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Review Paper

# Costs and healthcare utilisation due to respiratory syncytial virus disease in paediatric patients in Italy: a systematic review

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ABSTRACT

*Objectives:* Respiratory syncytial virus (RSV) is a frequent cause of acute lower respiratory infection in children, imposing a substantial economic burden on healthcare systems. This systematic review aimed to assess the economic burden and healthcare utilisation of RSV in children aged 0–59 months in Italy.
*Study design:* Systematic review.
*Methods:* A systematic search of PubMed, Embase, Scopus, and the International HTA Database, including studies published in English or Italian, was conducted between January 2000 and July 2022. Inclusion criteria required studies to be conducted in Italy and provide data on the economic costs and healthcare resource utilisation related to RSV infections.
*Results:* Out of 20,845 records screened, 18 articles met the inclusion criteria. Only one study provided comprehensive data on RSV disease costs, including hospitalisation, diagnostic tests, and medical procedures for infants with RSV-bronchiolitis. The mean cost per inpatient was higher for RSV-positive children (€5753.43 ± €2041.62) than that for RSV-negative children. Additionally, five studies reported a median length of hospital stay of 5 days for RSV-infected children, and four studies indicated a higher frequency of intensive care unit admissions for RSV-infected children than for those with other viral infections.
*Conclusions:* This is the first systematic review to examine the economic burden and healthcare utilisation of RSV in children aged 0–59 months in Italy. While limited data were available, the findings underscore the urgency to conduct further research and gather additional evidence on the costs and healthcare resource utilisation associated with RSV infections. Such efforts are essential for informing the development of effective prevention strategies for paediatric RSV infections in Italy.


## Introduction

Respiratory syncytial virus (RSV) is the most common cause of acute lower respiratory infection (ALRI), which poses a considerable global health burden for children aged <5 years.[1,2] Worldwide, infants aged <6 months are at higher risk of severe complications, which may lead to death.[1] The symptoms of RSV infection include coughing, tachypnoea, wheezing, dyspnoea, and otitis media.[3] Additionally, experiencing the illness for the first time does not guarantee immunity against future reinfections.[4] RSV infection often requires hospitalisation for infants; in addition, admission to the intensive care unit (ICU) and mechanical ventilation are common occurrences. Moreover, the illness can result in long-term morbidity, such as bronchospasm and asthma, leading to a substantial healthcare burden and economic costs associated with RSV disease.[5] RSV disease does not have any specific recommended

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treatments; therefore, medical care mainly focusses on providing supportive measures, including oxygen delivery, hydration, and antipyretic administration.[6] Over the past few years, significant progress has been achieved in the development of strategies to prevent RSV, including monoclonal antibodies (mAbs), and adult and maternal vaccines. Three products have received approval, and several additional candidates are currently in the advanced stages of clinical development.[7]

The primary focus of current RSV prevention strategies revolves around managing children who have a high risk of RSV infections.[8] Higher-risk groups include infants born preterm and with low birth weight, those with chronic respiratory diseases, and those with congenital or acquired immunodeficiency or other underlying medical conditions.[9,10] However, despite the increased risk of complications in these higher-risk groups, the majority of children hospitalised with RSV infection were previously healthy and/or born at term.[11–16]

Considering this significant RSV disease burden in paediatric patients, it is crucial to assess the economic burden of RSV infection and the resources used to treat the disease in order to efficiently allocate the limited healthcare resources and new preventive strategies (e.g. vaccines and mAbs). The aim of this study was to provide an overview of disease cost and healthcare utilisation, such as hospitalisation costs, length of stay (LOS), admission to the ICU, oxygen therapy (i.e. respiratory support, mechanical ventilation), and treatments with medications, in children aged 0–59 months infected by RSV in Italy.

## Methods

### *Protocol and study search*

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Supplementary file 1).[17] The protocol was recorded on International prospective register of systematic reviews (PROSPERO) on 8 August 2021 (registration number: CRD42021248309).[18] The research in the online databases included results from 1 January 2000 until 14 July 2022, when the record extraction was performed. The research was conducted on the following databases: PubMed, Embase, Scopus, and the International HTA Database. The search query was designed to retrieve articles containing information about paediatric patients with RSV infections in Italy. It was customised to meet the unique criteria of each database and was crafted to maximise sensitivity, ensuring that no potentially relevant articles were excluded. For example, the query used when 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 paediatric*).

### *Inclusion and exclusion criteria*

This systematic review included studies reporting data on paediatric patients aged 0–59 months who were admitted to the emergency department and/or were hospitalised in Italy with a clinical diagnosis of respiratory infection followed by a virological confirmation of RSV infection. Only studies that reported economic and healthcare resource utilisation data from 2000 to 2022 were selected. In detail, the studies had to include at least one of the following: disease costs, hospitalisation costs, LOS, oxygen therapy, and medication treatment regarding RSV infection in the paediatric population. Original studies, both in English and Italian, were reviewed. Studies that did not meet the criteria for inclusion, such as reviews, letters, posters, and conference abstracts, were read to extract any useful references but excluded from the final analysis.

