retrospectively using medical records. Source data will be medical records usually finalized during routine clinical practice.
Additionally, Investigators will be asked to obtain some social/sanitary/economic information using specific questionnaires.
A Source Data Location List will be generated at the start of the study, in order to map in detail the specific source of the requested data at each site level.
Clinical data required for the study will be entered into an electronic Case Report Form (eCRF), specifically developed to standardize the collection of the data done locally. The Investigator and/or delegated members of the site staff personnel (as identified in the relevant delegation log) will be responsible for entering data into the study specific eCRF.

8.9 Data Management

8.9.1 Data recording and Records keeping

A validated web-based electronic Case Report Form (eCRF) will be used to collect the requested data and must be completed and signed for each enrolled subject by the Investigator or authorized delegate from the Investigational Site Staff.
It is the Investigator's or authorized delegate's responsibility to ensure completion and to review and authorize release of all study eCRFs. These signatures serve to attest that the information contained on the eCRFs is true. At all times, the investigator has full responsibility for the accuracy, legibility, completeness, and timeliness of all data reported in the eCRFs and in all required reports. eCRFs and required reports must be legible. All the changes in the data will be tracked by a dedicated audit trail, which is a specific function of the eCRF. Information collected on the eCRFs must match source documents. In some cases, predefined data may be entered directly in the eCRF, in this case they will be considered as the source.
The data cleaning will be performed by the appointed Data Management who will provide the Investigator, through the eCRF, with the detected inconsistencies on each data analyzed. The validation of the inconsistencies (change or acceptance) will be made by the Investigator.

It is the investigator's responsibility to ensure the accuracy, completeness and timeliness of the study data reported in eCRF. A unique participant identifier will be assigned to all patients for registration in the eCRF system. The assigned code will not be used again if, for example, a participant is withdrawn from the study.

Any digital data transferred to or from the electronic database will be fully encrypted prior to transfer, in strict accordance with GDPR requirements.

Study data reported in the eCRF will be checked remotely for completeness and consistency by an appointed data manager and during site visits by the appointed Clinical Research Associates (CRAs). Discrepancies found will be notified to the Investigators by the eCRF queries system; Investigators will be asked to solve the reported queries by checking the entered data.
Once all the monitoring checks have been performed and all data queries have been resolved, the Database will be freezed. The Data Manager (DMr) in charge will provide the Biostatistics responsible with the cleaned Database for the Statistical Analyses. All the details relevant to the data management will be described in the Data Management Plan, which will be prepared by the Data Manager in charge of the study.

8.9.2 Study Records Retention

The investigator at each investigational site must make arrangements to store the essential study documents, (as defined in Essential Documents for the Conduct of a Clinical Trial, International Conference on Harmonisation (ICH) E6 R2, Guideline for Good Clinical Practice, which are applied with its general principles to the present study, although its observational nature) including the Investigator Site File. All study documents will be retained after the completion or premature termination of the trial for the timeframe defined by the applicable laws and regulation.
In addition, the investigator is responsible for archiving of all relevant source documents so that the study data can be compared against source data after completion of the study (e.g. in case of inspection from Authorities).
The specific timelines for long-term retention will be defined specifically within the Clinical Trial Agreement that the Sponsor will finalize with which clinical site involved in the study.

The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of the required storage period. Delegation must be documented in writing.

8.10 Statistical analysis

A detailed SAP will be developed in collaboration with a biostatistician.
Briefly, analysis will revolve around:

- Calculating proportion of LRTI hospitalization due to RSV and other respiratory pathogens
- Calculating incidence of LRTI hospitalization due to RSV and other respiratory pathogens per 1000 population
- Stratification of incidence rate by age, sex, pathogen, clinical severity, demographics
- Aggregating the total direct and indirect costs of medical services before, during and after hospitalization.

8.11 Sample Size

The sample size is based on three endpoints: RSV hospitalization prevalence, RSV incidence, and healthcare resources utilization/economic burden.

