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Hospitalizations for respiratory syncytial virus (RSV) in Sicily from 2008 to 2021: clinical features and predictors of severity

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Abstract

Background Respiratory syncytial virus (RSV) is the leading cause of bronchiolitis, resulting in 3.6 million hospitalizations for acute lower respiratory tract infections and 101,400 deaths in children under 5 years of age worldwide each year. In Europe, the estimated incidence of RSV-related hospitalizations in infants is 1.8%. We describe the incidence of RSV infection in patients hospitalized in Sicily (Italy) between 2008 and 2021, examine the clinical-epidemiological characteristics of RSV-positive patients, and assess comorbidities associated with illness severity.

Methods All data were retrospectively collected from standard hospital discharge records (HDRs). Significant factors from the univariate analysis were included in a multivariate logistic regression using the stepwise forward selection method to calculate adjusted odds ratios (aORs) and identify independent risk factors for ICU admission.

Results Collectively, within the study time frame, 4,485 hospital admissions were RSV-related, 271 patients (6%) were admitted to the ICU, and eight deceased (0.2%). The majority of hospitalized patients (86%) were infants (up to 1 year old), 16.5% were newborns (<28 days), and 10.1% were in the 1–4-year-old group. Several predictors of ICU admission, including neonatal sepsis, neonatal respiratory distress, and younger age (in months), were identified through multivariate logistic regression analysis.

Conclusions RSV-associated pathologies are important causes of hospitalization in Sicily, and young age (particularly 0–3 months) and comorbidities, including nutritional and metabolic disorders (with a stronger effect in the pediatric subgroup) and congenital heart diseases, are important outcome predictors. However, considering that RSV-related diseases continue to require hospitalizations in healthy children and adults, it is important to continue monitoring RSV-related hospitalizations through updated epidemiological studies, which can guide the implementation of existing preventive strategies and inform the cost–benefit analysis of new ones.

Keywords RSV, Respiratory syncytial virus, Bronchiolitis, RSV epidemiology, Children, Newborns, Pediatrics

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Background

Respiratory syncytial virus (RSV) is a single-stranded, negative-sense RNA virus belonging to the *Pneumoviridae* family [1]. RSV is highly contagious and widely spread, and it represents the main cause of bronchiolitis worldwide. Bronchiolitis is the most common lower respiratory tract infection (LRTI) in infants up to 12 months of age, and it presents with cough, dyspnea, and diffuse crackles on chest auscultation.

RSV bronchiolitis accounts for 3.6 million hospitalizations for acute LRTIs and 101,400 deaths in children under 5 years of age worldwide each year [2]. Despite the higher fatality rate in children with preexisting conditions, most RSV cases occur in healthy infants. Seasonal RSV epidemics generally begin in October-November and end in March-April, with a peak in December-January. During epidemics, overlaps with other respiratory viruses occur due to their shared transmission route (respiratory droplets or aerosols), causing frequent coinfections [3–8].

Notably, while more than 97% of RSV-related deaths occur in low- and middle-income countries, the infection burden of RSV also remains significant in high-income countries [2].

The Respiratory Syncytial Virus Consortium in Europe (RESCEU) conducted a birth cohort study to estimate the incidence of RSV-associated hospitalizations among infants in their first year of life in Europe. The study reported an incidence rate of 1.6 hospitalizations per 1,000 infant-months (a standardized measure that accounts for both the number of infants and the duration of observation) [9].

Studies conducted on RSV epidemiology in children in Sicily evidenced an atypical seasonal trend compared with other regions, with a peak in spring and no positive cases between October and December during the 2005–2006 season [10, 11]. RSV was isolated from 53% of the children with LRTIs included in this analysis [11]. Another study involving 32 Italian centers reported a prevalence of RSV of 40.6% in children admitted to tertiary care centers for LRTI, with a seasonal peak in February (52.2%) and the lowest prevalence in November (14.1%) [12].

A thorough understanding of the epidemiological impact of RSV, supported by conspicuous local data, is crucial to fully understand the seasonal patterns of RSV outbreaks, which in turn can inform the correct timing, implementation, and efficacy of current and new preventive strategies. This study aims to provide epidemiological evidence on RSV-related hospitalizations in pediatric and adult populations in Sicily over a 13-year period.

Materials and methods

Data collection and processing

This retrospective study is based on data gathered from hospital discharge records (HDRs) provided by the Regional Department of Sicily. A total of 9,343 HDRs registered in Sicily between September 2008 and December 2021 containing infectious disease diagnostic codes (e.g., measles, whooping cough, scarlet fever, chickenpox, RSV, etc.) were screened to select RSV-related pathologies. The screening was performed independently by two researchers, and in instances of discordance, the discrepancy was resolved through dialogue or consultation with a third reviewer, leading to a consensus. Data regarding the resident population each year, necessary to calculate incidence rates of RSV-related hospitalizations, were obtained from the Italian National Institute (ISTAT) of Statistics [13].

HDRs were formally introduced in Italy in 1991 and include clinical and logistical information on every patient discharged from a national public hospital [14]. Clinical diagnoses in HDRs are coded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD9-CM). Among all available HDRs, those containing the ICD-9-CM diagnostic codes 466.11 (RSV bronchiolitis), 480.1 (RSV pneumonia), and 796 (RSV infection) were selected for inclusion in the study, encompassing both pediatric and adult patients. Therefore, the inclusion criterion was the presence, in the HDR diagnoses section, of at least one of these three codes, whereas the exclusion criterion was the absence of all three.

The data extracted from HDRs include the following: (1) patient age and sex; (2) presence of comorbidities (cardiac diseases, respiratory failure, hematologic diseases, oncological diseases, metabolic and nutritional disorders); (3) coinfections (whooping cough, intestinal infections, bacterial infections, HIV, candidiasis, influenza, bacterial pneumonia); (4) neonatal clinical complications and respiratory conditions (preterm birth, neonatal sepsis, respiratory failure, respiratory distress, atelectasis); and (5) congenital and genetic disorders (Trisomy 21, congenital hypothyroidism, congenital heart disease, and congenital malformations).

Statistical analysis

Continuous variables are summarized as means with standard deviations (SDs) or medians with interquartile ranges (IQRs), while categorical variables are presented as absolute and relative frequencies. The unpaired Student's *t*-test or the Mann-Whitney *U* test were used for continuous data in univariate analysis. A p value < 0.05 was considered significant in all analyses. Crude odds ratios (cORs) and their 95% confidence intervals (CIs) were used to assess the associations between potential

risk factors and ICU admission. Significant factors from the univariate analysis ($p < 0.05$) were included in a multivariate logistic regression using the stepwise forward selection method to determine adjusted odds ratios (aORs) and identify risk factors for ICU admission. Variables were removed from the model if $p > 0.1$. The analysis was performed separately for the entire study population and for the pediatric subgroup. Only statistically significant results are reported.

The Kolmogorov-Smirnov test was employed to assess the differences in hospitalization duration between patients admitted to the ordinary ward and those admitted to the ICU. IBM SPSS Statistics and Microsoft Excel 2010 were used for data management and analysis.

Formal consent is not required for this type of study, as it relies solely on retrospective analysis of anonymized data collected from standard hospital discharge forms. In accordance with the Helsinki Declaration and Italian law (Legislative Decree of 30 June 2003, no. 196, Code on the Protection of Personal Data), all personal data were fully anonymized before analysis.

Results

Among the infectious disease-related HDRs collected from Sicilian hospitals relative to the period 2008–2021, 4,485 included RSV-related diagnostic codes.