### *Screening and study selection*

All selected studies were compiled in a dedicated spreadsheet, and duplicate entries were eliminated. Four independent reviewers, working in pairs, performed eligibility assessments by evaluating the titles and abstracts, and then decided on inclusion or exclusion by reading the full texts in a double-blind manner. In case of any discrepancies, a fifth, senior investigator was consulted to resolve the issue.

### *Data retrieval, analysis and quality assessment*

The articles were analysed for the following data: (1) study identification details, such as author names, publication year, and title; (2) study design, including cohort studies, case studies, surveys, retrospective, and prospective studies; (3) geographical context and observation time period; (4) study population characteristics, such as age group and sample size; (5) clinical diagnosis of respiratory infection and the number or percentage of RSV cases confirmed by laboratory testing with r*everse transcription polymerase chain reaction* or immunoenzymatic methods; and (6) any data regarding RSV disease–related costs, LOS, ICU admission, oxygen therapy use, and drug therapy. Only data from patients infected with RSV were selected and analysed. Moreover, studies were classified as prospective or retrospective based on what was reported in the methods section for each record. Key topics (e.g. RSV-related costs, LOS, etc.) that were identified during the data extraction process were further analysed and discussed within the team and then synthesised in tables and reported narratively in the manuscript.

Given the potential heterogeneity of outcomes and the limited number of studies available on this topic, a meta-analysis was not considered. The quality assessment of the included studies was conducted using the Newcastle–Ottawa Scale (NOS).[19] Each of the included studies was assigned a score range based on the NOS criteria, with a maximum score of 9 indicating the lowest risk of bias.

### *Definitions of costs and healthcare utilisation*

Cost estimation refers to the costs associated with the illness in patients diagnosed exclusively with RSV infection. Specifically, they include costs related to hospitalisation, medical procedures, visits, laboratory tests, and treatments. The healthcare utilisation categories included all data referring to the healthcare resources or health data linked to the treatment of RSV infection (e.g. LOS, ICU admission, oxygen therapy, and drug therapy). The LOS was reported as the length of hospital stay from admission to discharge. Access to the ICU is related to the number of children who were admitted to the neonatal intensive care unit (NICU) and/or the paediatric intensive care unit (PICU), and, where available, the duration of their stay. Under the definition of 'oxygen therapy', the following procedures and diagnoses were included: supplementary oxygen therapy rates, oxygen saturation rates, invasive and non-invasive ventilation, and length of oxygen therapy (days). Drug therapy referred to the treatment with medications administered to hospitalised patients (such as antibiotics, bronchodilator drugs, etc.).

## Results

The process of study selection is shown in Fig. 1.

A total of 20,845 records were obtained from the selected databases. Initially, duplicates ($n = 1991$) and records not in Italian or English language ($n = 2066$) were removed, leaving 16,788 records for eligibility screening based on their title and abstract. At this stage, 16,541 records were excluded, leaving 247 records for further consideration. Upon closer examination of these 247 records, 229 articles were excluded due to various criteria. This criteria included children with ages greater than 0-59 months, studies conducted outside of Italy or not within the appropriate time frame (investigated period before the year 2000), the wrong study type, or outcomes unrelated to RSV-associated hospitalisation. After applying all criteria, 18 articles were included and analysed in this study.[20–37] The included studies are listed in Table 1 and subsequent tables in chronological order. Among the selected articles, there were 11 prospective cohort studies and seven retrospective cohort studies. All studies in this systematic review were found to be of high quality during assessment (Supplementary File 2). Table 1 summarises the main characteristics of the selected studies.

For each study, the clinical diagnosis at the time of hospital admission, and the laboratory tests used to detect RSV in the collected samples (molecular or immunoenzymatic methods) are reported. All studies refer to hospitalised patients, except for two studies[22,29] where only a percentage of the patients were

