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Respiratory Syncytial Virus associated hospitalisations in children up to 6 years of age in Italy: a systematic review

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Abstract

Introduction. *Respiratory syncytial virus is a leading cause of respiratory hospitalisations in infants. This systematic review (registration number: CRD42021248309) aims to synthesise the available evidence on Respiratory Syncytial Virus-related hospitalisations among children aged 0 to 6 years in Italy.*

Methods. *The literature search was conducted on PubMed, Embase, Scopus, and International HTA, covering the period from January 2000 to July 2022, with a focus on studies that reported information on Respiratory Syncytial Virus-associated hospitalisation in children aged 0-6 years in Italy.*

Results. *Eight articles were included after screening 20,845 records. These retrospective studies reported that most hospitalisations were among those <1 year (71.5%-88.8%), infants aged <1 year were also at higher risk of hospitalisation in intensive care unit. Respiratory Syncytial Virus infections typically peaked December-February, with an atypical early start in August 2021. Subtype analysis showed alternating prevalence of Respiratory Syncytial Virus-A and Respiratory Syncytial Virus-B across different seasons. Coinfections were not uncommon (1.1%-37.4%), with rhinovirus and bocavirus being the most frequent.*

Conclusions. *All infants at their first Respiratory Syncytial Virus season showed an increased risk of severe infection and hospitalisation, regardless of the gestational age at birth, compared to older participants. This systematic review will enrich the understanding about Respiratory Syncytial Virus disease and help support decisions regarding prevention efforts in Italy.*

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Introduction

Respiratory syncytial virus (RSV) is one of the major pathogens responsible for hospitalisations due to lower respiratory tract infections (LRTIs) in young children <5 years of age (1). RSV can indeed spread to the lower respiratory tract, causing severe LRTIs including bronchiolitis, and/or pneumonia (2). Also, RSV infections may have short-term direct and indirect consequences such as an increased incidence of acute otitis media, pneumonia, and excessive antibiotic usage (3), or long-consequences such as early transient or recurrent wheezing, asthma, and impaired lung function (4). Respiratory Syncytial Virus (RSV) is estimated to be the causative agent in 80% and 40% of hospitalisations due to bronchiolitis and pneumonia, respectively, among children (5). Globally, it's projected that RSV accounts for a total of 55,000 to 200,000 annual fatalities and 3.2 million hospitalisations among children below 5 years old (6). The most severe cases are predominantly observed in infants under 1 year of age, with a notably higher incidence in nations with limited economic resources (1,6). Several vaccines targeting infants, pregnant women, and older adults are currently under development: while two adult vaccines have recently been approved, including one specifically for pregnant women that will therefore protect newborns, there is no available vaccine to prevent RSV infections in infants as of now (7). An effective monoclonal antibody, palivizumab, is available for prophylaxis and is recommended for high-risk infants in Italy (8). It is reimbursed for preventing severe lower respiratory tract illnesses caused by RSV in children at high risk of RSV disease, such as those with a gestational age ≤35 weeks and an age <6 months at the start of the RSV season, those aged <2 years who have received treatment for bronchopulmonary dysplasia in the last 6 months, and those aged <2 years with hemodynamically significant congenital heart disease (9). In addition, the extended half-life mAb nirsevimab is approved for all newborns and infants to protect against RSV-LRTI with a single dose for their first RSV season (at least 5 months) and also for at-risk infants during their second RSV season in Canada and the USA (10). Universal implementation of long-acting monoclonal antibodies nirsevimab in newborns during RSV season has proven to be effective and safe as tested in Galicia, France, and in Valle D'Aosta region (11-14). In the future, nirsevimab may be included in the national immunization calendar as it has already been recommended by Italian scientific societies (15). Given the substantial estimated impact of the RSV disease burden on children, coupled with the advent of new preventive measures, this systematic review seeks to analyse the epidemiological data regarding RSV disease in hospitalised paediatric patients aged 0-6 years in Italy, spanning the years 2000 to 2022, and set the scene for a comprehensive understanding of the current burden of RSV disease in terms of hospitalisations in the country. Specifically, we have collected data related to the age of hospitalized children, the presence of co-infections with RSV, the distribution of RSV-A and RSV-B, and gestational age at birth.