8.11.1 Sample size for RSV proportion of LRTI hospitalization in infants 0-<2 years of age (primary objective) and the Interim Analysis

A recent meta-analysis estimated the proportion of Acute Lower Respiratory-tract Infections admissions RSV positive for high-income countries to be 0.36 (95% CI 0.12–0.68) in infants aged

<1 year, and 0.22 (95% CI 0.06–0.51) in children aged 1 to 4 years [Johnson 2021]. If we perform a weighted average, we could assume a prevalence of infants <2 years of age positive for RSV of 0.29. The sample size to calculate the exact prevalence would be accordingly 317 [Epitools 2018]. Table 5 reports three different prevalence scenarios, with prevalence ranging from 0.22 to 0.36.

TABLE 5: ESTIMATED SAMPLE SIZE FOR RSV PREVALENCE STUDY.

Estimated prevalence	Prevalence Confidence interval	Estimated sample size for RSV positive cases
29%	0.24-0.34	317
36%	0.31-0.41	355
22%	0.17-0.27	264

**assumptions: precision 5%, population size: infinite.*

Therefore, at least 355 patients should be prospectively included to describe with acceptable certainty, even considering the high RSV-related hospitalization proportion scenario, the proportion of LRTI hospitalization in infants 0-<2 years of age attributable to RSV.

In any case, as anticipated in paragraph 3.1, an interim analysis of data collected during the first period of the prospective surveillance phase of the study will be conducted.
Descriptive analyses will be performed on targeted data (which are collected as Primary Data, according to the definition reported in the EMA "Guideline on registry-based studies" - EMA/426390/2021: *"collection of data directly from patients, caregivers, healthcare professionals or other persons involved in patient care"*) to gain an understanding of their qualitative and quantitative nature and to define, as much as possible, the characteristics of the patients enrolled. Details of the analyses to be carried out will be included in a dedicated Statistical Analysis Plan, which will be finalized before the end of the cited period. The results of this analysis will determine if surveillance should continue through the subsequent surveillance observation period and will also anticipate the basis for the possible implementation of a patient registry, i.e an *"organised system that collects uniform data (clinical and other) to identify specified outcomes for a population defined by a particular disease, condition or exposure"* (EMA "Guideline on registry-based studies" -EMA/426390/2021).

8.11.2 Sample size for incidence of LRTI hospitalization in infants 0-<2 years of age attributable to RSV (secondary objective):

McLaughlin, 2020 meta-analysis reported a hospitalization rate of 11.0 (95%CI 9.8 to 12.2) for infants aged <1year reported due to RSV infection. Dividing this estimate by a coefficient of 1.59, as suggested by the same paper, the average incidence rate for infants aged <2 years is 0.69% (Table 6) [McLaughlin 2020, Shi 2017].

TABLE 6: INCIDENCE RATE OF HOSPITALIZATION FOR RSV INFECTION IN INFANTS AGED <1YEAR AND <2 YEARS.

	Reported incidence rate	Lower CI	Higher CI
Hospitalization rate <1 year [McLaughlin, 2020]	11	9,8	12,2
Hospitalization rate <2 years [McLaughlin, 2020, Shi 2017]	6,9	6,2	7,7

Paediatric population figures by age and province for 6 provinces of interest (Rome, Milan, Turin, Genoa, Parma, Florence) have been extracted from ISTAT website [ISTAT 2021] in order to calculate the population basin of 6 selected hospitals that are or have been part of the INCiPiT Consortium () network and that will participate in the study. Data updated to the 1st Jan 2021 were extracted; retrieved data are reported in Table 7.

TABLE 7: INFANTS AGED 0 TO 1 YEAR IN THE SIX SELECTED PROVINCES (1ST JAN 2021).

YEARS OF AGE	ROME	MILAN	TURIN	FLORENCE	GENOA	PARMA
0	27737	23055	14150	6272	4707	3328
1	29457	24235	14637	6497	4776	3494
Total (<2years of age)	57194	47290	28787	12769	9483	6822