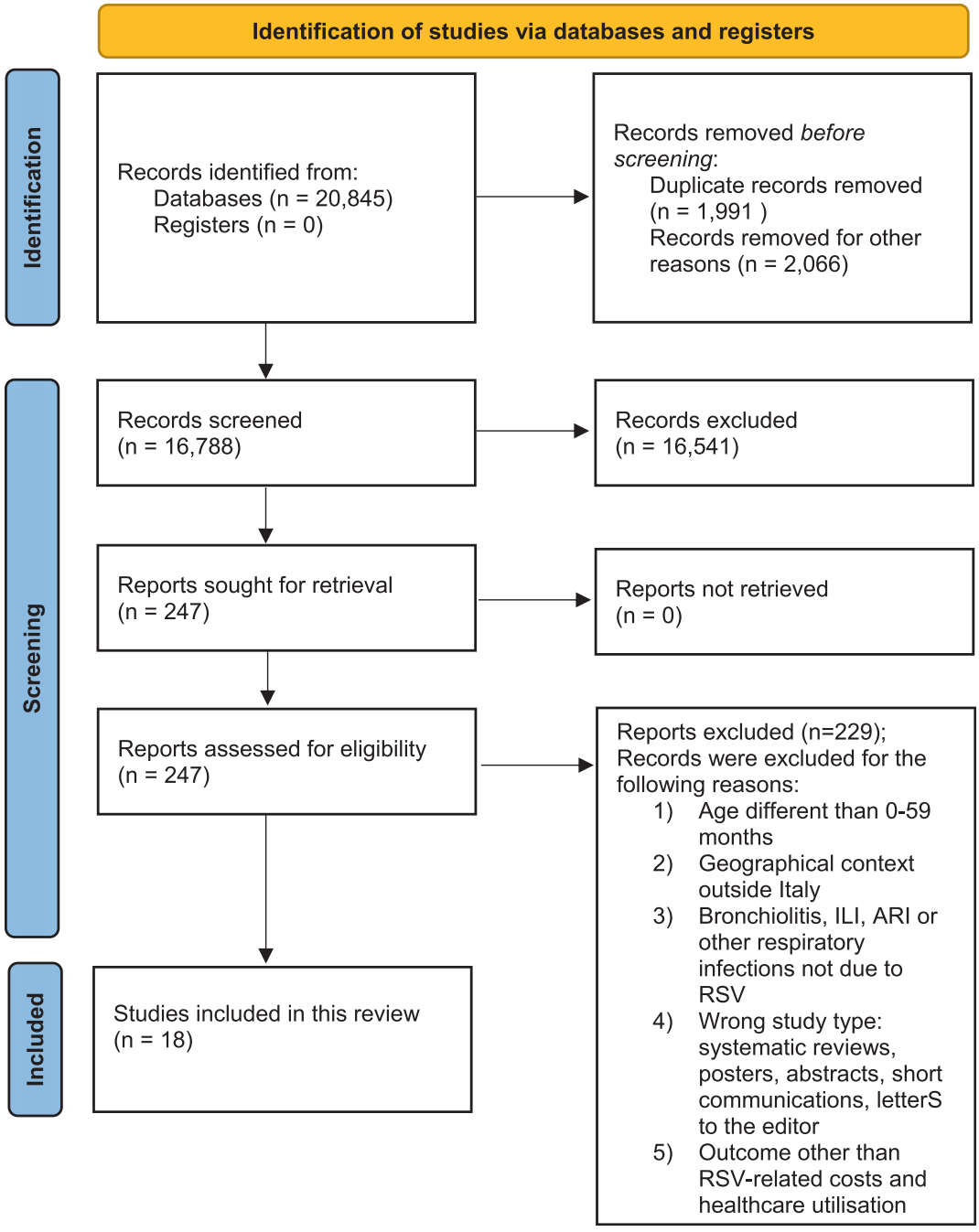


**Fig. 1.** Flow diagram for the systematic review (PRISMA statement).[17] PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