The prevalence was greater in males than in females (52.9% vs. 47.1%, $p < 0.001$), and the median age of the entire cohort was 3 months (IQR: 1–6). Most hospitalizations (86%) involved children younger than 1 year. Newborns (<28 days of life) accounted for 16.5% of all hospitalizations, and 10.1% of hospital admissions were in the 1–4 years age group (Fig. 1).

Within the infant group (up to 11 months), a significant incidence of RSV-related hospitalizations (24.3%) was observed in one-month-olds (Fig. 2).

Notably, between 2008 and 2020, the distribution of hospitalizations remained substantially unchanged (Fig. 3).

The trend of hospitalizations is characterized by periodic fluctuations, with a peak in 2019–2020, accounting for 10.4% of all hospital admissions during the study period. In approximately half of the cases (50.5%), the hospitalization duration was less than one week. (Fig. 4.)

Interestingly, hospitalization length was associated with age, as the average of 6 days observed in children aged 0–14 years increased to 8.5 days in those over 65 years.

Most hospital admissions (93%) were due to bronchiolitis, followed by pneumonia (4.4%) and unspecified RSV infection (2.4%). The distribution of hospitalizations by diagnostic codes, stratified by age group, is shown in Fig. 5.

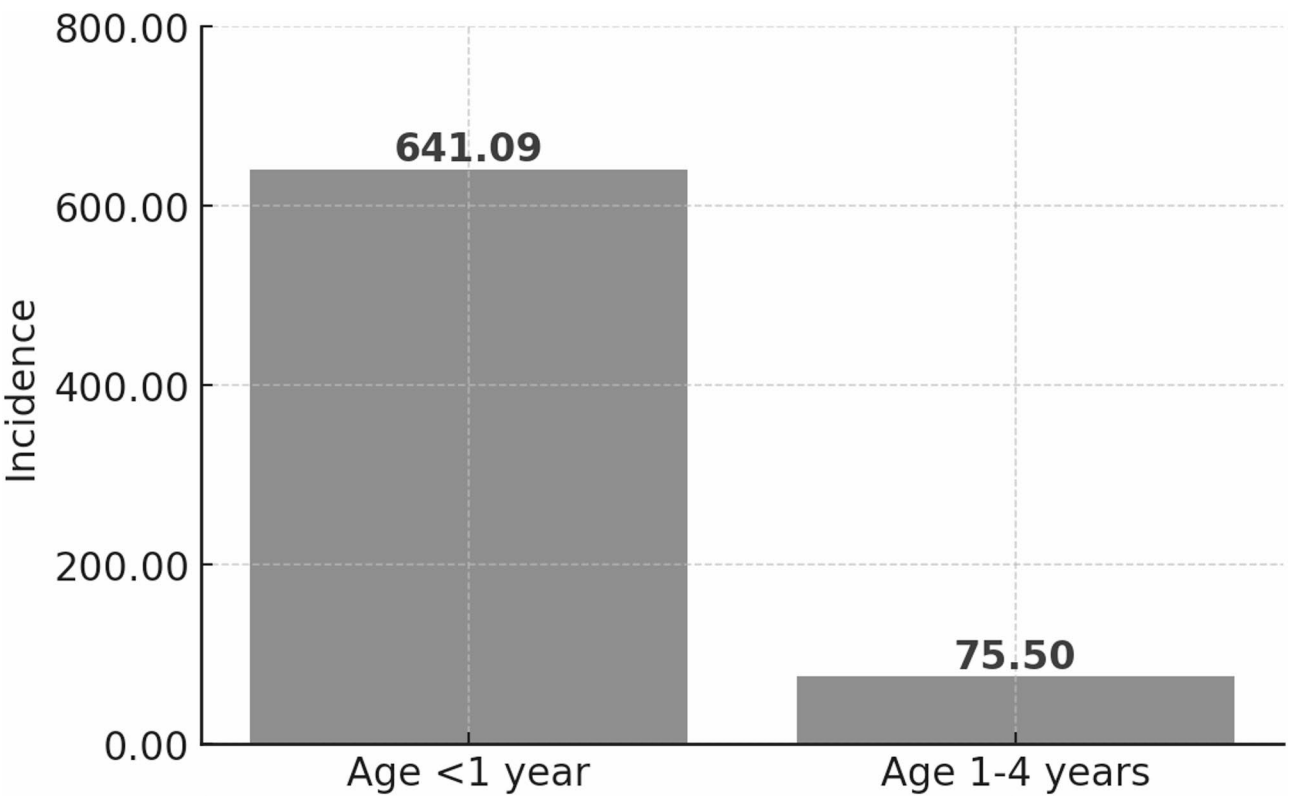

Fig. 1 Incidence of RSV-related hospitalizations per 100,000 inhabitants from 2008 to 2021.

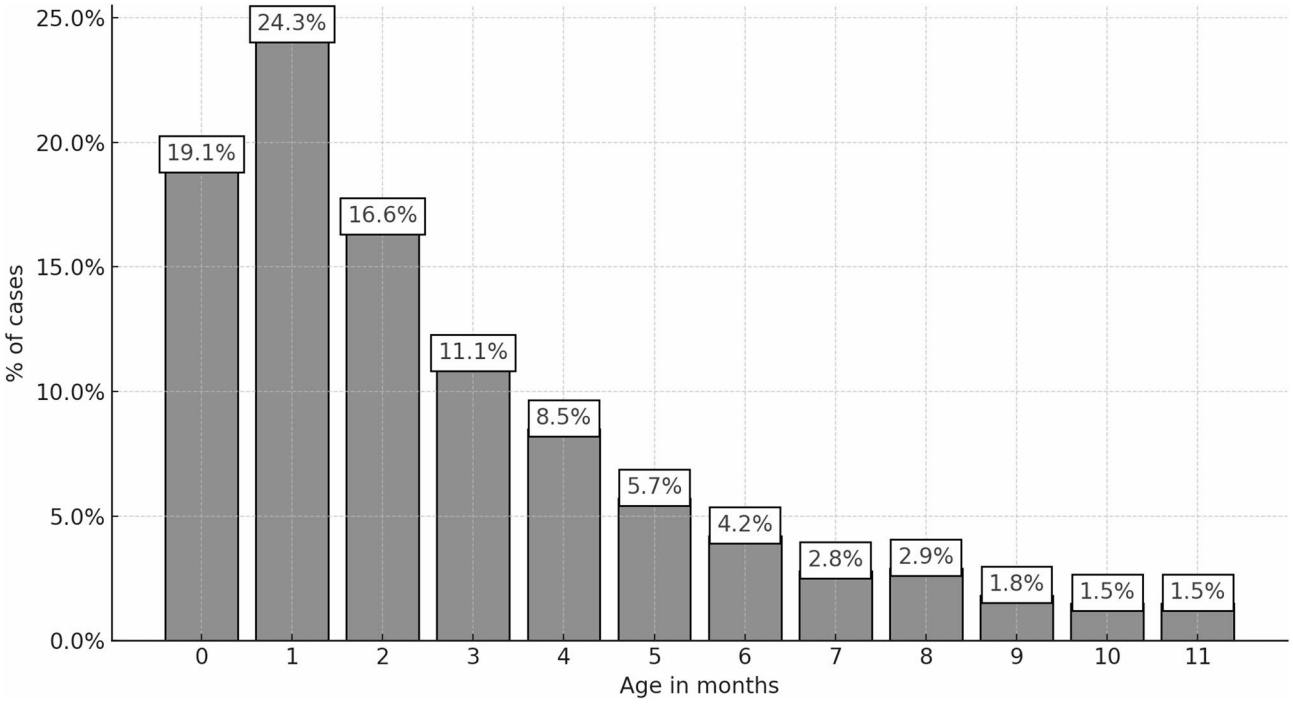

Fig. 2 Prevalence of RSV-related hospitalizations among children younger than 1 year in Sicily in the period under study (*n*=3,855).

