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Original Article

Epidemiology of acute bronchiolitis: what has changed after the SARS-CoV-2 pandemic? Analysis of pre-pandemic and post-pandemic hospitalisations in a Piedmont Spoke Centre

Epidemiologia della bronchiolite acuta: cosa è cambiato dopo la pandemia da SARS-CoV-2? Analisi dei ricoveri pre-pandemici e post-pandemici in un Centro Spoke piemontese

Nadia Fratangeli,[1] Marco Aicardi,[1] Marianna Farotto,[2] Marinella Bertolotti,[3] Carlotta Bertolina,[3] Mariachiara Strozzi,[4] Antonio Maconi[3]

[1]Paediatrics Unit, San Giacomo Hospital, Azienda Sanitaria Locale di Alessandria, Novi Ligure (AL); [2]Research and Innovation Department (DAIRI), Azienda Sanitaria Locale (ASL), Alessandria; [3]Research Innovation Training Infrastructure, Research and Innovation Department (DAIRI), Azienda Ospedaliero-Universitaria "SS. Antonio e Biagio e Cesare Arrigo", Alessandria; [4]Paediatrics Unit, Cardinal Massaia Hospital, Azienda Sanitaria Locale (ASL), Asti, Italy

Key words: RSV infection, hospitalization, paediatric, SARS-CoV-2 pandemic.

ABSTRACT

Background: Respiratory Syncytial Virus (RSV) affects the respiratory system, causing mild symptoms confined to the upper airways. The aim of this study, conducted in the Novi Ligure hospital, was to investigate the epidemiological and clinical variations in hospitalisations for RSV bronchiolitis in the pre- and post-SARS-CoV-2 pandemic periods.
Materials and Methods: all subjects referred for bronchiolitis or respiratory RSV infections to the paediatric unit in study between January 2016 and March 2023 were enrolled. Data were collected on the following SDO codes assigned to the patient at discharge. Data were collected on 208 admissions for bronchiolitis or RSV respiratory infection, with a total of 200 subjects.
Results and Conclusions: this study found that the incidence of RSV infection and overinfection in patients hospitalised for bronchiolitis has increased compared with the pre-pandemic period.

Background: il Virus Respiratorio Sinciziale (VRS) colpisce il sistema respiratorio, causando sintomi lievi limitati alle vie aeree superiori. Lo scopo di questo studio, condotto nell'Ospedale di Novi Ligure, è stato quello di indagare le variazioni epidemiologiche e cliniche dei ricoveri per bronchiolite da VRS nel periodo pre e post-pandemia da SARS-CoV-2.
Materiali e Metodi: tutti i soggetti ricoverati per bronchiolite o infezioni respiratorie da VRS, presso il reparto di Pediatria tra gennaio 2016 e marzo 2023, sono stati arruolati. I dati sono stati raccolti in base a specifici codici SDO assegnati al paziente al momento della dimissione. I dati sono stati raccolti su 208 ricoveri per bronchiolite o infezione respiratoria da VRS, per un totale di 200 soggetti.
Risultati e Conclusioni: questo studio ha rilevato che l'incidenza dell'infezione e della sovrainfezione da VRS nei pazienti ricoverati per bronchiolite è aumentata rispetto al periodo pre-pandemico.

Introduction

Respiratory Syncytial Virus (RSV) affects the respiratory system, causing mild symptoms confined to the upper airways. In other cases, however, it causes bronchiolitis, which is characterized by a partial obstruction of the small airways, leading to respiratory insufficiency.[1,2]

Worldwide, RSV is the leading infectious cause of respiratory morbidity and mortality in children under 5 years of age. There are an estimated 33 million episodes of acute lower respiratory tract infection associated with RSV each year.

RSV is also the most common cause of postnatal infant mortality worldwide after malaria.[3] Each year RSV is responsible for approximately 3.4 million hospitalisations worldwide, with high mortality in developing countries and 59,600 deaths in hospital[4].