Materials and Methods

1. Protocol registration and search strategy

The protocol of this systematic review was registered on the International Prospective Register of Systematic Reviews on August 8, 2021 (Registration number CRD42021248309). The review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (16) guidelines and a PRISMA Checklist was filled in (Supplementary File 1). Records were searched from 01 January 2000 until 14th July 2022 in the following databases: PubMed, Embase, Scopus, International HTA Database. The search query was built to search for all articles reporting data on patients hospitalised due to RSV infections in Italy. It was tailored to suit the specific requirements of each database, and it was developed to be as much sensitive as possible, to avoid the exclusion of any article that could be suitable for inclusion. As an example, the query used for searching on PubMed was as follows: (RSV OR hRSV OR Respiratory Syncytial Virus OR bronchiolitis OR ILI OR ARI OR SARI OR respiratory infection OR "respiratory tract infection" OR RTI OR URI OR URTI OR LRI OR LRTI OR "Viral pneumonia" OR otitis) AND (burden OR impact OR epidemiol* OR economic OR cost* OR hospital* OR incidence OR prevalence OR diagnos* OR diagnosis OR "laboratory confirm*" OR surveillance) AND (Italy OR Italian OR Italians OR Ital*) AND (paediatric OR child* OR toddler* OR newborn* OR infant* OR preterm OR pediatric*). The references of the included or relevant papers were then meticulously examined through a process of backward citation chaining.

1.1. Eligibility Criteria

This systematic review included studies conducted

in Italy between 2000 and 2022, focusing on RSV-related hospitalisations in patients aged 0 to 6 years. The review considered both observational studies and clinical trials for inclusion. To be eligible, a study had to exclusively include children hospitalized for RSV infection, ensuring that the inclusion criteria were 100% children hospitalized due to RSV. Studies that included and analyzed patients hospitalized due to other viruses were excluded. Additionally, the inclusion criteria required studies to provide at least one of the following data points: the proportion of RSV-associated hospitalizations by age, the distribution of RSV-A and RSV-B, RSV seasonality, and RSV co-infections with other infectious agents. Studies that did not meet the specified criteria were excluded from the final database: reviews, letters, posters, and conference abstracts reporting no data were excluded, as well as studies published in a language other than English or Italian.

1.2. Screening and study selection

All identified records were compiled in a Microsoft Excel sheet (Microsoft Excel® per Microsoft 365 MSO © Microsoft 2022 Microsoft Corporation). Duplicates have then been removed. Four reviewers worked in pairs in a double-blind manner to assess the eligibility of records based on title, abstract, and full text. Any discrepancies were resolved by a fifth, more experienced, investigator. Additionally, the reference lists of eligible papers and previously published literature reviews were further analysed to identify potentially relevant articles on the same topic.

1.3. Data retrieval, data analysis, and quality assessment

Following the selection process, the chosen articles underwent thorough analysis. Reviewers extracted key information from each record, encompassing general study details such as authors, title, and publication year. Study design, including cohort, case-control, and cross-sectional studies, was carefully noted. Additionally, geographical context and time of observation, along with participant characteristics such as age groups and sample sizes, were systematically recorded.

The data extraction process involved a comprehensive assessment of clinical and epidemiological outcomes. To ensure accuracy and reliability, data entries were cross validated by multiple reviewers. The data extraction encompassed identifying the clinical diagnosis of hospitalisation, the distribution of RSV cases among different age groups, and available characterization of RSV subtypes (RSV-A and RSV-B). When possible, information regarding coinfections with other pathogens and the seasonal patterns of RSV was also collected. The extracted data were then organized into designated tables for further analysis. The narrative analysis of this systematic review revolved around those topics identified as key during the data extraction (age distribution, seasonality, subtypes distribution, and coinfections identified in the hospitalised cases). The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS). Each study received a score based on NOS criteria, with a maximum score of 9, representing the lowest risk of bias.

Results

1. Selection process

A total of 20,845 records were initially retrieved (Supplementary File 2): after removing duplicates (n = 1,991) and records not in Italian or English language (2,066), 16,788 records underwent initial screening based on title and abstract. Out of these, 16,541 records were excluded at this stage, leaving 247 records for further consideration. Subsequently, 239 articles were excluded based on specific criteria: studies entirely focused on children over 6 years old, geographical context outside Italy, period outside the scope (before the year 2000), incorrect study type (e.g. reviews, letters without original data), and outcomes unrelated to RSV-associated hospitalisation. Eight articles, all judged of low risk of bias (score range 7-9), were selected for inclusion in this study (Supplementary File 3).

1.1. Analysis of RSV-associated hospitalisations in children under 6 years in Italy

The 8 articles analysed in this review are summed up in Table 1 (17-24). All studies are retrospective analyses published between 2007 and 2022.Table 2 summarizes the proportion of RSV-associated hospitalisations by age for the included studies, reporting related data, including those age groups that encompass children older than 6 years when present. Kuhdari et al. 2018 (20), analysed the Hospital Discharge Records (HDRs) supplied by the National Archive of HDRs data (Italian Ministry of Health) in the period 2001–2014. The sample population was represented by all age groups (from 0 to >75 years); however, for the purpose of this review, we considered only data referred to the 0-4 years old

Table 1. Characteristics of the articles included in the systematic review, inverse chronological order, as reported in the included manuscripts.