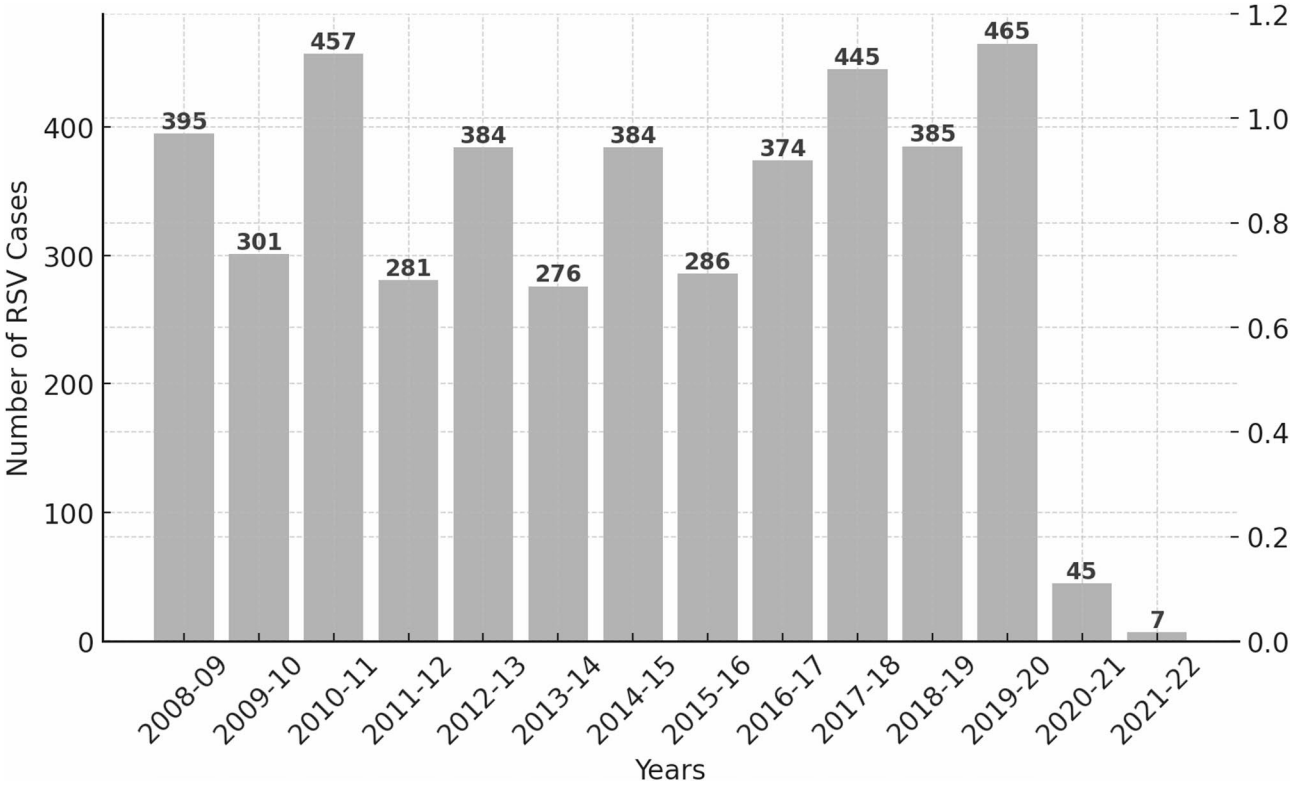

Fig. 3 Number of RSV-related hospitalizations registered from 2008 to 2021.

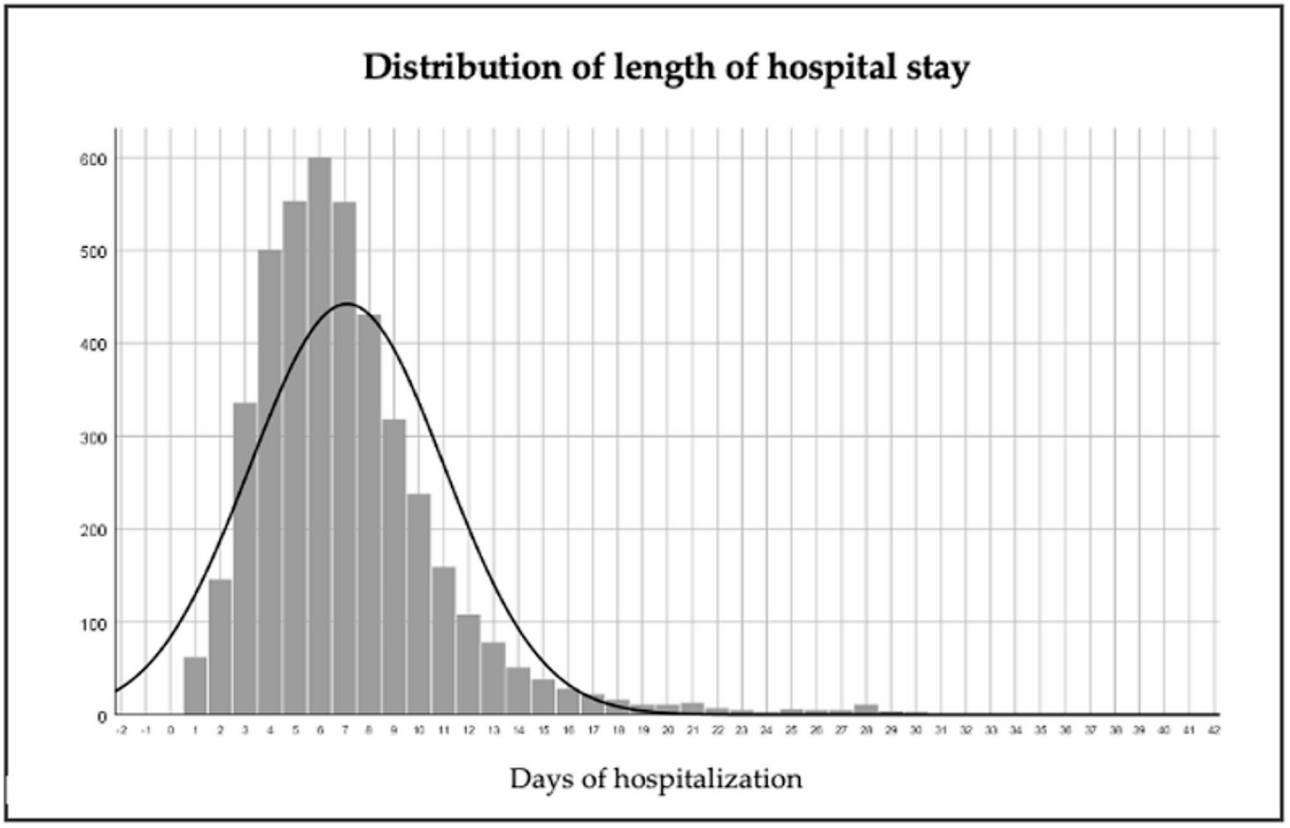

Fig. 4 Distribution of hospitalization length in the cohort under study. The negative values are a byproduct of the interpolation process and do not correspond to real data.

