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The acute bronchiolitis rebound in children after COVID-19 restrictions: a retrospective, observational analysis

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Abstract. *Background and aim:* Bronchiolitis represents the main cause of illness and hospitalization in infants and young children. The aim of this study was to compare the Pediatric Emergency Department (PED) admissions for bronchiolitis during the post-COVID (Coronavirus disease) period to those of previous seasons and to analyze their etiology during COVID and post-COVID period. *Methods:* We compared demographics, clinical and microbiological data of children admitted to PED with bronchiolitis between September 2021 and March 2022 (post-COVID period) to the previous seasons (COVID and pre-COVID period). *Results:* During the post-COVID period the bronchiolitis season started earlier than usual, with a peak reached in November 2021; a gradual reduction was subsequently observed between December 2021 and January 2022. Our data showed a prevalence of High Priority code in children admitted to the PED with bronchiolitis during the post-COVID period (61.4%) compared the pre-COVID period (34.8%) (p=0.00). Also regarding the hospitalization of these patients, we found a major rate of hospitalization during this epidemic season (p=0.035). In addition, only 4 (1.5%) of the tested children resulted positive for SARS-CoV-2 and all of them were admitted to PED during the post-COVID period. The search for the other respiratory viruses showed during the current season a prevalence of respiratory syncytial virus (RSV) (60.2%), followed by Human Rhinovirus (30.1%). *Conclusions:* The post-COVID period was characterized by an early and short-term peak in acute bronchiolitis, with an increased rate of hospitalization. In addition, SARS-CoV-2 infection was rarely cause of bronchiolitis in children under 2 years old. (www.actabiomedica.it)

Key words: Bronchiolitis; COVID-19; Pediatric Emergency Department; Respiratory Syncytial Virus; SARS-CoV-2

Introduction

Bronchiolitis is a lower respiratory tract infection that mainly affects the small airways and represents the main cause of illness and hospitalization in infants and young children (1-2). It typically occurs in children under 2 years of age and it is characterized by upper and lower respiratory symptoms including rhinorrhea, wheezing, labored breathing, tachypnoea and hypoxia (2-3).

Bronchiolitis is caused by a viral infection and Respiratory Syncytial Virus (RSV) is the most common etiological agent; it mostly affects children aged under 2 years during seasonal autumn and winter epidemics (4-5). However, also other respiratory viruses can be involved, especially in older children, such as

Human Rhinovirus, Influenza, Human Metapneumovirus, Parainfluenza virus and Coronavirus (6). The different socio-sanitary measures adopted from March 2020 to avoid the spread of SARS-CoV-2 infection helped also to contain the transmission of the other respiratory viruses (7). Thus, face masks, hands hygiene, social distancing and stay-home orders protected children from both Coronavirus disease (COVID-19) and other viral infections (8-9).

Subsequently, some Authors in the spring of 2021 hypothesized that the lack of immune stimulation due to personal non-pharmaceutical interventions (NPIs) may cause an "immunity debt" in children, with negative consequences once COVID-19 control is achieved (10).

Since the start of the vaccination campaign against COVID-19, Italy and other countries have booted a process of restarting the different activities. The schools have been kept open, with the surveillance testing, and distance learning was less used. There has been no new national lockdown and the use of green passes to gain access to public places has spread for children aged over 12. These measures have led to a reduction in the constraints and to a greater exposure of children to respiratory viruses.

This concept has worried researchers worldwide, who feared that exposure to respiratory viruses in children who had not encountered common viruses for about two years could cause a major clinical impact on the number and severity of respiratory diseases.

The main aim of the study was to compare Pediatric Emergency Department (PED) admissions for bronchiolitis during the 2021-2022 epidemic season (post-COVID period) to those of previous seasons (COVID and pre-COVID period). The secondary objective was to evaluate cases of bronchiolitis caused by SARS-CoV-2 during the COVID and post-COVID period.

Material and methods

This is a retrospective, observational, cross-sectional study conducted at the PED of "Fondazione Policlinico A. Gemelli - IRCCS" in Rome, a university third level Italian hospital with annual attendance of about 15,000 patients. We selected records - stored in the electronic Emergency Department information system (Gipse®) - of patients aged from 0 to 2 years admitted to PED with diagnosis of "acute bronchiolitis", "wheezing", "respiratory distress" and "acute respiratory failure". Children older than 2 years and those with previous episodes of bronchiolitis were excluded. The collected data included: age, gender, hospital triage code, prematurity and/or other comorbidities (such as bronco-pulmonary dysplasia, asthma, atopy, genetic syndromes), pediatric clinical history, modality of transport to the PED, hospitalization (ward or Pediatric intensive Care Unit (PICU)) and etiology. Hospital triage codes were assigned to patients by the triage nurse based on the child's general condition, symptoms and vital signs. The 5-code system, used in our region, included the assignment of code 1 for "emergency", 2 for "urgency", 3 for "deferable urgency", 4 for "minor urgency" and 5 for "non-urgent" cases. For the statistical analysis we grouped patients with 1, 2 and 3 codes in the "high priority" group and those with 4 and 5 codes in the "low priority" group.