Author	Hospital (Geographical region)**	Time of observation	Sample description
Loconsole D. et al., 2022	Giovanni XXIII Hospital (Bari, Southern Italy)	January 2017-December 2021	179 children aged 0-12 months, 13-24 months and >24 months
Barbati F. et al., 2020	Various centers in Tuscany, region of Central Italy	September 2014 - August 2019	624 children aged 0-6 years
Ciarlitto C. et al., 2019	Bambino Gesù Children's Hospital (Rome, Central Italy)	Winter seasons from 2015-2016 to 2017-2018	422 children aged < 1 year
Kuhdari P. et al., 2018	National Hospital Discharge Records	January 2001- December 2014	55,926* hospitalisations in children were children aged 0-4 years
Capizzi A. et al., 2017	Gaslini Hospital (Genova, Northern Italy)	Epidemic seasons from 2014-2015 to 2016-2017	366 children aged ≤ 1 year
Pierangeli A. et al., 2014	Umberto I Hospital (Rome, Central Italy), and United Hospitals (Ancona, Central Italy)	Epidemic seasons from 2010-2011 to 2012-2013	515 children: 165 in Rome (mean age: 4.8 months; median age: 2.75) and 350 in Ancona (mean age: 12.8 months; median age: 3 months; range: 0.1–163 months)
Scagnolari C. et al., 2012	Umberto I Hospital (Rome, Central Italy)	Winter seasons from 2006-2007 to 2009-2010	132 children (median age: 2.2 months, range: 0.23-32 months)
Rossi G.A. et al., 2007	Various centers in Northern, Central, and Southern Italy	Epidemic seasons from 2000-2001 to 2003-2004	145 children aged ≤ 4 years

*Calculated using data reported in the manuscript by Kuhdari et al.; **data retrieved from national or local medical records

Table 2. Distribution of RSV infections in hospitalised subjects by age group (%), when given.

Author	< 1 month	1-2 months	3-5 months	6-11 months	1-2 years	3-4 years	5-6 years	> 6 years
Loconsole et al., 2022	71.5				8.4	20.1*		
Barbati F. et al., 2020	41	21.5	19.1		18.4			
Kuhdari P. et al., 2018	88.8				8.2		3.0	
Capizzi A. et al., 2017 (full-term infants)	55.2**		21.4**	23.4**				
Capizzi A. et al., 2017 (pre-term infants)	62.5**		3.7**	33.8**				
Scagnolari C., 2012	78.6			21.4***				
Rossi GA. et al., 2007	41.4		33.1	21.4	4.1			

Note: * >24 months; ** calculated average value of three winter seasons; *** 6-32 months.

group hospitalised for RSV-related pathologies (97% of the entire population) with the following ICD9-CM codes: 466.11 (RSV bronchiolitis), 480.1 (RSV pneumonia) and 796 (RSV). Most hospitalisations involved patients < 1 year of age (88.8%), 8.2% referred to the 1–4 years age group and 3% the rest of the population. Moreover, the 1.7% of all RSV-related hospitalisations registered in the period 2001–2014 involved infants aged < 28 days of life (20). In Barbati et al., among 624 RSV-positive hospitalised children 0-6 years old from September 2014 to August 2019, 509 children were < 1 year, 390 were <3 months and 256 aged less than 30 days (81.6%, 62.5%, and 41% respectively). Prematurity (defined as <37 weeks of gestational age) was detected in 24.5% of children, of which 72.5% were born at 34-37 weeks. Furthermore, there were other predisposing factors for contracting RSV infection in 31 cases (5.0%), involving congenital heart conditions. Within the group of 624 children admitted to the hospital as part of the research, a total of 103 (16.5%) necessitated placement in the Intensive Care Unit (ICU), with the majority being infants aged less than 1 year (86.4% out of 103) (18).

In 2022, the research by Loconsole et al. retrospectively examined data related to the demographic and clinical characteristics, along with any existing health conditions and concurrent infections, of paediatric patients who had been hospitalised due to RSV infection. The study, conducted between August and December 2021, encompassed a total of 179 children (128 aged 0-12 months, 15 aged 13-24 months, 36 aged > 24 months). Among all children, 32 of them (equivalent to 17.9%) were born prematurely and 38 children (21.2%) have comorbidity (17).