**Table 1**
Study and population characteristics of the retrieved articles.

| Author and year of publication | Study design | Time of observation[c] | Diagnosis at hospital admission | Laboratory confirmation (methodology) | RSV cases (*n*) | Age (months) of the observed population |
|---|---|---|---|---|---|---|
| Lanari M., 2002[20] | Prospective | November 1999–April 2000 | Hospitalised with LRTI | ELISA for RSV (Abbott Testpack RSV). | 500 | <24 |
| Rossi GA., 2005[21] | Retrospective | October 2000–April 2001, October 2001–April 2002 | Infants referred to the ED for RTI involvement | Immunoenzymatic test (TestPack®RSV) | 86 in the first season and 145 in the second | ≤48 |
| Gerna G., 2007[22] | Prospective | November 2006–May 2007 | Infants admitted to the hospital with a diagnosis of LRTI | real-time RT-PCR | 47 | 5 (1–27)[a] |
| Canducci F., 2008[23] | Prospective | October 2004–September 2006 | Infants with a diagnosis of ARD and hospitalised. Main reasons for hospitalisation were bronchiolitis, pneumonia, bronchospasm or wheezing, rhinitis, bronchitis, and laryngitis. | RT-PCR | 90 | <24 |
| Bosis S., 2008[24] | Prospective | October 2005–March 2006 | Infants hospitalised because of a first acute episode of wheezing during the study period | real-time PCR for RSV types A and B | RSV-A in 13 infants and RSV-B in 39 | <12 |
| Corsello G., 2008[25] | Prospective | October 2005–April 2006 | Children hospitalised with symptoms suggesting LRTI or developing LRT symptoms | Enzymatic diagnostic test (Now RSV Test; Binax) | 67 | 3.5 ± 4.3[b] |
| Di Carlo P., 2009[26] | Prospective | 1/10/2005–30/04/2006 | Children hospitalised with symptoms suggesting LRTI | enzymatic diagnostic test (Now® RSV Test, Binax) | 178 | 3 ± 1.4[b] |
| Papoff P., 2011[27] | Prospective | October–May of 2004/2005, 2005/2006, 2006/2007, 2007/2008 and 2008/2009 | Infants hospitalised for their first episode of bronchiolitis, admitted to the EDPaediatrics and PICU | RT-PCR | 112 | <12 |
| Pierangeli A., 2011[28] | Prospective | November 2009–March 2010 | Children attending the hospital were eligible for enrolment if they presented with fever at admission or in the preceding days and/or with at least one acute respiratory symptom (rhinorrhoea, cough, wheezing, or respiratory distress) | PCR assays | 87 | 2 (0–51)[a] |
| Scagnolari C., 2012[29] | Retrospective | winter 2006–2010 | Infants with a clinical diagnosis of RSV-associated bronchiolitis | TaqMan-based real-time RT-PCR | 119 | 2.2 (0.23–32)[a] |
| Selvaggi C., 2014[30] | Retrospective | winter 2008–2011 | Infants admitted with a clinical diagnosis of acute bronchiolitis to the Paediatric Department | TaqMan-based real-time RT-PCR | 78 | <12 |
| Esposito S., 2015[31] | Retrospective | November–March (2009–2010, 2010–2011, 2011–2012, 2012–2013, 2013–2014) | Children attending the emergency room of the hospital because of influenza-like illness | RT-PCR | 165 | <24 |
| Petrarca L., 2017[32] | Prospective | 2004–2016 | Infants hospitalised for bronchiolitis in the paediatric emergency department | RT-PCR | 365 | <12 |
| Barbati F., 2020[33] | Retrospective | September 2014–August 2019 | Admitted to the hospitals with a diagnosis of RSV infection | RT-qPCR | 624 | <12 |
| Nenna R., 2020[34] | Prospective | November 2016 to April 2017 and October 2017 to April 2018 | Hospitalised with bronchiolitis | panel of RT-PCR or nested PCR assays | 90 | <12 |
| Bozzola E., 2021[35] | Retrospective | January 2017–December 2017 | Children with a diagnosis of bronchiolitis | Multiplex-PCR | 310 | 1–12 |
| Camporesi A., 2022[36] | Prospective | July 2021–January 2022 | Clinical diagnosis of bronchiolitis or a first episode of acute viral wheeze | ePlex Respiratory Panel PCR | 162 | <24 |
| Loconsole D., 2022[37] | Retrospective | August–December 2021 | Hospitalised with RSV infection | Real-time PCR | 179 | <12 |

ARD, acute respiratory disease; ARTI, acute respiratory tract infection; ED, emergency department; ELISA, enzyme-linked immunosorbent assay; LRTI, lower respiratory tract infection; PICU, paediatric intensive care unit; RSV, respiratory syncytial virus; U-ARD, upper acute respiratory disease; RT-PCR, reverse transcription polymerase chain reaction; RT-qPCR, Quantitative reverse transcription polymerase chain reaction, SD, standard deviation.

[a] Median age (range).

[b] Median age ± SD.

[c] Time of observation refers to the years in which the children were hospitalised and in general the period to which the collected data refer.

hospitalised. Overall, only two articles[33,37] reported a primary diagnosis of RSV infection for the entire study population; for the other articles, this study exclusively assessed RSV-confirmed cases among the sample population. The most frequently detected respiratory conditions related to RSV infection in the selected studies were bronchiolitis, lower respiratory tract infections (LRTIs), and acute respiratory disease. Moreover, the majority of patients with a diagnosis of RSV in the retrieved studies were aged <12 months.

The included studies were then analysed based on the various outcomes specified in the objectives of the current study.

### *Cost estimation*

Among the included studies, only Bozzola et al.[35] reported data on disease costs. These costs primarily covered hospitalisation, diagnostics, and medical procedures (Table 2).