The hospitals' capacity to catch paediatric hospitalization cases with respect to the population basin has been estimated in a range from 40% to 90%, depending on the presence of other major hospitals in the province of interest. Data for the population by age (table 7), for the estimated catchment of each hospital±10%, and for the incidence rate (table 6) were used to build an average incidence rate/average catchment scenario, a lower incidence rate/lower catchment scenario, and a higher incidence rate/higher catchment scenario for the expected RSV-hospitalization cases to be observed by the 6 considered hospitals.
According to the average scenario, the selected hospitals should observe a total of 687 RSV-associated hospitalizations in infants <2years of age every year (lower incidence rate/lower catchment scenario: 555 children; higher incidence rate/higher catchment scenario 843 children). Due to the variability that might occur between seasons, substantial differences are expected between seasons.
Giving the above, the retrospective surveillance phase of the present study will collect data for 1665 patients, i.e. considering for each season a total of 555 children and therefore targeting the lower incidence rate as above calculated. If, according to the variability expected in between the seasons, the incidence rate will show to be higher, the collection of data will be continued making reference to the subsequent slots of incidence, as above defined.
To be noted that this is identified as a secondary objective.

8.11.3 Sample size for healthcare resources utilization and economic burden associated with LRTI-RSV episodes within one month following LRTI hospitalization in infants 0-<2 years of age (secondary objective):

Enrolling all the parents of the prospective surveillance, and assuming that at least 80% of them will complete the scheduled surveys, we would expect a minimum of 284 returning

questionnaires per season (i.e. 80% of 355 infants as calculated for the estimate of RSV proportion of LRTI hospitalization).
With this survey size, the expected margin of error (ME) would be 5.77%. The ME would be 9.8% with 100 returned questionnaires, and 5% with 384. By pooling together data from both seasons (sample size=568, i.e. 284x2), the ME would result 4.05%. For feasibility reasons, we considered a 5.77% of ME to be acceptable (http://www.raosoft.com/samplesize.html).

8.12 Evaluation of the potential benefit/risk ratio for the population

No direct benefits are expected from participation in the study. Potential benefits to participants would be indirect, related to new knowledge developed by the study and its implementation.
No major additional risks associated with participation in the study are expected, since also the collection of biological samples is part of the standard of care.

8.13 Subject withdrawal, intervention modifications and premature study termination

According to the observational nature of the present study, a patient may be prematurely discontinued for the following reasons:

1. Patient requests to leave the study (withdrawal of informed consent)
2. Patient lost to follow-up
3. Sponsor or Ethics Committee (EC) decides to terminate the study.

8.14 Definition of study conclusion

Retrospective surveillance phase will be concluded when data for selected seasons will be collected and analyzed.

Prospective surveillance will be concluded when parents/legal tutors of children enrolled in season 2022-2023 will have concluded the day 28 follow-up.

8.15 Protocol deviations

According to “ICH guideline E3 - questions and answers (R1) Step 5” (released on July 2012) *protocol deviation* is any change, divergence or departure from the study design or procedures defined in the protocol.
Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. For example, important protocol deviations may include enrolling subjects in violation of key eligibility criteria designed to ensure a specific subject population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the trial.
Protocol violation and important protocol deviation are sometimes used interchangeably to refer to a significant departure from protocol requirements. The word “violation” may also have other meanings in a regulatory context. However, in Annex IVa, Subject Disposition of the ICH E3

guideline, the term protocol violation was intended to mean only a change, divergence, or departure from the study requirements, whether by the subject or investigator, that resulted in a subject's withdrawal from study participation. To avoid confusion over terminology, sponsors are encouraged to replace the phrase "protocol violation" with "protocol deviation".

9. Safety reporting

This is a non-interventional, non-pharmacological observational study and there are no study endpoints pertaining to the evaluation of the efficacy or safety of any drugs; therefore, Regulation (No 1235/2010) and Directive (2010/84/EU) as well as EU Directive 2001/20/EC are not applicable.

10. Administrative aspects

10.1 Study Funding

This study has been funded by Sanofi Pasteur (a Société Anonyme organized and existing under the laws of the French Republic, having its registered head office at 14, espace Henri Vallée, 69007 LYON, FRANCE). The relationship between the regulatory Sponsor and the Funder are fully compliant with the requirements outlined in the Italian Decree 30 November 2021 ("Misure volte a facilitare e sostenere la realizzazione degli studi clinici di medicinali senza scopo di lucro e degli studi osservazionali e a disciplinare la cessione di dati e risultati di sperimentazioni senza scopo di lucro a fini registrativi, ai sensi dell'art. 1, comma 1, lettera c), del decreto legislativo 14 maggio 2019, n. 52. (22A01189)") (GU Serie Generale n.42 del 19-02-2022).