The retrospective case-control study by Rossi et al. (23) shows the distribution of 145 children ≤4 years of age admitted to hospital for RSV-induced LRTI over four consecutive winter seasons (2000-2001 to 2003-2004), compared to LRTI cases due to other agents ("controls"). During the analysed period, the most represented age group were children aged <3 months old (41.4%), followed by those aged 3-5 months (33.1%), 6-11 months (21.4%) and those > 12 months (4.1%) (23). Scagnolari et al. enrolled 132 subjects (0-32 months) with a clinical diagnosis RSV-associated bronchiolitis between 2006 and 2010. The age distribution of RSV hospitalised patients was 78.6% in infants aged 0-5 months and 21.4% in the rest of the population analysed (24). In a retrospective analysis by Capizzi et al., three RSV epidemic seasons were analysed. A total of 366 infants (aged ≤12 months) were admitted to Gaslini Hospital due to RSV-induced ALRI: 137 in 2014-2015, 109 in 2015-2016, and 120 in 2016-2017. Notably, 7.7% of these cases involved preterm infants (29- < 36 weeks gestational age). The proportion of preterm admissions increased over the seasons. Among infants aged <6 months, 71.6%-80.8% of cases were full-term, with 48.2%-63.3% being younger than 3 months (21). In the study by Ciarlitto et al., all included children were 1 year old or less, and the median age at admission was 2 months and 10 days (no further detail was given), while in Pierangeli et al. (515 children), the median age at admission was 2.75 months. These two papers did not report an analysis by subgroup of age (19, 22).

1.2. RSV Seasonality

Three studies reported information on RSV seasonality for different seasons and are here reported in chronological order. In the winter seasons 2010-2011 and 2011-2012, Pierangeli and his team observed that the first hospitalisations due to RSV took place around mid-December and reached their peak during January and February. In 2012-2013 they observed an earlier start of both the RSV-season and RSV-associated hospitalisations (second half of November) (22).

The study by Barbati and cees described the trend of RSV infections in the paediatric population of Tuscany from September 2014 to August 2019. Their group observed a usual start of RSV epidemic in the late fall (November), with a peak during winter (January), and a variable end in early spring (April). Among 624 cases, 502 (80.4%) occurred in the period December-February, 584 (93.6%) if also considering the month of March (18).

The paper by Loconsole et al. studied the seasonal trends of RSV from 2017 to 2021 and reported that season 2021/2022 differed significantly from the previous years, being anticipated (first cases in August and peak in November) and with a higher peak, compared to the previous four seasons that saw the first cases in late October and the peak in late January/early February (17).

1.3. RSV-A and RSV-B distribution

Regarding the RSV subtype, three papers reported data on the percentage of RSV A and B (Supplementary File 4). RSV-A and RSV-B infections varied across the epidemic seasons considered, although RSV-A seemed to be more frequent (particularly, but not only, in preterm children) (17,19,22).

In the study conducted by Ciarlitto et al., it was

observed that among all the children examined, 64.4% were identified with RSV-A, 33.9% with RSV-B, and 1.7% exhibited a coinfection of both RSV-A and RSV-B. Throughout the investigated timeframe, RSV-A was the dominant strain in both term infants (64%) and preterm infants (68%). Specifically, during the first season (November 2015 - March 2016), RSV-A displayed predominance (90.1%), the second one RSV-B exhibited higher prevalence (62.3%), and the third one saw RSV-A as more frequent again (58.2%). The data reported by Ciarlitto et al., were consistent in both the term and pre-term groups of children. Although in terms of quantity the majority of children were infected with RSV-A, the data highlighted an alternating predominance between RSV-A and RSV-B strains in different seasons (19). Pierangeli et al. (who analysed seasons 2010-2011, 2011-2012 and 2012-2013) also reported an alternating trend with 83 cases of RSV-A and 97 RSV-B in 2010-2011, 119 RSV-A and 46 RSV-B in 2011-2012, 158 RSV-A and 12 RSV-B in 2012-2013 (22). Lastly, Loconsole et al. reported data for 179 children hospitalised between August and December 2021, being 136 of them infected with RSV-B (76%), 41 infected with RSV-A (23%), and 2 with both the RSV subtypes (1%) (17).

1.4. Coinfections with RSV

Finally, the coinfected association of RSV with other pathogens was assessed by molecular techniques by all studies, when reported (Supplementary File 5). The RSV coinfection rates ranged from 1.1% (21) to 37.4% (17). Among the other coinfection agents, rhinovirus was one of the most common pathogens found, ranging from 19% (19) to 47.8% (17) and bocavirus infections ranged from 26.9% (17) to 53.8% (24). Loconsole et al., 2022 reported that the 9% of the coinfected children was infected also with SARS-CoV-2 (17). Among 366 cases, Capizzi et al. 2017 reported 4 coinfections with a bacterial agent (Hib) (21).