Therefore, we analyzed data of all children diagnosed with bronchiolitis admitted to our PED between September 2021 and March 2022 (post-COVID period), comparing them to those admitted during the same months in 2020-2021 (COVID period), in 2018-2019 and 2019-2020 (pre-COVID period). In addition, during COVID and post-COVID period nasopharyngeal swabs for the identification of SARS-CoV-2 were obtained from all children admitted in the PED. In some cases, a real-time reverse-transcriptase polymerase chain reaction for the detection of Rhinovirus, RSV, Influenza A and B, Parainfluenza virus, Human metapneumovirus and other Coronaviruses was performed. The study protocol was approved by the Institutional Review Board and Ethics Committee of our institution.

Statistical analysis

Categorical variables are reported as counts and percentages. Normality of distribution of continuous variables was tested by means of Shapiro Wilk test. Not normally distributed continuous variables are reported as median and interquartile ranges (IQR).

Statistical comparisons between groups were obtained by Chi-squared test or Fisher's exact test, as appropriate, for categorical variables and Mann–Whitney U test for not normally distributed continuous variables. We considered statistically significant a two□sided p-values less than 0.05. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS for Windows, version 25.0, SPSS Inc.,7 Chicago, IL, USA).

Results

Our study included a total of 937 children, aged between 0 and 2 years, affected by acute bronchiolitis, of which an average of 331 for year during the pre-COVID period, 20 during the COVID period and 254 in the post-COVID period. During the post-COVID period, the total number of bronchiolitis admitted to PED was lower than the average of the two years before the SARS-CoV-2 pandemic (pre-COVID period). However, it is interesting to note the different monthly distribution in the three periods considered in our study. In fact, during the post-COVID period we observed an initial increase in PED admissions for bronchiolitis in October 2021, with a peak reached in November 2021. The following months then saw a gradual bronchiolitis cases reduction as shown in Figure 1.

However, the median age of all children enrolled was 0.6 years (0.2-1.2) and 54.2% of them were female; no significant differences in terms of age was observed in the three periods analyzed (p=0.69, p=0.109).

All demographics and clinical characteristics of the study population, divided in the three groups, are detailed in Table 1.

First, we compared the characteristics of children admitted to PED with bronchiolitis during the post-COVID period and those during the COVID period. No statistically significant differences emerged as for age, gender, prematurity, triage code, hospitalization and admission unit (ward or PICU). Instead, a significant difference was found for the patients' comorbidity: during the COVID period 10% of children admitted to PED with bronchiolitis presented a comorbidity compared to 4.7% of patients admitted during the post-COVID period ($\chi 2(1, N=149)=4.2$, p=0.04).

Subsequently, we analyzed the differences between children with bronchiolitis admitted to PED during the post-COVID period and the pre-COVID one. In this case we observed a statistically significant difference as for triage codes in the two periods, with a prevalence of High Priority code in children