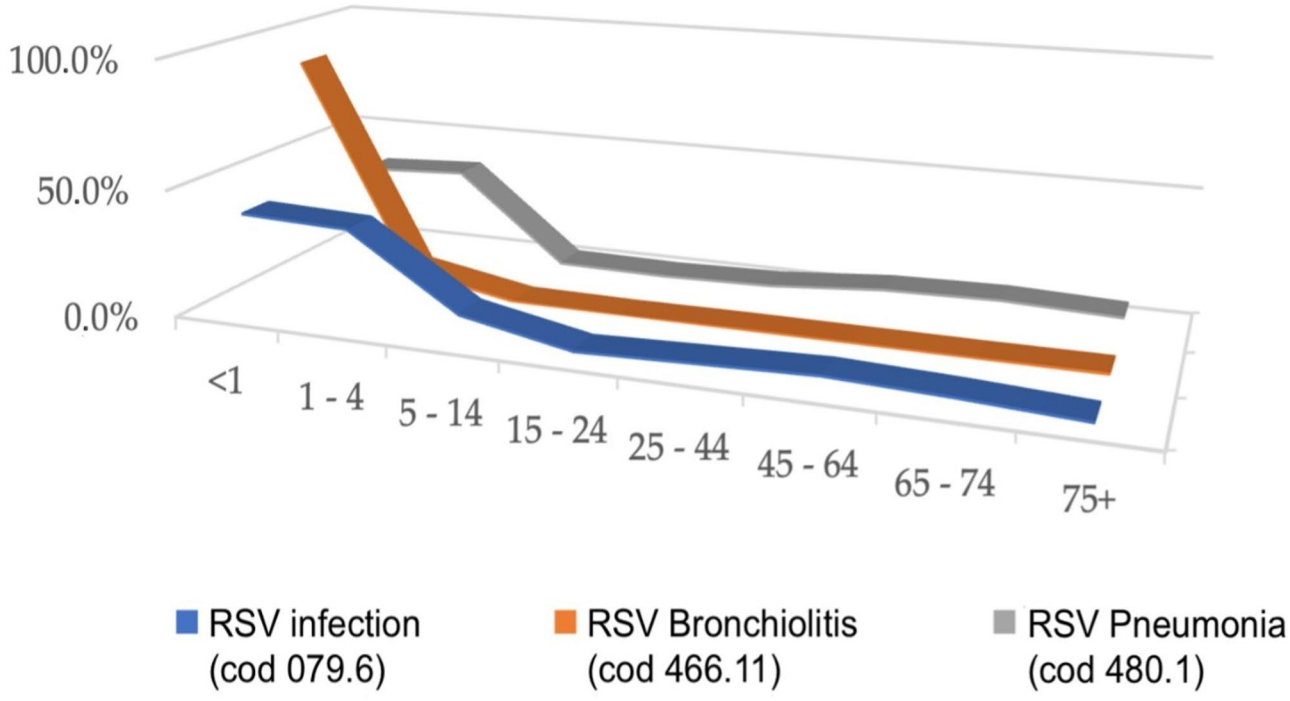

Fig. 5 Representation of the prevalence of different diagnostic codes in all HDRs, stratified by age group.

Of all the Sicilian territories, the Palermo area accounted for the highest hospitalization incidence (16.35 per 100,000), followed by the area of Trapani (5.47 per 100,000; Fig. 6).

Data from each season allowed the definition of a seasonal trend of RSV infection in the Sicilian population between October 2008 and September 2021.

Between December and February, 2,732 out of 4,485 hospitalizations (60.9%) were recorded, while 3,624 out of 4,485 cases (80.8%) occurred between December and March. The seasonal patterns of RSV-related hospitalizations during the years 2018–2020 are shown in Fig. 7.

Of the 4,485 hospitalized patients, 178 (4%) required transfer to the intensive care unit (ICU), while 271 (6%) needed intensive care overall, regardless of whether they were admitted to the ICU directly or transferred upon worsening clinical conditions. Specifically, 260 out of 271 (95.9%) were less than one year old; 153 out of 271 (56.5%) were up to one month (0–29 days), 64 out of 271 (23.6%) were between one and two months, and 24 out of 271 (8.9%) were between two and three months. None of the adults in our population necessitated intensive care. Age strongly correlated with the risk of ICU admission in our cohort, with an aOR of 6.78 (95% CI: 4.99–9.20) considering the entire cohort, and 7.05 (95% CI: 5.16–9.65) considering the pediatric population.

There were 632 patients who presented with respiratory failure, of whom 253 (40%, 253/632) were less than 30 days old. Among the pediatric population aged 0–4 months, the risk of respiratory failure was significantly greater, with an odds ratio (OR) of 3.24 (95% CI: 2.53–4.14) and a p value < 0.001.

The Kolmogorov-Smirnov test revealed a statistically significant difference between the hospitalization length