The World Health Organization (WHO) estimates that RSV causes around 60% of acute respiratory infections in children[5] and is the most common cause of lower respiratory tract infections in the first two years of life (accounting for more than 80% of lower respiratory tract infections in infants under one year of age during the peak of the virus season), 60-90% of hospital admissions for bronchiolitis and 25-50% of pneumonia infections in Europe. RSV is, therefore, the most frequent cause of pediatric bronchiolitis and pneumonia. In countries with a temperate climate, including Italy, epidemics have a seasonal pattern, beginning in autumn and continuing into spring. Symptoms appear 2-6 days after contact, and the average duration of bronchiolitis is 5-7 days.[6]

RSV spreads easily from person to person, especially through contact with nasal secretions and saliva, but also through droplets. Infants almost always become infected after close contact with a

family member or sibling who goes to nursery school and has a cold. The virus can survive for several hours on surfaces (tables, handles, mobile phones, computer keyboards) and can also be spread by touching contaminated toys or other materials.[6]

VRS spreads rapidly in close proximity to groups of young children, such as kindergartens.

A recent article aimed to retrospectively evaluate a population of hospitalised children aged 0-6 years with a laboratory-confirmed diagnosis of RSV infection in Italy over a 5-year period (September 2014 - August 2019). The most important result of this study concerns the seasonal trend of the virus in Italy. In particular, the RSV epidemic period would begin in late autumn (November), peak in winter (January), and end in early spring (April).[6]

Bronchiolitis is an acute obstructive bronchopathy of viral etiology with a predominantly seasonal epidemic character. It manifests as a descending virosis of the respiratory tract. Other causative agents of this infection include parainfluenza (5-20%), influenza V, adenovirus, rhinovirus, and others.[7]

During the 2019 global coronavirus disease pandemic, the epidemiology of RSV and influenza appears to have changed dramatically, with significant reductions in both influenza and bronchiolitis during the normal peak winter season.[8] The use of face masks, hand washing, and social distancing during the COVID-19 pandemic reduced bronchiolitis outbreaks by 70-80%, but when these regulations were slowed down, major RSV epidemics occurred in many countries around the world. This scenario has led to a reconsideration of the paradigm that children and young schoolchildren are the main drivers of seasonal outbreaks of RSV and respiratory epidemics in general. The shift in epidemiological trends observed in other parts of the world seems to have occurred in Italy as well. Literature reported RSV hospitalisation rates in Italy from SDOs (hospital discharge forms) during the period 2001-2014, in children aged 0-2 years were 224.8/100,000 for bronchiolitis due to RSV, 9.6/100,000 for RSV pneumonia and 4.6/100,000 for RSV infection not otherwise specified.[9] This study also reports the rate of hospitalisation stratified by age group, confirming that children under one year of age are most at risk.[9]

In both Europe and the USA, hospitalisations for RSV bronchiolitis are on the rise: although the cause is not yet clear, air pollution has been linked in the literature, particularly in large cities, but studies of non-metropolitan areas are scarce. A significant increase has also been described in the post-lockdown period of the SARS-CoV2 pandemic, both in terms of incidence, severity, and anticipation of the epidemic period, but little evidence has yet been described in this context.

Clinical manifestations vary from person to person (depending on age, concomitant diseases and environmental factors), some are asymptomatic, others show mild signs of inflammation of the upper respiratory tract, which can sometimes progress to respiratory distress due to lower respiratory tract involvement, characterised by tachypnoea, retractions, catarrhal cough and wheezing.[10-12]

With regard to diagnosis, the following data are basic anamnestic-clinical data (risk factors, exposure, age, clinical situation), supported by antigenic and molecular laboratory tests, whereas general laboratory and radiological data are not very specific.[13-15]

Several therapies have been proposed for the treatment of bronchiolitis, although there are currently no specific treatments with proven efficacy, only symptomatic therapies and respiratory and nutritional support where necessary.[14,16,17]

In recent years, the spread of high-flow oxygen therapy has provided a new option for treating patients with bronchiolitis in emergency departments and non-intensive care units, in some cases avoiding admission to intensive care or transport to a referral centre.[18-20] There are also preventive measures to be taken to reduce the spread (within the household and in the community), including the promotion of breastfeeding and the reduction of indoor and outdoor pollution (possible risk factors for incidence and severity) [21].