10.2 Insurance

Not applicable, being this an observational study.

10.3 Protocol Amendments

According to the nature of the present study, the ethical and regulatory requirements applicable are described in the "Determinazione 20 Marzo 2008: Linee guida per la classificazione e conduzione degli studi osservazionali sui farmaci" and in the Italian Decree 30 November 2021. Nevertheless, in terms of protocol amendments the Sponsor will in general comply with the profile of substantial and non-substantial amendments, as defined in the D.M. of 21/12/2007, which characterized as substantial "an amendment that has an impact on the safety or physical or mental integrity of the subjects and the ethical aspects of the trial, on the scientific value of the study, on the conduct or management of the study, on the quality or safety of each IMP or Medical Device used in the study".

Therefore, in case a substantial amendment will be generated during the course of the present study, it will be submitted to all the Ethics Commitees involved and submission will be accompanied with a letter of intent detailing the reasons that led to the modification/s applied, including a new benefit/risk analysis and a description of the possible consequences for the evaluation of the results obtained from the subjects already included in the study.

According to the above, patients (i.e. the parents or legal representatives) will be duly informed about any substantial modification done to the protocol and will be requested to confirm their decision to participate to the study by signing an updated informed consent form.

11. Ethical consideration

11.1 Protection of human rights

This study was designed and will be conducted in accordance with the current revision of the Declaration of Helsinki (Fortaleza, Brazil, 2013), Ethical Principles for Medical Research Involving Human Patients, applicable Good Clinical Practices (GCPs) principles, Good Pharmacoepidemiology Practice (GPP) [Epstein, 2016] issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA), European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and with local regulation for observational studies conduction.

11.2 Ethical compliance

The Investigator will perform the study in accordance with the regulations and guidelines governing medical practice and ethics in Italy.

This protocol and the related study documents (including, but not limited to, informed consent and privacy forms) will be submitted to the Independent Ethics Committee (IEC) relevant to each clinical site involved. Being this an observational study no approval from the Italian Competent Authority is requested, but the study will be notified to the national RSO (Register for Observational Studies). Notification in writing of ethical approvals must be in place before study initiation is implemented at each site.

The research will be conducted by clinically and scientifically qualified personnel under the supervision of a clinically competent medical person.

The Investigator will maintain adequate study records including eCRFs, medical records, laboratory reports, informed consent forms, any information regarding participants who discontinued and other pertinent data, such as, but not limited to, letters and administrative documents exchanged between the Sponsor and the clinical site related to the implementation, conduction and management of the present study.

11.3 Informed consent procedure

An Informed consent compliant with the Declaration of Helsinki and applicable international and local laws will be sought from the parents (or legal representatives) of the infants identified to be

included in the study. A description of the study objectives and public health impact in layman terms will be given to consented individuals for reference and during the procedure of administration of the informed consent adequate time to address any question will be given.

Data will not be collected before the relevant informed consent procedure will be duly completed.

11.4 Confidentiality

All subjects' data and samples will be identified only by subject identification number to maintain subject confidentiality, therefore the GDPR pseudonymization asset will be applied to this study. All subject study records will be kept at each site respecting local procedures, ensuring the limited and controlled access by the authorized site personnel; identification code lists linking the patients' names to subject identification numbers will be archived in the Investigator Site File (ISF), which will be kept in a locked cabinet at the investigator site only. Any other party involved in the study will review study data in a pseudonymised format only, except as necessary for monitoring by Regulatory Authorities or the study Sponsor.

11.5 Monitoring and Quality Assurance

The Sponsor, the Principal Investigator and/or delegates are responsible for ensuring the quality of the data. All reported information will be systematically checked for consistency, completeness and accuracy by the Principal Investigator and/or delegates. The Sponsor will allocate certified CRAs (Monitors) to appropriately monitor the study. The eCRF will be reviewed on site and/or remotely and checks will be made against the relevant Source Documents. In this regard, the Principal Investigator and/or delegates must allow regular visits by the study monitors (the frequency of such visits will be assessed based on enrollment) and must ensure full access to the study documents. All people involved, bound by professional secrecy, will not disclose any identity or medical information. The frequency and nature of the monitoring visits will be defined in the study specific Monitoring Plan.