Discussion

This systematic review aimed to collect and analyse the RSV-hospital burden in children aged 0-6 years old in Italy between 2000 and 2022.

Among the 8 retrieved studies in the period 2000-2021, we found that the RSV most affected age group were hospitalised children < 1 year old (71.5%-88.8%) (17,20) and especially those < 3 months (up to 62.5%, often requiring intensive care). Consistent information was reported by a recent modelling study aimed at estimating the number of RSV-associated hospitalisations in EU children under 5 years, that estimated that 78.3% (19,858/25,354) of annual RSV-associated hospitalisations occur among the age group 0-11 months in Italy (25). Other countries worldwide have reported interesting and similar data to what we hereby present. A Spanish study conducted from 2014 through 2018, in several hospitals of the Valencia Region, reported that the highest rates of hospitalisation related to RSV occurred in infants under 3 months old and in those born either before or at the onset of the RSV season (26). Moreover, a Swedish study showed that hospitalisations due to RSV have increased greatly between 2004 and 2011 and children < 1 year old were the most affected age group showing an annual incidence of 17/1,000 (27). Similarly, the average annual hospitalisation rates for RSV in the USA were 17/1,000 for children <6 months of age and 3/1,000 for children < 5 years of age (28). A recent European birth cohort study set in Spain, Finland, England, Scotland, and the Netherlands in children born between 2017 and 2020 showed again that the highest RSV-associated hospitalisations were reported in children <3 months (29). Loconsole et al. did not find a statistically significant association between prematurity and severity of the disease but highlighted that the symptoms severity was associated with younger age and chronic disease (17). Regarding the seasonality, RSV cases usually peak between December and February, in line with the data from the Temperate Northern Hemisphere (30). The reasons to explain this epidemiological pattern are described by the lower temperatures and low humidity conditions of the wintertime that may promote the stability of RSV in fomites; additionally, the consequent increased indoor crowding may also enhance viral transmission (30). Looking at the number of RSV cases in the period of our systematic review (2000-2021) it is remarkable to notice how the distribution of RSV hospitalised case changes in the different seasons: Rossi et al., 2007 reported that hospitalised patients were 17.2% in the season 2000-2001, 28.3% in the season 2001-2002, 34.5% in 2002-2003 and a slightly lower one in the 2003-2004 season (20%) (23). Alongside, Barbati et al., 2020 reported a similar distribution of RSV hospitalised patients in more recent seasons with values ranging from 13.3% in the 2014-2015 season to 25.2% in the 2018-2019 one (18). This trend can be related to the fact that clinicians become in the time more aware about the

RSV disease burden, requesting additional tests to have a more accurate diagnosis. Moreover, diagnostic tests have been developed greatly in the recent years, making the molecular characterization by RT-PCR the leading routine lab test for RSV, able also to discriminate between the RSV-A and RSV-B subtypes. It should be also highlighted that the COVID-19 pandemic greatly affected the global epidemiology of all infectious diseases, including RSV. The ban restrictions to reduce SARS-CoV-2 infections have significantly reduced hospitalisations due to RSV in Italy and worldwide in 2020 (31, 32), and disrupted seasonality, with one of the most recent seasons (2021-2022) being characterized by an unusual start of the season in August, as also reported by Loconsole et al (17). When analysing the subtypes, it is possible to notice how RSV-A and RSV-B prominence varied across the epidemic seasons considered, with no regular pattern, although RSV-A seemed to be generally more frequent. In this regard, two important factors should be mentioned, being that the subtype does not seem to be linked to a different severity of the symptoms (33) or to an increased risk of being infected (33-34), and that the current RSV preventive strategies target both RSV-A and RSV-B, including under investigation vaccines that are targeting protein F as the target molecule, which is conserved in both RSV-A and RSV-B (35). Regarding RSV infections in combination with other pathogens, the review reports a significant variability among the included studies, both in terms of coinfection rates and the involved pathogens. This considerable variability is likely due to the different circulation of pathogens linked to the extensive time frame considered in this review work. Nevertheless, it was possible to observe that rhinovirus ranks among the most prevalent infectious agents both in the pre-pandemic and pandemic eras.

Our study faces several challenges. The few studies we used could limit the scope of our findings, particularly as most predate the COVID-19 era and others follow it, with possible shifts in circumstances. In addition, the limited number of epidemic seasons represented in the studies is a limitation because it may not capture the full variability and trends in RSV hospitalizations over time. In terms of the precision of the selection process, we haven't calculated inter-rater reliability (IRR) to estimate inter-coder agreement, nor the κ statistic to measure accuracy and precision among researchers involved in the screening process. This could have helped identify inconsistencies or biases in study selection and ensure a more robust and reliable review process. We haven't assessed unpublished or unreviewed results (grey literature), which might have prevented us from retrieving more evidence on RSV in Italy. Finally, it must be noted that identification of RSV cases in most studies relies on ICD-9-CM coding, which introduces the potential for misclassification, miscoding, and missed opportunities for RSV testing, considering that physicians' coding practices may vary.