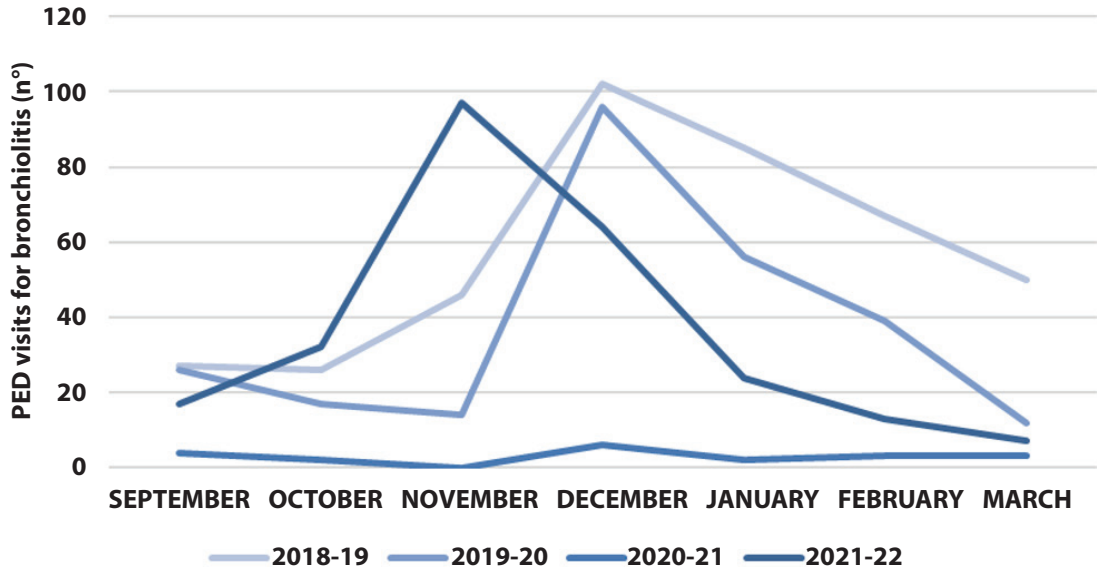

Figure 1. Monthly distribution of PED visits for bronchiolitis in children, autumn/winter seasons 2018-2022.

Table 1. Demographic and clinical features of the study population (N=937).

		Pre-COVID period (n=663)	COVID period (n=20)	Post COVID period (n=254)	p-value*	p-value**
Age (years), median (IQR)		0.6 [0.2-1.2]	0.5 [0.2-1.3]	0.5 [0.2-1.1]	0.686	0.109
Gender (M)		287 (43.3%)	7 (35.0%)	135 (53.1%)	0.118	**0.007**
Prematurity		6 (0.9%)	1 (5.0%)	9 (3.5%)	0.320	0.346
Comorbidity		11 (1.65%)	2 (10.0%)	12 (4.72%)	**0.040**	0.687
Urgency level (Triage code)	High Priority Code	231 (34.8%)	11 (55.0%)	156 (61.4%)	0.571	**0.000**
	Low Priority Code	432 (65.2%)	9 (45.0%)	98 (38.6%)		
Type of access	Autonomous	580 (87.5%)	20 (100.0%)	231 (90.9%)	0.372	0.251
	Ambulance	77 (11.6%)	0 (0.0%)	20 (7.9%)		
	Helicopter	6 (0.9%)	0 (0.0%)	3 (1.2%)		
Destination	Hospitalization	172 (25.9%)	5 (25.0%)	83 (32.7%)	0.465	**0.035**
	Home	491 (74.1%)	15 (75.0%)	171 (67.3%)		
Hospitalization	Ward	119 (69.2%)	5 (100.0%)	65 (78.3%)	1.000	0.849
	PICU	53 (30.8%)	0 (0.0%)	18 (21.7%)		
SARS-CoV-2 positive		N/A	0 (0%)	4 (1.6%)	N/A	1.000

* Post-COVID vs COVID period
** Post-COVID vs pre-COVID period

admitted to PED during the post-COVID period (61.4%) compared the pre-COVID period (34.8%) ($\chi2(1, N=917)=53.17$, p=0.00). Also regarding the hospitalization, we found a major rate of hospitalization in children admitted to PED with bronchiolitis during the post-COVID period (32.9%) compared to the pre-COVID period (25.9%) ($\chi2(1, N=915)=4.44$, p=0.035). On the other hand, no statistically significant difference emerged as for the admission unit (Table 1).

For the secondary objective of the study, we analyzed nasopharyngeal swabs of children affected by bronchiolitis and admitted to the PED during the COVID and post-COVID period.

Only 4 (1.5%) of the tested children resulted positive for SARS-CoV-2 and all of them were admitted to PED during the post-COVID period. The search for the other respiratory viruses was available for only 93 of them, which correspond to 34.2% of this group. Among these children, viruses detected were: 56 (60.2%) RSV, 28 (30.1%) Human Rhinovirus, 6 (6.4%) Bocavirus, 4 (4.3%) Parainfluenza virus, 4 (4.3%) Metapneumovirus and 4 (4.3%) Adenovirus. However, ten (10.7%) children presented viral coinfection. In addition, comparing the RSV etiology in children with bronchiolitis admitted to PED in the two periods, we found an increase in RSV positivity at the nasopharyngeal swab during the post-COVID period compared to the COVID period (56 vs 0, p=0.00).

Discussion

Our study analyzed the admissions to PED for acute bronchiolitis in a hospital in the center of Italy during the last epidemic seasons. During the post-COVID period, the number of accesses for bronchiolitis in our hospital was almost lower than in the pre-COVID period. However, it is interesting to highlight that during the post-COVID period the bronchiolitis season started earlier than usual, with an increased rate of hospitalization.