In terms of long-term prognosis, it has also been reported that more than half of children who develop RSV bronchiolitis appear to be at increased risk of recurrent wheezing, even into adolescence.[22,23] It has been described in the literature that acute RSV infection is associated with a 3-fold increased risk of developing asthma compared with healthy controls. It is unclear whether this is due to direct damage by RSV to the bronchial epithelium or whether there is an individual predisposition to the development of severe bronchiolitis and subsequent respiratory disease.[24,25]

Certainly, improving primary prevention of RSV infection in children may help prevent the development of chronic lung disease in adulthood.[26]

The aim of the study, conducted at the San Giacomo Hospital in Novi Ligure of the Alessandria Local Health Authority (ASL AL), was to investigate the epidemiological and clinical variations in hospitalisations for RSV bronchiolitis in the pre- and post-SARS-CoV-2 pandemic periods.

Materials and Methods

This was a retrospective and prospective observational clinical study. All subjects referred for bronchiolitis or respiratory RSV infections to the pediatric unit of Novi Ligure Hospital, in ASL AL, between January 2016 and March 2023, were enrolled. The years 2017-2020 were considered in the context of the study to precede the pandemic, while 2021-2022 followed the pandemic period of SARS-CoV-2 infection.

Data were collected on the following SDO codes assigned to the patient at discharge: 0796 RSV; 4801 RSV pneumonia; 46611 acute bronchiolitis due to RSV; 46619 acute bronchiolitis due to other infectious agents. For each enrolled patient, demographic variables (year of birth, sex) and clinical variables (date of admission and discharge, need for oxygen therapy and possible duration, presence of respiratory distress on admission, presence of overinfection) were collected. Patients received treatment and care according to usual clinical practice and medical literature.

Infection with RSV or other pathogens was documented using the Molecular Film Array test (nested multiplex Polymerase Chain Reaction, PCR). The pathogens tested were *Adenovirus*, *Coronavirus* HKU1, *Coronavirus* NL63, *Coronavirus* 229E, *Coronavirus* OC43, Human *Metapneumovirus*, Human *Rhinovirus*/*Enterovirus*, Influenza A (including subtypes H1, H1-2009 and H3), Influenza B, Middle East Respiratory Syndrome *Coronavirus* (MERS-CoV), Parainfluenza 1, Parainfluenza 2, Parainfluenza 3, Parainfluenza 4, Respiratory Syncytial Virus, *Bordetella parapertussis*, *Bordetella pertussis*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*).

Statistical analysis

The data required for the study are those contained in the patients' medical records for the period identified. Data were tested by descriptive statistical analysis performed on the entire sample. For qualitative variables, absolute and relative frequencies are reported, and for numerical variables, mean and standard deviation or median and interquartile range, as appropriate. Continuous variables were analysed by calculating mean and standard deviation or median and interquartile range. The variables of interest were compared before and after the COVID-19 pandemic, and statistically significant differences were tested using the Student's t-test for continuous variables and the Mann-Whitney U two-sided test when the parameters did not have a Gaussian distribution. Statistical significance was set at a p-value <0.05 and analyses were performed using dedicated software: Microsoft Excel and Stata/BE 17.

Ethical approval

The study was approved by the Institutional Review Board of the Azienda Ospedaliera Nazionale SS Antonio e Biagio e Cesare Arrigo, Alessandria (protocol number Asl21.Ped.21.04 del CE 16/12/2021).

The necessary data were collected from the electronic records of the centre where the study was conducted. Consent for the processing of these data is routinely given by the parents of the minor subject at the time of hospitalization. Furthermore, only aggregate information is reported in this article. Therefore, it was not necessary to obtain specific consent for the present study. This work was conducted in accordance with the ethical standards of the Declaration of Helsinki of 1964 and its subsequent amendments, and with the guidelines of good clinical practice.

Results

Data were collected on 208 admissions for bronchiolitis or RSV respiratory infection, with a total of 200 subjects, that occurred in the pediatric unit studied between January 2016 and March 2023. The characteristics of the study population are summarised in Table 1.

The distribution of the admissions considered over the study period is shown in Figure 1.

The aim of this work is to assess the presence of differences in hospitalisations for bronchiolitis or RSV inversion in pediatric subjects before and after the COVID-19 pandemic. Table 2 describes the characteristics of the population and hospitalisations analysed before and after March 2020, which was assumed to be the start of the COVID-19 pandemic.