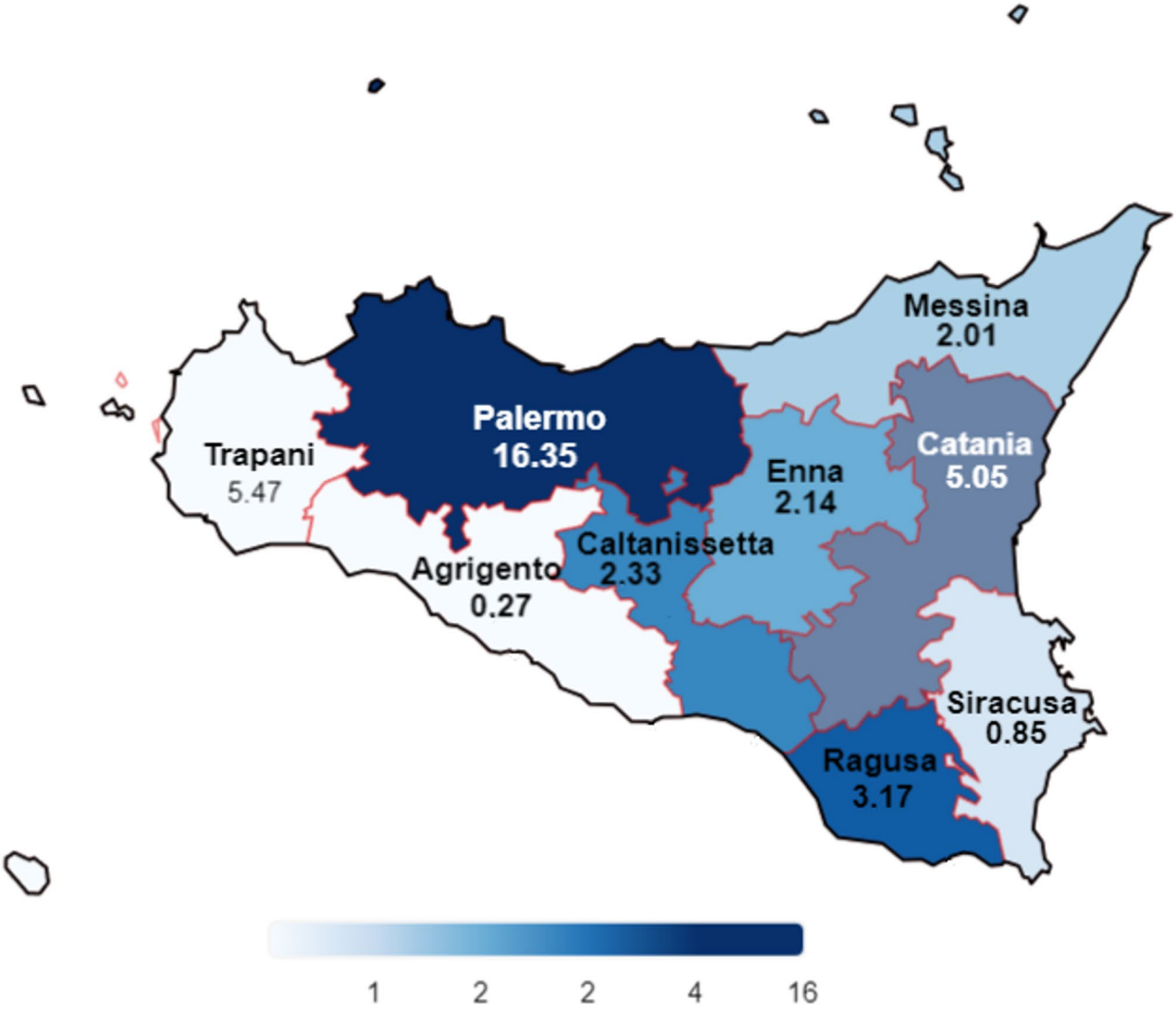

Fig. 6 Average incidence of RSV-related hospitalizations per 100,000 inhabitants in the Sicilian provinces during the period 2008-2021.

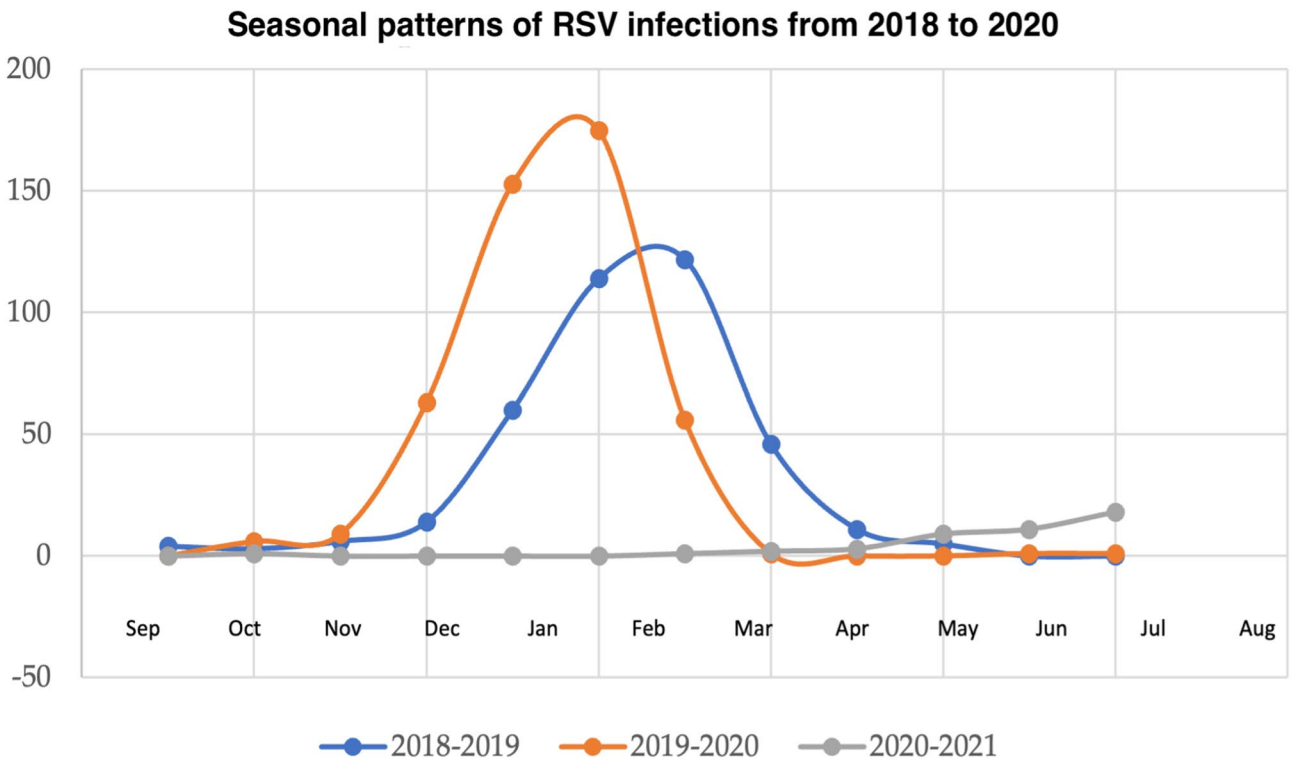

Fig. 7 Seasonal patterns of RSV-related hospitalizations from 2018 to 2020

in the ordinary ward, which was, on average, 6 days, and the length of stay in the ICU, which was approximately 10 days. Eight patients (0.2%) died, 3 of whom were younger than 1 year and 5 of whom were older than 18 years.

The following conditions, with relative frequencies, were identified in the pediatric component of the study cohort (0–17 years, $n = 4{,}345$): congenital heart diseases ($n = 97$, 2.23%), respiratory comorbidities (excluding respiratory insufficiency; $n = 70$, 1.61%), non-cardiac congenital malformations ($n = 29$, 0.67%), and cardiovascular comorbidities ($n = 28$, 0.64%). The most common congenital heart diseases were interventricular defects (16/4,345) and patent ductus arteriosus (16/4,345). Among non-cardiac congenital malformations, trisomy 21 was the most represented (8/4,345).

In the study cohort, prematurity affected 15 out of 738 infants (2%), and it was associated with a longer hospital stay: 9 days vs. 6 days (p value = 0.04, cOR 4.71, 95% CI: 1.50–14.81). Of the 15 preterm infants, 6 were admitted to the ICU, and none died.

Regarding the adult population, 138 cases were registered, 5 of whom died (3.6%). The cohort included 75 females and 63 males, with a median age of 66 years. Five patients died: two females aged 66 and 67 years and three males aged 30, 54, and 78 years. They were hospitalized for RSV pneumonia associated with respiratory failure [4], HIV [2], cardiovascular disease [2], diabetes [1], sepsis [1], and acute renal failure [2].

Univariate analysis revealed an association between ICU admission and the following aspects gathered from the HDRs: female sex, age under 3 months, prematurity, neonatal sepsis, respiratory distress, atelectasis and respiratory failure in newborns, congenital heart disease, respiratory failure, metabolic and nutritional disorders, and trisomy 21 (Table 1). Tables 2 and 3 provide more details regarding the variables "metabolic and nutritional disorders" and "oncological diseases," including the number of individuals affected by specific pathologies and the affected age groups.

The multivariate logistic regression analysis, which was conducted separately on the entire study population ($n = 4{,}483$) and the pediatric subgroup ($n = 4{,}345$), showed consistent results across both models. In the overall population, the strongest predictors of ICU admission were neonatal sepsis (OR 22.99, 95% CI: 5.33–99.19), neonatal respiratory distress (OR 20.91, 95% CI: 8.01–54.63), and younger age in months (OR 6.78, 95% CI: 4.99–9.20) (Table 4). In the pediatric population, the results were similar, and the strongest predictors were the same; however, conditions grouped under the label "metabolic and nutritional diseases" had a stronger impact in this group (OR 12.27, 95% CI: 2.36–63.81) (Table 4).

Variables such as prematurity, neonatal atelectasis, Down syndrome, and other neonatal respiratory problems were excluded from the final models because of a lack of statistical significance (Table 5).