Conclusions

To our knowledge, this is the first study to collect data on Italian paediatric patients hospitalised for RSV infection. This comprehensive systematic review sheds light on the significant burden of respiratory syncytial virus hospitalisations among children aged 0-6 years in Italy from 2000 to 2021, underscoring the vulnerability of infants under 1 year old, who are more prone to severe RSV-related illnesses requiring ICU care. Notably, the dynamics of RSV hospitalisations have shown fluctuations over the years, possibly due to increased awareness among clinicians and advancements in diagnostic technologies. The influence of the COVID-19 pandemic on RSV epidemiology is undeniable, with significant declines in hospitalisations during the restrictions implemented to curb the spread of SARS-CoV-2. The disruption of seasonality in the 2021-2022 season further highlights the intricate interplay between infectious diseases. This study not only provides a deep understanding of RSV's impact on paediatric healthcare in Italy but also contributes to the broader global perspective on RSV-associated hospitalisations in young children. By offering detailed, region-specific data, it helps fill gaps in the global epidemiological understanding of RSV. Here, we emphasize the urgent need for good national data on RSV hospitalizations at the national level because of the imminent introduction of new prophylactic measures in Italy.

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Conflict of interest: L.B., S.P., B.M., M.A., and F.P. are employees of Sanofi and may hold shares. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflict of interest.

Data availability statement: Template data collection forms, data extracted from included studies, data used for all analyses, and any other materials used in the review will be made available by the authors upon request.

PRISMA Checklist: A complete PRISMA Checklist is provided as supplementary material (Supplementary File 1). Items Nos. 13, 14, 15, 20, 21, and 22 were considered 'not applicable,' as they relate to a quantitative synthesis of results (e.g., meta-analysis), which was not conducted in this study.

Riassunto

Ospedalizzazioni dovute al Virus Respiratorio Sinciziale nei bambini minori di 6 anni in Italia: una revisione sistematica della letteratura

Introduzione. Il virus respiratorio sinciziale è una delle principali cause di ricoveri ospedalieri per problemi respiratori nei neonati. Questa revisione sistematica (numero di registrazione: CRD42021248309) ha lo scopo di sintetizzare le evidenze disponibili sulle ospedalizzazioni correlate al virus respiratorio sinciziale tra i bambini di età compresa tra 0 e 6 anni in Italia.

Metodi. La ricerca bibliografica è stata condotta su PubMed, Embase, Scopus e International HTA, coprendo il periodo da gennaio 2000 a luglio 2022, con un focus sugli studi che riportavano informazioni sulle ospedalizzazioni associate al virus respiratorio sinciziale nei bambini di età compresa tra 0 e 6 anni in Italia.

Risultati. Otto articoli sono stati inclusi dopo aver esaminato 20.845 voci bibliografiche. Gli studi retrospettivi inclusi hanno riportato che la maggior parte delle ospedalizzazioni riguardava bambini di età inferiore a 1 anno (71,5%-88,8%), e i neonati di età inferiore a 1 anno avevano anche un rischio più elevato di ricovero in unità di terapia intensiva. Il virus respiratorio sinciziale ha tipicamente raggiunto il picco tra dicembre e febbraio, con un inizio atipico precoce ad agosto 2021. L'analisi dei sottotipi ha mostrato una prevalenza alternata di virus respiratorio sinciziale-A e virus respiratorio sinciziale-B in diverse stagioni. Le coinfezioni non erano rare (1,1%-37,4%), con rhinovirus e bocavirus come i più frequenti.

Conclusioni. Tutti i neonati durante la loro prima stagione di virus respiratorio sinciziale hanno mostrato un rischio aumentato di infezione grave e ospedalizzazione, indipendentemente dall'età gestazionale alla nascita, rispetto ai bambini di età superiore a un anno. Questa revisione sistematica contribuisce a migliorare la comprensione della malattia da virus respiratorio sinciziale in Italia e fornisce un supporto importante nelle decisioni riguardanti le strategie di prevenzione in Italia.