Although this is an observational study, the GCPs' principles will be applied in order to ensure that the data collected will be in compliance with the ALCOAC standards for Source Data and Source Documents (Attributable, Legible, Contemporaneous, Original, Accurate, and Complete).

12. Responsibilities and Publication Policies

12.1 Intellectual Property

All the data, results obtained during or deriving from the execution of the Trial and in pursuit of its objectives (the "Results"), are the exclusive property of the Sponsor.

12.2 Publication Policies

The study results will be summarized in a final report in accordance with the GPP and the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [Vandenbroucke et al., 2007].

Prior to the initiation, the study will be registered in the "Registro Studi Osservazionali" of the Italian Competent Authority (AIFA), or into corresponding recipient (as per specific suggestion possibly received from AIFA).

Upon study completion and finalization of the study report, the results of this study may be either submitted for publication and/or posted in a publicly accessible database of result, such as ClinicalTrials.gov.

In agreement to applicable laws and regulations the final study report and/or progress reports, including interim reports of study results, if applicable and when required, will be provided to all IECs and to Investigators.

13. References

- American Academy of Pediatrics, Subcommittee on Diagnosis and Management of Bronchiolitis. Diagnosis and Management of Bronchiolitis. Pediatrics. 2006;118(4):1774-1793.
- Anderson EJ, Carbonell-Estrany X, Blanken M, et al. Burden of severe respiratory syncytial virus disease among 33-35 weeks' gestational age infants born during multiple respiratory syncytial virus seasons. Pediatr Infect Dis J. 2017;36(2):160-167.
- Barbati F, Moriondo M, Pisano L, Calistri E, Lodi L, Ricci S, Giovannini M, Canessa C, Indolfi G, Azzari C. Epidemiology of Respiratory Syncytial Virus-Related Hospitalization Over a 5-Year Period in Italy: Evaluation of Seasonality and Age Distribution Before Vaccine Introduction. Vaccines (Basel). 2020 Jan 4;8(1):15. doi: 10.3390/vaccines8010015. PMID: 31947976; PMCID: PMC7157234.
- Borchers AT, Chang C, Gershwin ME, et al. Respiratory syncytial virus – a comprehensive review. Clin Rev Allergy Immunol. 2013; 45(3): 331-79.
- Boyce TG, Mellen BG, Mitchel EF Jr et al. Rates of hospitalization for respiratory syncytial virus infection among children in medicaid. J. Pediatr. 2000; 137: 865-70.
- Boe J, Dennis JH, O'Driscoll BR, et al. for the European Respiratory Society Task Force on the use of nebulizers, European Respiratory Society Guidelines on the use of nebulizers. Eur Respir J. 2001;18(1):228–
- Bozzola E, Ciarlitto C, Guolo S, Brusco C, Cerone G, Antilici L, Schettini L, Piscitelli AL, Chiara Vittucci A, Cutrera R, Raponi M, Villani A.Front Pediatr. 2021 Jan 18;8:594898.
- Bhuiyan MU, Stiboy E, Hassan MZ, Chan M, Islam MS, Haider N, Jaffe A, Homaira N. Epidemiology of COVID-19 infection in young children under five years: A systematic review and meta-analysis. Vaccine. 2021 Jan 22;39(4):667-677. doi: 10.1016/j.vaccine.2020.11.078. Epub 2020 Dec 5. PMID: 33342635; PMCID: PMC7833125.
- Calderaro A, De Conto F, Buttrini M, Piccolo G, Montecchini S, Maccari C, Martinelli M, Di Maio A, Ferraglia F, Pinardi F, Montagna P, Arcangeletti MC, Chezzi C. Human respiratory viruses, including SARS-CoV-2, circulating in the winter season 2019-2020 in Parma, Northern Italy. Int J Infect Dis. 2021 Jan;102:79-84. doi: 10.1016/j.ijid.2020.09.1473. Epub 2020 Oct 2. PMID: 33017694; PMCID: PMC7530558.
- Ciarlitto C, Vittucci AC, Antilici L, Concato C, Di Camillo C, Zangari P, Villani A. Respiratory Syncityal Virus A and B: three bronchiolitis seasons in a third level hospital in Italy. Ital J Pediatr. 2019 Aug 28;45(1):115. doi: 10.1186/s13052-019-0704-0. PMID: 31462274; PMCID: PMC6712785.
- Cohen C, Walaza S, Moyes J, et al. Epidemiology of Viral-Associated Acute Lower Respiratory Tract Infection among Children <5 Years of Age in a High HIV Prevalence Setting, South Africa, 2009-2012. Pediatr Infect Dis J. 2015; 34(1): 66–72.