The study by Bozzola et al.[35] involved 531 patients, including 310 with RSV infections (219 had only RSV, whereas 91 had coinfections with other viruses). RSV infection costs were compared to those of other respiratory viruses identified through laboratory tests. Notably, no significant differences were found within the RSV patient group, regardless of coinfections. In detail, the study,[35] conducted in 2017 on infants aged 1 month to 1 year with bronchiolitis, found that RSV was the main cause (58.4% of cases). The total cost associated with RSV-related bronchiolitis was €1,783,562.76, and 72.2% of cases required admission to the PICU. Patients in the PICU had a mean cost of €8859.99 (±€2056.53), which was significantly higher than that for patients in regular wards. The overall cost of hospitalisation for bronchiolitis, regardless of the cause of illness, was €2,958,786, with an average cost per patient of €5572.10 (±€2037.79) [compared to €5753.43 per patient for RSV-associated hospitalisations]. The study also found higher costs for radiological imaging and laboratory tests in RSV-positive cases than those in RSV-negative cases.[35]

### *Healthcare utilisation*

All studies included in this analysis provided data related to both disease severity and utilisation of healthcare resources in treating RSV infection. Table 3 reports data regarding the use of healthcare utilisation divided into different outcomes: LOS; admission to the ICU (where specified, NICU and/or PICU); oxygen therapy (where present the percentage is also specified for those who needed mechanical ventilation and other data including: the oxygen saturation parameters, the type of oxygen flow they needed and the length of oxygen therapy, if available); and drug therapy.

Among the studies included in this systematic review, in those that provided a comparison with non-RSV-infected patients, the LOS appears to be longer for RSV-positive patients.[25,26,35] Specifically, five studies identified a median LOS of 5 days,[28–30,32,34] while one study reported a longer duration (median of 8 days) for patients hospitalised with an initial diagnosis of LRTI.[22] Additionally, Corsello et al.[25] showed that the most frequent age group ($n = 75$, 54.7 %) for LRTI or LRT symptoms were children aged 3 months. Four of the studies compared data on LOS for different subtypes of RSV.[22,23,30,31] Among these studies, Gerna et al.[22] and Esposito et al.[31] found no difference in hospitalisation rates between infants with RSV-A and infants with RSV-B.

Another parameter observed was the rate of admission to the ICU. Four studies reported a higher frequency of PICU admission for children with RSV infection than for those affected by other viruses.[25,26,28,34] Corsello et al.[25] reported that RSV infection was associated with a higher likelihood for admission to the NICU (10 of 67 RSV-positive patients vs. none of 97 RSV-negative patients). Di Carlo et al.[26] also specified that the average LOS recorded in the ICU was 11.3 days, while Barbati et al.[33] reported that 89 of 103 (86.4%) patients who required PICU admission were aged <1 year.

Oxygen therapy was also analysed. In some of the included studies, it was reported that for children infected with RSV, supplemental oxygen was required but not invasive ventilatory support.[27,34,36] Three studies[20,25,26] reported a mean duration of oxygen therapy that ranged from 2.1 ± 2.7 to 5.4 ± 2.8 days. Furthermore, a difference between the number of days oxygen therapy was administered for RSV-positive and RSV-negative patients was reported by Lanari et al.[20] In children with a gestational age of <36 weeks, the number of days on oxygen therapy was higher for RSV-positive infants.[20] Furthermore, Lanari et al.[20] and Di Carlo et al.[26] suggest that RSV-positive children required a longer duration of oxygen therapy than did RSV-negative patients. In contrast, Corsello et al.[25] did not find any significant differences in the proportion of patients requiring oxygen therapy or in the number of days of oxygen therapy.

Lastly, among the 18 selected studies, four[21,24,31,36] provided data on drug therapy for children aged 0–59 months infected with RSV. Rossi et al.[21] reported that treatment with corticosteroids or bronchodilators was higher in RSV-negative than in RSV-positive children with LRTI in both seasons considered ($P < 0.05$). Bosis et al.[24] analysed RSV-positive children admitted to the hospital for wheezing episodes and reported the rates of medication utilisation based on age group. Specifically, among infants aged <3 months, all received bronchodilators, 26.7% steroids, and 53.3% antibiotics. Among patients aged 3–12 months, all received bronchodilators, 36.4% steroids, and 31.8% antibiotics. Esposito et al.[31] reported a comparison in medication usage based on the subtype of RSV for children hospitalised with influenza like illness (ILI) diagnosis. The rates of drug utilisation in RSV-A patients included 96.1% receiving antibiotics, 89.0% antipyretics, and 91.6% aerosol therapy, whereas in RSV-B patients, all received antibiotics, 88.2% antipyretics, and 82.3 % aerosol therapy. Finally, Camporesi et al.[36] reported that drug therapy for hospitalised children with bronchiolitis due to RSV included corticosteroid (23.5%) and antibiotic treatment (31.5%).

## Discussion

This systematic review aimed to of gather information on the costs and utilisation of healthcare resources associated with RSV infection in children aged 0–59 months in Italy. In total, 18 studies conducted between 1999 and 2022 were analysed.