Table 1 Association of ICU admissions with demographics, comorbidities and coinfections (and focus on newborns)– Univariate analyses

Variables	ICD-9 codes	Hospitalizations (*n* = 4,485)	ICU (*n* = 272)	non-ICU (*n* = 4,213)	*p* value	cOR (95% CI)
Demographics						
Age, median (IQR) months		3 (1–6)	1 (1–2)	3 (2–7)	< 0.001	8.61 (6.51–11.37)
Gender						
Male		2,371 (52.9%)	126 (46.5%)	2,245 (53.3%)	0.03	1.31 (1.03–1.68)
Female		2,112 (47.1%)	145 (53.3%)	1,967 (46.7%)		
Comorbidities						
Cardiac diseases	390-429.90	83 (1.9%)	9 (3.3%)	74 (1.8%)	0.06	-
Respiratory failure	518.81-518.84	353 (7.9%)	43 (15.8%)	310 (7.4%)	< 0.001	2.36 (1.67–3.34)
Hematologic diseases	280.10-288.60	84 (1.9%)	3 (1.1%)	81 (1.9%)	0.33	-
Oncological diseases	162–239.00	27 (0.6%)	2 (0.7%)	25 (0.6%)	0.76	-
Metabolic and Nutritional Disorders	251.10-273.10	12 (0.3%)	3 (1.1%)	9 (0.2%)	0.01	5.21 (1.40-19.35)
Diabetes	250.00-250-82	14 (0.3%)	1 (0.4%)	13 (0.3%)	0.87	-
Coinfections						
Whooping cough	33.00-33.80	4	0	4	-	-
Intestinal infections	008.43–008.80, 009.00-009.30	90 (2%)	2 (0.7%)	88 (2.1%)	0.12	-
Bacterial infections	041.00-041.90	142 (3.2%)	8 (2.9%)	134 (3.2%)	0.83	-
HIV	042.00	4 (0.1%)	1 (0.4%)	3 (0.1%)	0.11	-
Candidiasis	112-117.90	74 (1.6%)	1 (0.4%)	73 (1.7%)	0.09	-
Influenza	487.00-487-80	36 (0.8%)	1 (0.4%)	35 (0.8%)	0.40	-
Bacterial pneumonia	481.00, 482.00, 482.20, 484.80, 486.00	350 (7.8%)	21 (7.7%)	329 (7.8%)	0.96	-
Conditions affecting newborns						
Preterm	765.04-765.19	15 (0.3%)	6 (2.2%)	9 (0.2%)	< 0.001	10.54 (3.72–29.82)
Neonatal sepsis	771.81	12 (0.3%)	9 (3.3%)	3 (0.1%)	< 0.001	48.02 (12.92-178.44)
Respiratory distress	769.00	24 (0.5%)	17 (6.3%)	7 (0.2%)	< 0.001	40.06 (16.46–97.47)
Atelectasis	770.50	11 (0.2%)	4 (1.5%)	7 (0.2%)	< 0.001	8.97 (2.61–30.83)
Respiratory failure	770.84	290 (6.5%)	62 (22.8%)	228 (5.4%)	< 0.001	5.16 (3.77–7.06)
Other respiratory diseases	770.89	136 (3%)	15 (5.5%)	121 (2.9%)	0.01	1.97 (1.14–3.43
Congenital pathologies						
Trisomy 21	758.00	8 (0.2%)	2 (0.7%)	6 (0.1%)	0.03	5.19 (1.04–25.86)
Congenital hypothyroidism	243.00	3 (0.1%)	0	3 (0.1%)	-	-
Congenital heart disease	745.20-747.30	97 (2.2%)	23 (8.5%)	74 (1.8%)	< 0.001	5.17 (3.18–8.39)
Congenital malformations	748.30-759.89	30 (0.7%)	4 (1.5%)	26 (0.6%)	0.09	-

Table 2 Conditions coded as "metabolic and nutritional disorders", including ICD-9 codes 251.10 through 273.10

Specific condition	Number of cases
Unspecified hypoglycemia (251.2)	2
Other neuro-hypophyseal disorders (253.8)	1
Unspecified protein-caloric malnutrition (263.9)	1
Unspecified deficiency of vitamin D (268.9)	2
Unspecified nutritional deficiencies (269.9)	1
Phenylketonuria (270.1)	2
Other and unspecified hyperlipidemias (272.4)	3

Table 3 Conditions coded as "oncological diseases"

Age	Malignant Neoplasms (ICD 200–208, 160–199)	Uncertain/ Benign (ICD 210–239)	Total
Pediatrics (< 18y)	0	13	13
Adults (≥ 18y)	13	1 (Uncertain Behavior)	14
Total	13	14	27

Table 4 Multivariate logistic regression analysis: adjusted odds ratios (aOR) and 95% confidence intervals for ICU admission in total and pediatric populations

Variable	Total Population OR (95% CI)	Pediatric Population OR (95% CI)
Neonatal Sepsis	22.99 (5.33–99.19)	22.98 (5.31–99.50)
Neonatal Respiratory Distress	20.91 (8.01–54.63)	20.46 (7.82–53.55)
Age (in months)	6.78 (4.99–9.20)	7.05 (5.16–9.65)
Metabolic and Nutritional Disorders	8.53 (1.78–40.85)	12.27 (2.36–63.81)
Congenital Heart Disease	4.24 (2.45–7.31)	4.26 (2.46–7.35)
Neonatal Respiratory Insufficiency	2.15 (1.50–3.07)	2.10 (1.47-3.00)
Respiratory Failure	3.63 (2.48–5.31)	3.18 (2.13–4.74)
Sample size	*N* = 4,483	*N* = 4,345

aOR = adjusted odds ratio

Table 5 Variables not included in the model due to lack of significance

Prematurity
Neonatal atelectasis
Down syndrome
Other neonatal respiratory problems
Gender

Discussion

Epidemiology of RSV-related hospitalizations

In Europe, there are approximately 245,244 (95% CI: 224,688–265,799) annual hospitalizations for respiratory infections associated with RSV in children under 5 years of age [15]. Most of these cases occur in children younger than 1 year, who account for 75% of all RSV-related hospitalizations. Infants younger than 2 months are the most affected age group, with a hospitalization rate of 71.6 per 1,000 children (95% CI: 66.6–76.6) [15].

Mortality due to RSV-related infections in pediatric patients is greater in low- and middle-income countries. Studies indicate that RSV is responsible for an estimated 66,000 to 199,000 deaths annually (year 2005), whereas influenza accounts for 28,000 to 111,500 deaths in children younger than 5 years (year 2008) [6, 16–18]. RSV pneumonia is considered the second leading cause of postnatal death in children, following malaria, and is responsible for approximately 137,000 deaths worldwide each year, accounting for 6.7% of all neonatal deaths [19]. Consistent with the findings of similar studies, in our cohort, most hospitalizations lasted less than a week, and mortality was very low (0.2%) [20].

This study highlights the burden of RSV on hospitalizations in children aged 0–4 years, with an incidence of RSV-related hospitalizations of 641/100,000 in children under 1 year and 75.5/100,000 in those aged 1–4 years, within the period 2008–2021. These findings are consistent with other European studies showing a greater impact of RSV in children under 2 years, especially in those under 6 months.

A Swedish retrospective survey with a focus on children under 5 years hospitalized in the period 2004–2011 found a hospitalization rate of 17.4/1,000 for children younger than one year and 0.6/1,000 for those aged 1–4 years [21]. A British birth cohort study focused on the first year of life revealed that most RSV-related hospitalizations occur in the first few months of life, with a peak in the first month [22]. A Spanish observational study covering the period 1997–2011 reported a hospitalization rate of 2,413/100,000 in children under 2 years old and 4,136/100,000 in infants. The mean age of the hospitalized children in this cohort was approximately 5.8 months [23].