- Comar M, Benvenuto S, Lazzerini M, Fedele G, Barbi E, Amaddeo A, Risso FM, Strajn T, Di Rocco P, Stefanelli P, Rezza G. Prevalence of SARS-CoV-2 infection in Italian pediatric population: a regional seroepidemiological study. Ital J Pediatr. 2021 Jun 5;47(1):131. doi: 10.1186/s13052-021-01074-9. PMID: 34090486; PMCID: PMC8179691.
- De Crescenzo F, Amato L, Cruciani F, Moynihan LP, D'Alò GL, Vecchi S, Saulle R, Mitrova Z, Di Franco V, Addis A, Davoli M. Comparative Effectiveness of Pharmacological Interventions for Covid-19: A Systematic Review and Network Meta-Analysis. Front Pharmacol. 2021 May 3;12:649472. doi: 10.3389/fphar.2021.649472. PMID: 34012398; PMCID: PMC8126885.
- Dembiński Ł, Vieira Martins M, Huss G, Grossman Z, Barak S, Magendie C, Del Torso S, Dornbusch HJ, Mazur A, Albrecht K, Hadjipanayis A. SARS-CoV-2 Vaccination in Children and Adolescents-A Joint Statement of the European Academy of Paediatrics and the European Confederation for Primary Care Paediatricians. Front Pediatr. 2021 Aug 23;9:721257. doi: 10.3389/fped.2021.721257. PMID: 34497784; PMCID: PMC8419337.
- Deshpande SA and Northern V. The clinical and health economic burden of respiratory syncytial virus disease among children under 2 years of age in a defined geographical area. Arch Dis Child. 2003; 88: 1065-9.
- Diez-Domingo J, Perez-Yarza EG, Melero JA, et al. Social, economic, and health impact of the respiratory syncytial virus: a systematic search. BMC Infect Dis. 2014;14:544.
- EMA “Guideline on registry-based studies” -EMA/426390/2021
- Empey KM, Peebles Jr RS, Kolls JK. Pharmacologic Advances in the Treatment and Prevention of Respiratory Syncytial Virus. Clin Infect Dis. 2010; 50(9):1258–1267.
- GenMark Diagnostics, Inc. ePlex® Respiratory Pathogen Panel 2 - Package Insert. Posted on 5th October, 2020. Available at: https://www.fda.gov/media/142905/download.
- Sergeant, ESG, 2018. Epitools Epidemiological Calculators. Ausvet. Available at: http://epitools.ausvet.com.au. Last access: 3rd October 2021.
- Feltes TF, Sondheimer HM. Palivizumab and the prevention of respiratory syncytial virus illness in pediatric patients with congenital heart disease. Expert Opin. Biol. Ther. 2007; 7(9):1471-1480.
- Fisher RG, Gruber WC, Edwards KM, et al. Twenty years of outpatient respiratory syncytial virus infection: a framework for vaccine efficacy trials. Pediatrics. 1997; 99(2): E7.
- García CG, Bhore R, Soriano-Fallas A, et al. Risk factors in children hospitalized with RSV bronchiolitis versus non-RSV bronchiolitis. Pediatrics. 2010; 126: e1453-60.
- Graham BS. Biological challenges and technological opportunities for respiratory syncytial virus vaccine development. Immunol Rev. 2011; 239:149-66.
- Griffin MP, Yuan Y, Takas T, Domachowske JB, Madhi SA, Manzoni P, et al. Single-dose nirsevimab for prevention of RSV in preterm infants. N Engl J Med. 2020;383(5):415–25. https://doi.org/10.1056/NEJMoa1913556.
- Haerskjold A, Kristensen K, Kamper-Jørgensen M, Nybo Andersen AM, Ravn H, Graff Stensballe L. Risk Factors for Hospitalization for Respiratory Syncytial Virus Infection: A

Population-based Cohort Study of Danish Children. Pediatr Infect Dis J. 2016 Jan;35(1):61-5. doi: 10.1097/INF.0000000000000924. PMID: 26398871.

- Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med. 2009; 360: 588-98.
- Holman RC, Curns AT, Cheek JE, et al. Respiratory syncytial virus hospitalizations among American Indian and Alaska Native infants and the general United States infant population. Pediatrics. 2004; 114: e437-44.
- Influnet. Sorveglianza Epidemiologica e Virologica dei casi di sindrome simil-influenzale, di influenza e di Sars-CoV-2. PROTOCOLLO OPERATIVO. Stagione 2020-2019. Last accessed: 30 September 2021. Available at: https://www.salute.gov.it/imgs/C_17_pubblicazioni_2963_allegato.pdf.
- ISTAT. Demo-Geodemo – Popolazione residente. Disponibile su: http://demo.istat.it/popres/index.php?anno=2021&lingua=ita . Last accessed 1st Nov 2021.
- Iwane MK, Edwards KM, Szilagyi PG, et al. Population-based surveillance for hospitalizations associated with respiratory syncytial virus, influenza virus, and parainfluenza viruses among young children. Pediatrics. 2004; 113: 1758-64.
- Leidy N, Margolis M, Marcin J, et al. The impact of severe respiratory syncytial virus on the child, caregiver, and family during hospitalization and recovery. Pediatrics. 2005;115(6):1536-1546.
- Kosmeri C, Koumpis E, Tsabouri S, Siomou E, Makis A. Hematological manifestations of SARS-CoV-2 in children. Pediatr Blood Cancer. (2020) 67:e28745. doi: 10.1002/pbc.28745
- Kuhdari P, Brosio F, Malaventura C, Stefanati A, Orsi A, Icardi G, Gabutti G. Human respiratory syncytial virus and hospitalization in young children in Italy. Ital J Pediatr. 2018 May 4;44(1):50. doi: 10.1186/s13052-018-0492-y. PMID: 29728106; PMCID: PMC5935991.
- Krilov LR. Respiratory syncytial virus disease: update on treatment and prevention. Expert Rev. Anti. Infect. Ther. 2011; 9(1): 27–32.
- Madhi SA, Kuwanda L, Cutland C, et al. Five-year cohort study of hospitalization for respiratory syncytial virus associated lower respiratory tract infection in African children. J Clin Virol. 2006; 36: 215-21.
- McLaughlin JM, Khan F, Schmitt HJ, Agosti Y, Jodar L, Simões EAF, Swerdlow DL. Respiratory Syncytial Virus-Associated Hospitalization Rates among US Infants: A Systematic Review and Meta-Analysis. J Infect Dis. 2020 Dec 21:jiaa752. doi: 10.1093/infdis/jiaa752. Epub ahead of print. PMID: 33346360.
- Mehta NS, Mytton OT, Mullins EWS, Fowler TA, Falconer CL, Murphy OB, et al. SARS-CoV-2 (COVID-19): what do we know about children? A systematic review. Clin Infect Dis. (2020) 71:2469–79. doi: 10.1093/cid/ciaa556
- Mejias A, Rodríguez-Fernández R, Oliva S, Peeples ME, Ramilo O. The journey to a respiratory syncytial virus vaccine. Ann Allergy Asthma Immunol. 2020 Jul;125(1):36-46.

doi: 10.1016/j.anai.2020.03.017. Epub 2020 Mar 23. PMID: 32217187; PMCID: PMC7311299.