**Table 2**
Hospitalisation costs of infants with RSV infection and infants with other respiratory infection.

| Hospitalisation costs | RSV-associated hospitalisations ($n = 310$)[a] | Other virus-associated hospitalisations ($n = 217$) |
|---|---|---|
| Total cost for bronchiolitis | €1,783,562.76 | €1,170,746.54 |
| Mean cost (±SD) per patient | €5753.43 (±2041.62) | €5395.15 (±2040.87) |
| Mean imaging cost (± SD) per patient | €18.95 (±28.62) | €16.00 (±26.41) |
| Mean laboratory tests cost (± SD) per patient | €3486.38 (±1126.19) | €3454.70 (±1204.50) |

RSV, respiratory syncytial virus; SD, standard deviation.
[a] With or without coinfection.

**Table 3**
RSV-related healthcare utilisation.

| Author and year | Diagnosis at hospital admission | Length of stay (days) | Intensive care unit admission (*n*/%) | Oxygen therapy (%) | Drug therapy |
|---|---|---|---|---|---|
| Lanari M., 2002[20] | LRTI | | | 1) Higher respiratory rate (53.3 ± 17.0) in RSV-positive, compared to 50.2 ± 13.3 in RSV-negative; $P < 0.002$);<br>2) lower SaO2 on admission in room air (91.2 ± 9.3% in RSV-positive, compared to 92.9 ± 6.7% in RSV-negative; $P < 0.003$);<br>3) higher number of oxygen therapy days (1.3 ± 2.2 for RSV-positive, compared to 0.8 ± 1.9 in RSV-negative; $P < 0.01$).<br>In children with a gestational age of <36 weeks, the number of days on oxygen therapy was 2.1 ± 2.7 for RSV-positive and 1.5 ± 3.0 days for RSV-negative patients | |
| Rossi GA., 2005[21] | LRTI | | | | Treatment with corticosteroids or bronchodilators was higher in RSV-negative than in RSV-positive children ($P < 0.05$) |
| Gerna G., 2007[22] | LRTI | infants with RSV-A vs infants with RSV-B [median: 8 (3–11) vs. 8 (2–16); $P$ = ns]. LOS in young patients with coinfection vs patients with a single RSV infection [9 (6–11) vs. 8 (2–16); $P$ = ns] | | | |
| [23] Canducci F., 2008 | ARD | RSV-A median: 4.5; RSV-B median: 3 | | Hypoxia (<92%) for RSV: 61% (RSV-A: 73% and RSV-B: 70%) | |
| Bosis S., 2008[24] | First acute episode of wheezing | Mean (± SD) 5.47 (±2.15) in the 3–12 months. In those aged <3 months 5.96 (± 2.43). | | Among the <3-month-old RSV-positive: 33.3% supplemental oxygen, 10% chest physiotherapy. Among the 3- to 12-month-old RSV-positive: 9.1% supplemental oxygen, 9.1% chest physiotherapy. | <3-month-old infants: 100% use bronchodilators, 26.7% use steroids, 53.3% antibiotics; 3- to 12-month-old patients: 100% use bronchodilators, 36.4% use steroids, 31.8% antibiotics |
| Corsello G., 2008[25] | Symptoms suggesting LRTI or developing LRT symptoms | RSV-positive vs RSV-negative children (mean 7.2 ± 5.5 vs 5.8 ± 4.2 days; $P = 0.061$). Age class at the hospitalisation: 3 m ($n = 75$) 54.7 %. 3–6 m ($n = 39$) 35.9 %. 6 m ($n = 50$) 24.0 % | $N = 10/67$ hospitalised in the NICU. Days of NICU hospitalisation = 11.3 ± 11.3 (mean ± SD) | No differences in the proportion of patients requiring oxygen therapy or in the days of oxygen therapy were found between RSV-positive and RSV-negative children ($P = 0.441$ and 0.337).<br>% Subjects in oxygen therapy ($n = 108$, 53.7%)<br>Days of oxygen therapy 5.4 ± 2.8 mean (±SD) | |
| Di Carlo P., 2009[26] | Symptoms suggesting LRTI | Mean (± SD), RSV-positive: 6.4 ± 3.5 vs RSV-negative: 5.6 ± 3.1; $P < 0.05$ | 10 RSV+ infants were admitted to the PICU, on average for 11.3 days vs no one infant in the RSV − patients | Longer oxygen therapy was detected in RSV-positive infants than in RSV-negative infants. Only 1 patient required assisted ventilation. Days of oxygen therapy: ($n = 235$) 4.9 ± 3.3 mean (± SD) | |
| Papoff P., 2011[27] | Bronchiolitis | | | Group 0, conservative treatment no need for supplemental oxygen or intravenous fluids: 30.1% group 1, intravenous fluids or oxygen treatment, or both, for <12 h; 50.9%<br>group 2, oxygen for more than 12 h without ventilatory support and intravenous fluids; 35.4%<br>group 3, either mechanical ventilation or non-invasive respiratory support 62.5% | |