Cangiano et al., in a study on the epidemiological characteristics of children hospitalized for bronchiolitis in Italy over ten consecutive epidemic seasons (2004–2014), detected RSV in 32.4% of cases, confirming the predominance of RSV as the main etiological agent of bronchiolitis [24]. Another Italian study identified RSV in 34.1% of children (up to 15 years) admitted for acute respiratory syndrome in two pediatric clinics in Milan in 2008–2009 [25].

Khudari et al. collected all HDRs with the codes "RSV bronchiolitis," "RSV pneumonia" or "RSV infection" as primary diagnoses registered in Italy between 2001 and 2014 and reported a higher prevalence of RSV-related diseases in boys younger than one year, a correlation between age and hospitalization length, and seasonal trends similar to those we described [19].

The seasonal trends we observed in the prepandemic period align with historical national trends and differ from the local patterns observed in previous studies conducted in Sicily, possibly because of their smaller sample size and shorter timeframe [10–12].

Risk factors for ICU admission in patients hospitalized for RSV infection

Our analyses led to the identification of several key independent risk factors for ICU admission, including very young age (particularly less than three months), neonatal conditions such as sepsis or respiratory distress, and certain comorbidities (including some metabolic and nutritional disorders and congenital heart disease). Similarly, others reported a 2.10-fold (95% CI: 1.14–3.79) increased risk of ICU admission in infants younger than 6 months, with prematurity also increasing the likelihood of needing intensive care (aOR 2.35, 95% CI: 1.26–4.41) [26]. Another retrospective cohort study based on ICD-10 codes identified age 0–5 months (OR: 20.29, 95% CI: 18.37–22.41) and cardiovascular disorders

of the perinatal period (OR: 1.32, 95% CI: 1.11–1.57) as risk factors for contracting RSV-related diseases [27]. These, together with preterm birth (OR: 6.71, 95% CI: 2.19-20.61) and congenital cardiovascular malformations and diseases, also represented risk factors for ICU admission in RSV patients [27]. In our analyses, prematurity was excluded from the model due to lack of statistical significance, probably because of the reduced representation in our cohort (only 15 infants were preterm), or because of the presence of stronger competing risk factors, such as neonatal sepsis and neonatal respiratory distress, which had a greater impact on the multivariate analysis. Respiratory distress and apnea are also consistently reported as predictors of ICU admission for RSV infection in hospitalized children [26, 28]. Conditions grouped as "metabolic and nutritional disorders" (detailed in Table 2) also appeared to be predictors of ICU admission in our pediatric population, which is unsurprising considering the detrimental effects of malnutrition and vitamin D deficiency on the immune system and infection severity, as has been observed more recently with COVID-19 infection [29–32].

Despite the minor representation of adults in our cohort (138 out of 4,485 hospitalizations, or 3%), notably, the 5 deaths recorded due to RSV pneumonia all occurred in adults with comorbidities (such as HIV, cardiovascular diseases, diabetes, or other respiratory infections), coherently with findings on the role of chronic respiratory and cardiovascular comorbidities in RSV-related ICU admissions in adults [33]. While RSV can lead to complications in elderly patients, its impact on younger populations remains more significant in terms of ICU burden. In our cohort, there were no ICU admissions among adults, while infants under 3 months of age were disproportionately affected by severe RSV-related diseases requiring intensive care.

Regional differences in RSV hospitalization rates

We observed significant differences in the prevalence of RSV-related hospitalizations in different areas of Sicily, particularly between the area of Palermo and other areas. The most striking difference is that between the area of Trapani and Palermo. There are several aspects to consider in explaining this difference. First, the Palermo metropolitan territory (formerly the province of Palermo) is larger and more densely populated than other regions, with an area of 5,009.28 km^2, 82 cities and a population of 1,195,678 inhabitants as of January 2024 [13]. For comparison, the Agrigento area includes 43 cities, with an overall extension of 3,052.59 km^2 and a total population of 416,181 [13]. Additionally, the metropolitan area of Palermo serves as a healthcare hub for Western Sicily, including several referral centers where patients (especially children) with severe RSV disease are transferred from other regions, adding to the overall number of hospitalizations. The Children's Hospital "G. Di Cristina," for instance, hosts a Level II Emergency Department, increasing the chances of transfers of severe cases from the surrounding territories [34].

Impact of the SARS-CoV-2 pandemic on RSV seasonality

We observed a peak in RSV infection in the prepandemic season of 2019–2020. During the same period, a study conducted in the Italian regions of Lazio and Puglia on children under 5 years of age revealed 119 RSV-positive children out of 293 (41%) with acute respiratory infection symptoms [35]. Of note, six of the RSV-positive children (5%) were premature, 61 (51%) had coinfections with at least one other virus, and 44% of the entire cohort was under one year old [35].

During the pandemic, RSV infection rates decreased significantly in Europe, dropping from peaks of 2,000–2,500 cases per week during prepandemic seasonal epidemics (2016–2020) to fewer than 700 cases per week in 2020–2021 [36, 37]. The global seasonal pattern of RSV outbreaks has been disrupted by the SARS-CoV-2 pandemic and nonpharmaceutical interventions aimed at controlling it [38].

National surveillance systems in France, Belgium, Finland, and Spain recorded a rapid decline in RSV outbreaks compared with previous seasons and a delay in their peak [39–43]. In Italy, studies based on influenza surveillance samples have indicated that RSV infection in children nearly disappeared during the 2020–2021 season, with an 84–95% lower rate of acute bronchiolitis in the 2020–2021 season than in previous seasons [44–47]. Specifically, from the 46th week of 2020 to the 16th week of 2021, no influenza viruses were isolated in Italy through the RespiVirNet surveillance system, which includes RSV surveillance since 2019–2020 [48, 49], and the incidence of influenza-like illnesses remained below the epidemic threshold of 3.16 cases per 1000 inhabitants. This was probably due to viral competition with SARS-CoV-2, immunological memory, increased flu vaccine coverage, and, most importantly, pandemic-related social distancing and personal protection measures.

Our analyses (Fig. 7) are consistent with the reduced circulation of RSV in Sicily during the 2020–2021 season, which is largely attributable to pandemic control measures, such as physical distancing, the use of personal protective equipment, and the switch to distance learning.

With the easing of SARS-CoV-2 restrictions in the 2021–2022 season, influenza virus circulation returned, albeit at lower levels than in the pre-2020 seasons. The 2021–2022 season was characterized by a delayed onset and a shorter duration, with a peak at the end of December 2021, largely attributable to RSV. The second peak

was caused mostly by influenza viruses [48, 50]. The resurgence of RSV in 2021 was noted in many countries, with mathematical models predicting large outbreaks in the coming years due to an increase in the number of vulnerable children [51]. A study conducted in Bari (Italy) from January 1, 2017, to December 31, 2021, identified 1,082 children hospitalized for RSV infection, with an average number of admissions per year of 216 [36]. The same study revealed that the 2021 epidemic was markedly different from previous ones, with no cases recorded until August 2021 [36]. Unlike prior seasons, where hospitalizations peaked in February, the 2021 epidemic began much later and peaked in November [36].