- Midulla F, Nenna R, Scagnolari C, Petrarca L, Frassanito A, Viscido A, Arima S, Antonelli G, Pierangeli A. How Respiratory Syncytial Virus Genotypes Influence the Clinical Course in Infants Hospitalized for Bronchiolitis. J Infect Dis. 2019 Jan 29;219(4):526-534. doi: 10.1093/infdis/jiy496. PMID: 30204889.
- Nam HH, Ison MG. Respiratory syncytial virus infection in adults. BMJ. 2019 Sep 10;366:l5021. doi: 10.1136/bmj.l5021. PMID: 31506273.
- Navarro Alonso JA, Bont LJ, Bozzola E, Herting E, Lega F, Mader S, Nunes MC, Ramilo O, Valiotis G, Olivier CW, Yates A, Faust SN.RSV: perspectives to strengthen the need for protection in all infants. Emerg Themes Epidemiol. 2021 Oct 21;18(1):15.
- Paramore LC, Ciuryla V, Ciesla G et al. Economic impact of respiratory syncytial virusrelated illness in the US: an analysis of national databases. Pharmacoeconomics. 2004; 22: 275-84.
- Rietveld E, De Jonge HC, Polder JJ, et al. Anticipated costs of hospitalization for respiratory syncytial virus infection in young children at risk. Pediatr Infect Dis J. 2004; 23: 523-9.
- Rudan I, Boschi-Pinto C, Biloglav Z, Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. Bull. World Health Organ. 2008; 86(5):408-416.
- Shi T, McAllister D, O'Brien K, et al. for the RSV Global Epidemiology Network. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet. 2017;390(10098):946-958.
- Schwarz TF, Johnson C, Grigat C, Apter D, Csonka P, Lindblad N, Nguyen TL, Gao FF, Qian H, Tullio AN, Dieussaert I, Picciolato M, Henry O. Three dose levels of a maternal respiratory syncytial virus vaccine candidate are well tolerated and immunogenic in a randomized trial in non-pregnant women. J Infect Dis. 2021 Jun 19:jiab317. doi: 10.1093/infdis/jiab317. Epub ahead of print. PMID: 34146100.
- Simoes EAF. Respiratory syncytial virus infection. Lancet. 1999; 354: 847–52.
- Synagis® EPAR Summary. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000257/WC500056736.pdf. Accessed on 13 November 2019.
- Stein RT, Bont LJ, Zar H, Polack FP, Park C, Claxton A, Borok G, Butylkova Y, Wegzyn C. Respiratory syncytial virus hospitalization and mortality: Systematic review and meta-analysis. Pediatr Pulmonol. 2017 Apr;52(4):556-569. doi: 10.1002/ppul.23570. Epub 2016 Oct 14. PMID: 27740723; PMCID: PMC5396299.
- STROBE: STrengthening the Reporting of OBservational studies in Epidemiology. Available at: https://www.strobe-statement.org
- van Summeren JJGT, Rizzo C, Hooiveld M, Korevaar JC, Hendriksen JMT, Dückers MLA, Loconsole D, Chironna M, Bangert M, Demont C, Meijer A, Caini S, Pandolfi E, Paget J.

Evaluation of a standardised protocol to measure the disease burden of respiratory syncytial virus infection in young children in primary care. BMC Infect Dis. 2021 Jul 26;21(1):705. doi: 10.1186/s12879-021-06397-w. PMID: 34311699; PMCID: PMC8311415.

- Vicente D, Montes M, Cilla G, et al. Hospitalization for respiratory syncytial virus in the pediatric population in Spain. Epidemiol Infect. 2003; 131: 867-72.
- Virazole® Summary of Product Characteristics. http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1493963375540.pdf. Accessed 1 March 2018.
- Zhang S, Akmar LZ, Bailey F, Rath BA, Alchikh M, Schweiger B, et al. Cost of respiratory syncytial virus-associated acute lower respiratory infection Management in Young Children at the regional and global level: a systematic review and meta-analysis. J Infect Dis. 2020;222(Supplement_7): S680–7. https://doi.org/10.1093/infdis/jiz683.
- Zhou H, Thompson WW, Viboud CG, et al. Hospitalizations associated with influenza and respiratory syncytial virus in the United States, 1993-2008. Clin Infect Dis. 2012;54(10):1427-1436.
- Zomer-Kooijker K, Uiterwaal CS, van der Gugten AC, Wilbrink B, Bont LJ, van der Ent CK. Decreased lung function precedes severe respiratory syncytial virus infection and post-respiratory syncytial virus wheeze in term infants. Eur Respir J. 2014;44(3):666-74.
- Wainwright C. Acute viral bronchiolitis in children – a very common condition with few therapeutic options. Paediatr Respir Rev. 2010; 11(1):39-45.
- WHO. Weekly epidemiological update on COVID-19 - 28 September 2021. Available at: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---28-september-2021. Last access: 3rd Oct 2021.