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Supplementary File 1. Prisma 2020 Checklist

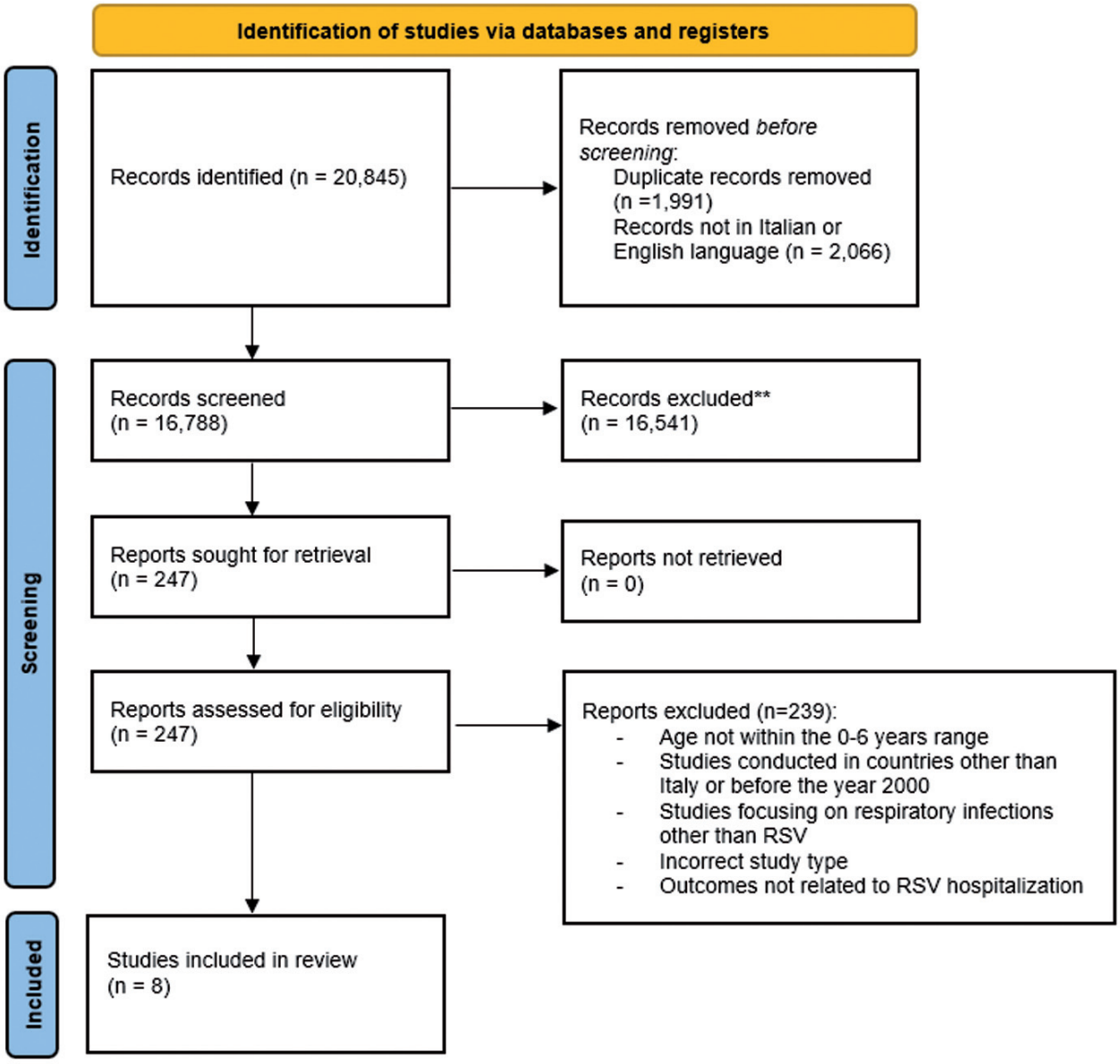
Section and Topic	Item #	Checklist item	Location where item is reported (page number; line number)
TITLE			
Title	1	Identify the report as a systematic review.	1; 2
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2; 23-38
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3; 51-74
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4; 75-81
METHODS			Pages 4-6
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5; 103-114
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4; 85-90
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	4; 90-101
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	5; 117-122
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	5-6; 117-140
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6; 130-140
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6; 130-140
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6; 138-140
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	6-7; 144-151
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Not applicable
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Not applicable
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Not applicable
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Not applicable
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Not applicable
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not applicable
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not applicable
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not applicable
RESULTS			Pages 6-10
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	6-7; 142-151, Supplementary file 2
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	6; Supplementary file 2