In Europe during the COVID-19 lockdown, several studies highlighted a marked reduction or near

absence of cases of infant bronchiolitis (8, 11-12). School closures, smart working, social distancing, mask wearing, hands hygiene and other NPIs have inhibited inter-human transmission of respiratory viruses, as well as preventing the COVID-19 (13-14).

As early as December 2020, Baker et al, in an epidemiological study conducted in the United States using laboratory surveillance data and predictive mathematical models, expected an increase in the severity of RSV and Influenza outbreaks after the use of NPIs in the winter 2021-22 (15). In May 2021, Cohen et al hypothesized that long-term reduced exposure of children to different microbial agents could lead to a lack of immune system stimulation, inducing an "immunity debt" with negative consequences when NPIs are abandoned at the end of the COVID pandemic (10).

Also Delestrain et al., in a recent study conducted in different French metropolitan regions during the 2020-21 season, observed a 12-week delayed RSV outbreak compared to previous seasons, raising concerns about the spread of RSV in the context of a healthcare system already suffering because of the pandemic (16).

Our data at the moment would not seem to confirm these assumptions. However, our retrospective study revealed during the post-COVID period an earlier peak of acute bronchiolitis, in November 2021, with a gradual reduction a December 2021 and January 2022. This monthly distribution is different from bronchiolitis previous seasons. In fact, previous epidemiological studies showed that RSV, which is the main etiological agent of bronchiolitis, is active from November to the end of April, with a peak in February (17).

Moreover, a particular finding was the early decline of new cases of bronchiolitis between December 2021 and January 2022. This could be due to both the early peak of bronchiolitis in November 2021 but also the maximum prevalence during this period of SARS-CoV-2 infection in the pediatric population. In fact, the Omicron variant that spread in Italy from the end of November 2021, and became the prevalent variant a few months later, caused many more pediatric infections compared to the previous variants. Some yet unpublished data from a study conducted in our hospital, showed during the current season a peak of SARS-CoV-2 positive cases in children in December 2021 and January 2022

Consequently, between December 2021 and January 2022, the high circulation of SARS-CoV-2 among children, resulting in an increase home isolation, may have halted the spread of RSV and other respiratory viruses among younger children.

However, in addition to controlling the COVID-19 pandemic during this year, it should be also very important to monitor the transmission of other respiratory viruses such as RSV. Indeed, RSV and SARS-CoV2 have the same transmission route: they spread through droplets and contact with contaminated surfaces (18). This occurs mainly in public places, mostly frequented by children, such as schools (18). Previous studies reported that the basic reproduction rate, *R0*, is estimated at 3.0 for both RSV and SARS-CoV-2 (19-20).

Besides, our study showed an increase in the number of bronchiolitis admitted to the PED with a higher acuity code during the post-COVID period compared to the pre-COVID one. Also, the number of hospitalized cases increased markedly during this epidemic season compared to the pre-COVID period. This increase in the severity of the illness, could be due to a greater virulence of the RSV circulating during this epidemic season but above all to the previous assumed "immunity debt" of children born during the COVID-19 pandemic (10). Instead, no difference emerged as for triage code comparing cases of bronchiolitis admitted to PED during the post-COVID period with those from the previous COVID period. The explanation could be that at the beginning of COVID pandemic nurses and physicians did not know the evolution of COVID-19 disease in children, consequently nurses assigned them a higher priority code to the triage, even if not necessary, and pediatricians kept under observation children for a longer time.

Finally, analyzing the etiology of bronchiolitis in children admitted to PED during the COVID and post-COVID period we observed a prevalence of RSV, in line with previous reports (6, 21). However, in our study population only 4 (1.5%) children with bronchiolitis were tested positive for SARS-CoV-2 during the post-COVID period. This finding agrees with previous studies, which showed that SARS-CoV-2-realated

bronchiolitis was rare and above all was characterized by a mild clinical course (8, 22).

This study present different limitations. First, the retrospective design of the study did not allow us to collect and compare more clinical and demographical data from the population analyzed. Secondly, we could not analyze the microbiological data of children admitted to the PED during the pre-COVID period, because previously nasopharyngeal swabs for viruses' search were not performed in all children with bronchiolitis. After the COVID-19 emergency in our hospital a SARS-CoV-2 nasopharyngeal swab was required for all children admitted to the PED and this led pediatricians to also require the search for other respiratory viruses on the same swab.

In conclusion, our study showed that during the post-COVID period the bronchiolitis season started earlier than usual, with an increased rate of hospitalization. In addition, SARS-CoV-2 infection was rarely cause of acute bronchiolitis in children under 2 years old. Future epidemiological surveillance studies are needed to assess the monthly trend of RSV and susceptibility of the pediatric population to this virus.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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