**Table 3** (*continued*)

| Author and year | Diagnosis at hospital admission | Length of stay (days) | Intensive care unit admission (*n*/%) | Oxygen therapy (%) | Drug therapy |
|---|---|---|---|---|---|
| Pierangeli A., 2011[28] | Acute respiratory symptom | Median of 5 (range 3–27) for patients aged ≤1 year and 5 (2–18) for >1 year | RSV-infected children were more frequently admitted to the PICU than those infected with other virus groups. PICU: 17/78 (22%) | RSV-infected children were presented with significantly lower saturation rates. SaO2 < 95%, *n* (%): 30/81 (37%) | |
| Scagnolari C., 2012[29] | RSV associated bronchiolitis | Median: 5 (range: 0–27) | | | |
| Selvaggi C., 2014[30] | Acute bronchiolitis | Median: 5 (range: 1–15); RSV-A: 5 (range 1–13); RSV-B: 4 (range 2–15) | | | |
| Esposito S., 2015[31] | Influenza-like illness | Mean duration for RSV-A: days ± SD 5.7 ± 2.5 and for RSV-B: 6.8 ± 1.8 ($P = 0.06$) | | | RSV-A: antibiotics 96.1%, antipyretics 89.0 %, aerosol therapy 91.6%<br>RSV-B: antibiotics 100.0%, antipyretics 88.2%, aerosol therapy 82.3% |
| Petrarca L., 2017[32] | Bronchiolitis | Median of 5 (range: 1–27) | PICU admission required in 38 patients (11.9%) | $O_2$ therapy required in 81 patients (25.9%) | |
| Barbati F., 2020[33] | RSV infection | | ICU required for 103 patients; 89/103 (86.4%) were under 1 year old, 73/103 (70.9%) were under 3 months, 47/103 (45.6%) were under 1 month | | |
| Nenna R., 2020[34] | Bronchiolitis | Median of 5.5 (range: 2–11) | 14 (15.6 %) infants were hospitalised in ICU only during the epidemic peak | Median 94% $SaO_2$ (range: 80%–99%) and 40 (44.4%) required oxygen supplementation. None of the patients in the ICU required intubation or invasive ventilator support. | |
| Bozzola E., 2021[35] | Bronchiolitis | Mean (±SD): 4.98 days (±2.18) for RSV vs other: 4.22 (±2.16) | PICU admissions: RSV: 4.19%. Other viruses: 2.3% | | |
| Camporesi A., 2022[36] | Bronchiolitis or a first episode of acute viral wheeze | | PICU required for 9/162 (5.56%) | Need for low-flow oxygen , *n* (%): 74/162 (45.68%); need for high-flow oxygen, *n* (%): 57/162 (35.19%); mechanical ventilation: 1/162 (0.62%); | Corticosteroid treatment: 23.46%; antibiotic treatment: 31.48%; other bronchodilator: 8.64% |
| Loconsole D., 2022[37] | RSV infection | The average was 5.8 (range: 1–16) | Ten (5.6%) of the 179 hospitalised children were admitted to the ICU, all of whom were aged <5 months | Oxygen support required by 49.2% patients | |

ED: emergency department; GA: gestational age; HFNC: high-flow nasal cannula; ICU: intensive care unit; LOS: length of stay; NICU: neonatal intensive care unit; PICU: paediatric intensive care unit; RSV: respiratory syncytial virus; $SaO_2$: oxygen saturation of arterial blood; LRTI: lower respiratory tract infection.

Only one study[35] provided data on RSV disease costs, regarding hospitalisation, diagnostic tests, and other medical procedures, for young children with bronchiolitis: this result highlights the fact that economic data related to RSV in Italy are rarely reported. However, despite the scarcity of data, some of the results reported appear to be aligned with data from other European countries. In the study conducted by Torres et al.,[38] the average hospitalisation cost is similar to results reported by Bozzola et al. Additionally, Torres et al.[38] provide details on differentiated costs based on the age groups of patients. The average cost of hospitalisation per patient in the National Health System (NHS) for cases related to RSV and ALRI was €2406 (standard deviation [SD]: €3203). Among these patients, children aged <2 years incurred a higher mean cost per patient at €2417 (SD: €3330) than those aged 24–59 months, whose mean cost per patient was €2360 (SD: €2095).[38] RSV-positive infants incur higher costs due to longer hospital stays and more frequent admissions to the PICU than other causes. These findings align with a previous study showing significantly higher expenses for infants treated for bronchiolitis in the PICU than for those treated in a regular ward or emergency department.[39] Similar to the study by Bozzola et al.,[35] a Spanish study highlighted that for cases specifically related to RSV, the average cost of healthcare per visit was higher, primarily due to the need for hospitalisation. In the first year of life, the mean direct healthcare cost per medically attended case was €3362, with 72.9% attributed to hospitalisations.[40]