There were no statistically significant differences in age (p-value=0,225), sex (p-value=0,411), days of hospitalisation (p-value=0,061), presence of respiratory distress (p-value=0,767), need for oxygen therapy (p-value=0,631) or days of oxygen therapy (p-value=0,952) between the two periods. RSV diagnoses increased by approximately 70% after March 2020 compared to the previous period in a statistically significant manner (p-value<0,001). The occurrence of additional overinfections as a cause of hospitalisation was statistically significantly higher by about 10% after March 2020 compared to the previous period (p-value=0,009).

Table 1. Characteristics of the study population.

Variables	Median (IQR)	Min	Max
Age (months)	3,75 (6,11)	0,21	57,71
Length of hospitalisation (days)	4 (3)	0	12
Oxygen therapy duration (days)	3 (3)	1	14
Variables	**Frequency (%)**	**Missing**	**Cumulative frequency (%)**
Gender			
Male	122 (61)	0	61
Female	78 (39)		100
Date of hospitalisation			
Pre-March 2020	158 (75,96)	0	75,96
Post-March 2020	50 (24,04)		100
Respiratory distress			
Absent	28 (34,15)	126	34,15
Present	54 (65,85)		100
Oxygen therapy			
Absent	40 (47,62)	124	47,62
Present	44 (52,38)		100
Diagnosis			
RSV	72 (34,62)	0	34,62
Others	136 (65,38)		100
Overinfections			
Absent	26 (65)	168	65
Present	14 (35)		100

IQR, Interquartile Range; RSV, Respiratory Syncytial Virus.

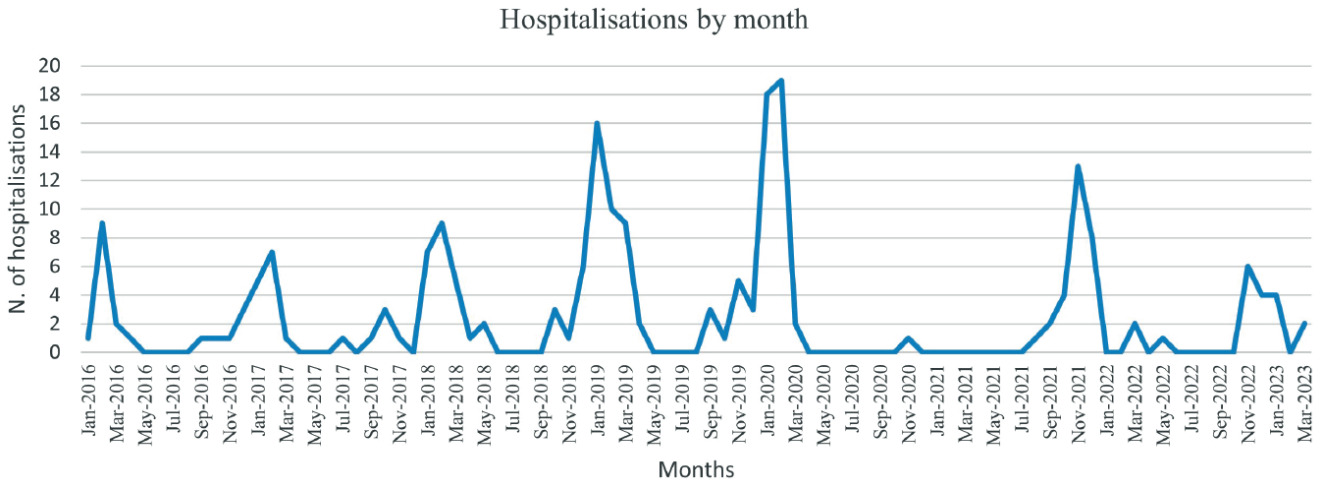

Figure 1. Distribution of the number of admissions per month from January 2016 to March 2023.

Table 2. Characteristics of the population and hospitalisations analysed before March 2020 (pre) and after March 2020 (post).