Several explanations have been proposed as to why the epidemiology of RSV drastically changed after the COVID-19 pandemic, including the development of an "immunity debt" created by the lack of immune stimulation by viruses for a prolonged period [52] or the immune dysregulation induced by SARS-CoV-2 documented in some studies [53–55]. Another possibility is that the circulation of multiple respiratory viruses during the resurgence period may have led to a high level of interaction between viruses through both coinfections and/or superinfections. These interactions may have both additive and subtractive effects, as supported by experimental models, clinical cases, and epidemiological data [56].

While recent studies have focused on RSV epidemiology in children, its impact on adults is often underestimated. In elderly individuals, RSV typically causes mild URT inflammation or asymptomatic infection. However, in older adults and those with high-risk conditions (e.g., chronic obstructive pulmonary disease, asthma, congestive heart failure), RSV can cause an illness similar to nonpandemic influenza A [57].

Available and new preventive strategies for RSV-related diseases

The RSV genome encodes a total of 11 proteins, including three membrane proteins: a small hydrophobic (SH) protein, an attachment glycoprotein (G), and a fusion protein (F). The F and G proteins are the major pathogenic factors of RSV, mediating the invasion process, the development of cell syncytia, and the ability to escape the host immune response while also inducing protective neutralizing antibody responses [58–62].

On the basis of variations in the protein G sequence, RSV can be divided into A and B subtypes, which usually circulate simultaneously during epidemic seasons, with a typical prevalence of one subtype over the other in different seasons [62].

The F protein interacts with several receptors that are constitutively expressed by respiratory epithelia and are the main target of RSV. The interaction between the F protein and target receptors enables the fusion of the target cell membrane with the virus, causing viral RNA to enter the host cells. Therefore, a timely and effective immune response against protein F could prevent clinical manifestations of RSV infection [63].

Currently, several options are available to prevent RSV infection globally, including Abrysvo® (Pfizer), Arexvy® (GSK), and nirsevimab (Beyfortus®) [64–67].

Abrysvo (RSVpreF) consists of prefusion F antigens from RSV subgroups A and B in equal amounts and is recommended for use in adults over 60 years of age and pregnant women between the 32nd and the 36th week, providing active immunization in adults and passive immunization of infants born to vaccinated mothers [64, 67]. Arexvy consists of a recombinant RSVPreF3 antigen and an AS01E adjuvant and is used to protect adults 60 years of age and older through active immunization [65, 67]. Nirsevimab, approved in the EU in 2022, is a recombinant human monoclonal antibody (IgG1) that prevents RSV from entering cells by binding to and thus blocking the RSV prefusion protein [66–68]. Unlike its predecessor, palivizumab, nirsevimab is recommended for children up to 2 years old, regardless of the presence of conditions predisposing them to severe RSV disease, and it has a roughly threefold longer half-life (approximately 71 days), allowing for a single administration for the entire RSV season [66, 67]. Nirsevimab has been shown to be safe and effective in preventing RSV infection in newborns, with a significant reduction in RSV-related diseases requiring medical treatment (74%) and hospitalization (76%) compared with placebo [69–71]. Several European studies have collected evidence on the effectiveness of nirsevimab at reducing hospitalizations, ambulatory consultations, and ICU admissions [72–76].

A recent metanalysis on the safety and efficacy of RSV vaccines revealed a 57.3% efficacy of maternal vaccines (such as RSVpreF) in protecting newborns in the first 90 days of life, with an even greater efficacy in preventing serious disease (81.9%) [77]. In older adults, Arexvy (RSVPreF3) and mRESVIA, or mRNA-1345, an mRNA vaccine encoding the membrane-anchored RSV-A glycoprotein F, have been effective at reducing RSV-related LRTD by 78.3% and serious diseases by 86.5%, with an acceptable safety profile [77, 78].

Post marketing studies aimed at identifying extremely rare adverse events associated with new vaccines are currently ongoing, and more research is needed on their long-term effects, with attention to their efficacy and safety in different populations.

Strengths and limitations

This constitutes, to the best of our knowledge, the largest observational study on the impact of RSV-related illnesses on hospitalizations in the Sicilian population. Its strengths include the numerosity of the cohort, the broad

time period under analysis (spanning from 2008 to 2021), the inclusion of all RSV-related hospitalizations (chiefly, bronchiolitis, pneumonia, and unspecified RSV-related infections), and the consideration of both primary and secondary diagnostic codes recorded in HDRs. Furthermore, the use of the stepwise forward selection method in the multivariate analysis reduced the impact of collinearity between strongly correlated risk factors, isolating the main predictors of ICU admission in RSV-related hospitalizations.

Its limitations include the retrospective nature of the analysis, the operator-dependent accuracy of data registered in HDRs, the synthetic nature of the comorbidity and coinfection codes routinely used in HDRs, and the lack of outpatient data. Comparisons between the adult and pediatric populations included in this study were limited by epidemiology-dependent sample numerosity differences. To address these limitations, future research based on HDRs should aim to integrate detailed clinical charts and laboratory-confirmed RSV diagnoses to improve data reliability. Additionally, further research into the role of coinfections in RSV severity, the long-term impacts of postpandemic shifts in RSV seasonality, and the economic burden of RSV hospitalizations could help better define the cost-effectiveness and implementation challenges of preventive strategies.

Conclusions

RSV-associated pathologies remain a significant cause of hospitalization in Sicily. Bronchiolitis and pneumonia caused by RSV are serious conditions that often require respiratory and/or nutritional support and sometimes necessitate admission to intensive care. RSV-related diseases have a significant effect on children, particularly those under 2 years of age, with the highest burden observed in infants younger than 6 months, who account for most RSV-related hospitalizations worldwide.

During the 2020–2021 season, RSV-related diseases nearly disappeared due to the pandemic, whereas during the postpandemic period (2022–2023 and 2023–2024 seasons), when isolation measures were lifted, an increase in RSV cases was observed, affecting younger children, with slightly different seasonality.

Young age, congenital heart disease, respiratory insufficiency, respiratory distress and failure in newborns, and comorbidities are significant risk factors for ICU admission. However, RSV-related diseases continue to require hospitalizations in both healthy children and adults. For these reasons, it is important to continue monitoring RSV-related diseases and hospitalizations through updated epidemiological studies, which can guide the implementation of existing preventive strategies and inform the cost-benefit analysis of new ones.

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Conceptualization, A.C. (Condemi), D.M., C.C., Data Curation A.C. (Condemi), D.M.; Formal Analysis, A.C., D.M.; Investigation, A.C. (Condemi), D.M., C.A., G.L., V.G., G.B., L.V.; Methodology, A.C. (Condemi), D.M., A.C. (Cascio), C.C.; Project Administration, A.C. (Cascio), C.C.; Resources, A.C. (Condemi), D.M., G.L., V.G., G.B., A.C. (Cascio), C.C., Software A.C. (Condemi), D.M.; Supervision, A.C. (Cascio), C.C.; Validation, A.C. (Condemi), D.M., A.C. (Cascio), C.C.; Visualization, A.C. (Condemi), D.M.; Writing– Original Draft, A.C., D.M., C.A.; Writing– Review & Editing, A.C. (Condemi), D.M., C.A., L.V., C.C.

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Data availability
All data supporting the findings of this study are included within the article. Further inquiries can be addressed to the corresponding author.

Declarations

Ethics approval and consent to participate
For this type of study, formal consent is not needed, as no patients are identifiable. All personal data were protected according to the Helsinki Declaration and Italian law (Legislative Decree of 30 June 2003, n. 196. Code on the protection of personal data).

Consent for publication
Not applicable, as no individual patient data were included in the study.

Competing interests
The authors declare no conflicts of interest.

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