In terms of healthcare resources, several international studies have reported data in line with findings from this systematic review. For example, the study by Hartman et al.[41] that measured the clinical burden of RSV in hospitalised children aged ≤5 years highlighted a median LOS of 5 days (interquartile range: 4.0–7.0), and 57.7% of patients with RSV required supplemental oxygen during hospitalisation. Overall, the current review observed that even if RSV-positive infants were not admitted to the PICU for ventilatory support, they very frequently required oxygen supplementation, in particular, oxygen low flow and intravenous fluids for ≤12 h. Other supporting evidence comes from a European study by Linssen et al.[42] that included all children aged ≤24 months with RSV bronchiolitis between 2003 and 2016 from a nationwide PICU registry in the Netherlands. The authors observed that non-invasive respiratory support significantly increased; in particular, the use of high-flow nasal cannula (HFNC), whereas the use of invasive ventilation remained stable.

In terms of pharmacological treatment of children with RSV, the results of the current review appear to be in line with the

international literature: bronchodilators, corticosteroids, and antibiotics are the most frequently used drugs.[43,44] In particular, this review showed that antibiotics were frequently administered during RSV hospitalisation. This observation aligns with evidence available in the literature.[45,46] However, the American Academy of Pediatrics guidelines for the management of RSV respiratory infections, as well as the Italian guidelines, do not recommend the use of antibiotics, except in cases of strong suspicion or clear evidence of a secondary bacterial infection. The use of bronchodilators and corticosteroids is also not recommended; instead, only supportive care, oxygen therapy, and HFNC therapy are recommended.[47,48] The lack of effective treatments remains a substantial medical challenge and highlights the urgent need for effective preventive strategies for all infants.

This study has some limitations. The articles included in this review had different study designs, and the data were distributed over a long time period. In addition, only one article was included that provided data on costs and specifically studied infants with RSV-related bronchiolitis.

Even with the introduction of new preventive strategies, such as vaccines and long-acting mAbs, such as nirsevimab (Beyfortus®),[49] it is necessary to collect and analyse data to design more appropriate prevention strategies in the future. Furthermore, additional paediatric and maternal vaccines and mAbs are currently under development,[7] and decisions regarding their management and administration will need to be made imminently. In the future, the use of new synthetic parameters for calculating healthcare utilisation could be beneficial: comparing data is indeed complex, but utilising new synthetic measures could provide valuable insights into the healthcare resources required. This review highlights that data regarding the costs associated with RSV diseases, and the utilisation of related resources remain scarce for Italy. Beyond simply acknowledging the scarcity of data, there is a critical requirement for innovative research methodologies that can capture the economic ramifications of RSV, particularly in the context of recent advancements in preventive interventions. This includes a future deep dive into the cost effectiveness of these interventions and their real-world impact on healthcare spending. Furthermore, linking these economic evaluations to clinical outcomes and the adherence to recommended treatment guidelines could elucidate pathways to optimise patient care and resource allocation. Such research would offer a dual perspective, highlighting not only the fiscal consequences but also the practical implications of RSV management in the healthcare system.

### *Conclusions*

Despite the limited data available in Italy, evidence from this systematic review provides a valuable description of the impact of RSV infection on healthcare management in the hospital setting, both in regular wards and ICUs (NICU and PICU). The need for further investigations and cost-effective interventions targeting RSV is increasingly urgent. Gathering evidence on costs and healthcare utilisation for RSV (in particular, RSV-related bronchiolitis and ALRI) could be crucial for implementing appropriate prevention strategies to manage paediatric RSV disease in Italy.

## Author statements

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None required.

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### *Competing interests*

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 a potential conflict of interest.

### *Author contributions*

Conceptualisation, S.B., B.B., M.DR., L.B., S.P., F.T., B.M., M.A., P.B., A.B..; search strategy, S.B., B.B., M.DR., L.B., S.P., F.T., B.M., M.A., P.B., A.B.; search literature, B.B., C.S., E.S., M.B., G.I., J.I., D.B., P.B., G.C., C.C., L.S., C.C., M.C., A.S., S.P.; data extraction, B.B., C.S., E.S., M.B., G.I., J.I., D.B., P.B., G.C., C.C., L.S., C.C., M.C., A.S., S.P.; quality assessment, M.DR., C.S., A.B., S.B.; data analysis, B.B., C.S., M.DR., A.B., S.B.; writing – original draft, B.B.,C.S., M.DR. A.B., S.B.; writing – review and editing, S.B., B.B., C.S., E.S., M.B., G.I., J.I., D.B., P.B., G.C., C.C., L.S., C.C., M.C., A.S., S.P., M.D.R., L.B., S.P., B.M., M.A., F.T., P.B., A.B. All authors have read and agreed to the published version of the manuscript.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.11.039.

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