Variables	Median (IQR)		Min		Max	
	Pre	Post	Pre	Post	Pre	Post
Age (months)	3,64 (4,86)	4,09 (11,21)	0,25	0,21	51,57	57,71
Length of hospitalisation (days)	4 (3)	5 (4)	0	1	12	11
Oxygen therapy duration (days)	3 (2)	5 (4)	1	1	8	11
Variables	**Frequency (%)**					
	Pre		**Post**			
Gender						
Male	89 (59,33)		33 (66)			
Female	61 (40,67)		17 (34)			
Respiratory distress						
Absent	12 (32,43)		16 (35,55)			
Present	25 (67,57)		29 (64,45)			
Oxygen therapy						
Absent	17 (44,74)		23 (50)			
Present	21 (55,26)		23 (50)			
Diagnosis						
RSV	27 (17,09)		45 (90)			
Others	131 (82,91)		5 (10)			
Overinfections						
Absent	153 (96,83)		43 (86)			
Present	5 (3,17)		7 (14)			

IQR, Interquartile Range; RSV, Respiratory Syncytial Virus.

Discussion

RSV is the most common respiratory virus and a major cause of morbidity and mortality worldwide. Several papers in the literature have therefore investigated whether and how the COVID-19 pandemic has changed the epidemiology, symptomatology, and management of this infectious disease.[27-28] In our case history, we confirm what has emerged in the literature, *i.e.*, that the RSV epidemic season was "earlier" than in the pre-pandemic period, when the peak of bronchiolitis was expected between February and March.[8-9] In fact, as shown in Figure 1, in the period 20-21 the curve starts to rise as early as September and we see a peak in hospitalisations between October and December 2021, with the persistence of bronchiolitis even in late spring 20-21. In 2022-2023, there is also a constant number of cases from October to January, with a peak in March. Figure 1 also shows an early peak of bronchiolitis in January 2020, which expanded and worsened in February 2020, before the pandemic was declared. This finding is consistent with what has been described in the literature.[29] A peak

that does not seem to have an epidemiological explanation, except to speculate that an as yet unidentified SARS-COV2 co-infection may have played a key role.[29]

Analysing the pre and post-period separately, we found a higher number of Respiratory Syncytial Virus-positive swabs in the post-period. This would indicate a higher incidence of RSV infections after COVID-19, in line with findings in the literature.[29] Undoubtedly, the reopening of schools and other recreational and sporting activities, the reopening of borders, and the resumption of international travel, but also the reduced pressure of COVID-19 and the consequent reduction in the rigour of preventive hygiene measures, have contributed to increased exposure and circulation of respiratory viruses.[30] In addition, a key role is undoubtedly played by the immune system, which needs constant stimulation to produce rapid and effective responses, and which was severely limited by the precautions taken during the pandemic. The same reasons could also explain the statistically significant increase in overinfections in bronchiolitis admissions after March 2020 compared to the previous period.

This work has numerous limitations. Firstly, when the pandemic broke out, the ward where the study took place was closed as part of the extraordinary security measures put in place to limit the spread of the COVID-19 virus. This resulted in no admissions from March 2020 until early 2021. During this period, there is no information on cases of bronchiolitis in the study population, which reduces the information available for the period after March 2020 compared to the period before. As this was a single-centre study, the number of cases analysed was limited. In addition, the sample collected may be biased in relation to the general population, as not all possible enrolled cases come from the centre under study. This factor may be more significant in the period after March 2020, when the responsibilities for admitting and treating patients were redistributed among the various local hospitals following the reopening of the centre. The variables on respiratory distress, oxygen therapy use and days, and presence of overinfection had more than 50% missing data.

Conclusions

Consistent with findings in the literature, this study found that the incidence of RSV infection and overinfection in patients hospitalised for bronchiolitis has increased compared with the pre-pandemic period. Further multicentre studies with a more representative sample of the general population and larger sample sizes are needed to confirm these findings.

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Correspondence: Marianna Farotto, Research and Innovation Department, Azienda Sanitaria Locale (ASL), Alessandria, Italy.
E-mail: mfarotto@aslal.it

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Informed consent: written informed consent was obtained from legally authorized representatives for anonymized patient information to be published in this article.

Availability of data and materials: all data generated or analyzed during this study are included in this published article.

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