Section and Topic	Item #	Checklist item	Location where item is reported (page number; line number)
Study characteristics	17	Cite each included study and present its characteristics.	7; 154, Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	6; 150-151, Supplementary file 3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	6-7; 144-151,Table 1
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Not applicable
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Not applicable
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not applicable
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not applicable
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not applicable
DISCUSSION			Pages 10-13
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	10-12; 244-294
	23b	Discuss any limitations of the evidence included in the review.	12-13; 295-306
	23c	Discuss any limitations of the review processes used.	12-13; 295-306
	23d	Discuss implications of the results for practice, policy, and future research.	13; 318-323
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	4; 85-86
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	4; 85-86
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	4; 85-101
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	13-14; 325-338
Competing interests	26	Declare any competing interests of review authors.	14; 340-343
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	14; 345-347

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Supplementary File 2. Flow diagram for the systematic review (PRISMA statement). Databases: Pubmed, Embase, PubMed, Embase, Scopus, International HTA Database

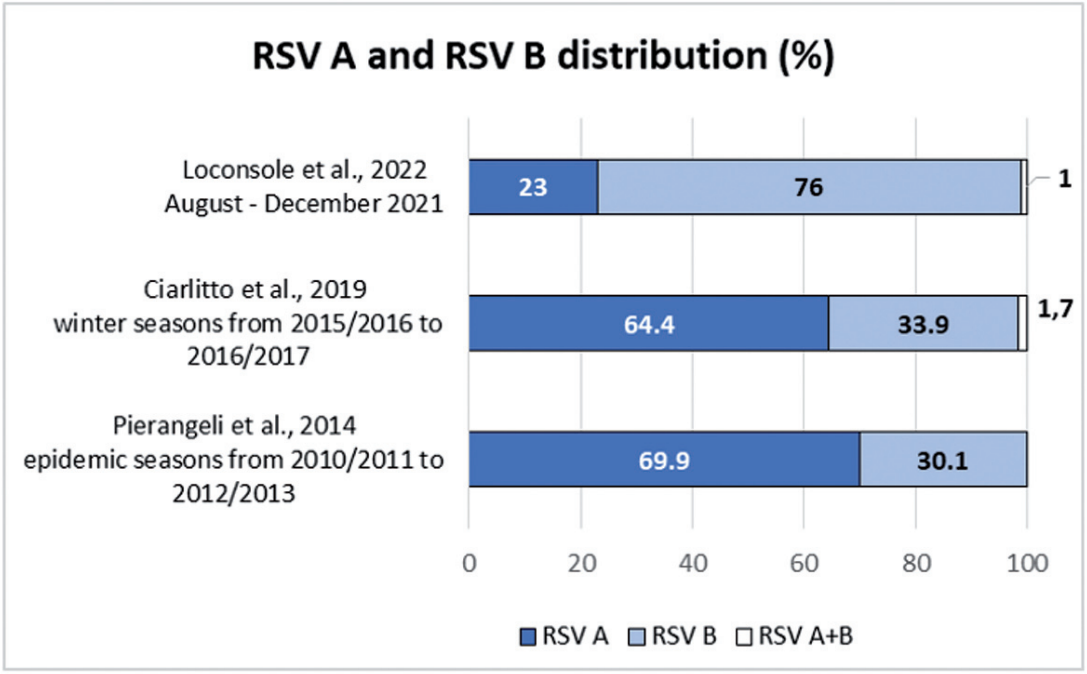


From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Supplementary File 3. The Newcastle-Ottawa Scale (NOS) for assessing the quality of the selected studies

Author and year	Selection/ comparability	Exposure/outcome	Total quality score
Loconsole D., 2022	5	3	8
Barbati F., 2020	5	3	8
Ciarlitto C., 2019	5	3	8
Kuhdari P., 2018	4	3	7
Capizzi A., 2017	4	3	7
Pierangeli A., 2014	5	3	8
Scagnolari C., 2012	5	3	8
Rossi G.A., 2007	5	3	8

Supplementary File 4. Distribution of RSV A and RSV B (%).



Supplementary File 5. RSV coinfection rates with other pathogens

Author	Coinfection rates % (n/N)	Patients with agents of coinfection
Loconsole D. et al., 2022	37.4% (67/179)	32/67 (47.8%) with rhinovirus,18/67 (26.9%) with bocavirus, 12/67 (17.9%) with adenovirus, 12/67 (17.9%) with other viruses and (6/67; 9%) with SARS-CoV-2
Barbati F. et al., 2020	2.2% (7/320)	4/7 (57.1%) with Influenza A/H3N2, 2/7 (28.6%) with rhinovirus, 1/7 (14.3%) with Influenza B
Ciarlitto C. et al., 2019	35.6% (150/422)	19% with rhinovirus
Capizzi A. et al., 2017	1.1% (4/366)	100% with *Haemophilus influenzae*
Scagnolari C. et al., 2012	9.9% (13/132)	7/13 (53.8%) with bocavirus, 3/13 (23.1%) with rhinovirus, 3/13 (23.1%) with metapneumovirus