

Clinical characteristics of hospitalized children with bronchiolitis before and after the COVID-19 pandemic: a single-centre study

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ABSTRACT

Aim Acute respiratory infections caused by viral pathogens are the most common reason for hospitalization of children. Annually, 150 million infants worldwide are diagnosed with bronchiolitis, and 2-3% of them are hospitalized. This study aimed to compare bronchiolitis severity before and after the COVID-19 pandemic.

Methods This retrospective study was conducted at the Department of Pulmonology, Paediatric Clinic, Clinical Centre University of Tuzla, covering the period from 1 November 2018 to 30 April 2019 (pre-COVID period) and 1 November 2023 to 30 April 2024 (post-COVID period). A total of 129 children under the age of 2 years were involved.

Results No significant differences in the age, body mass, comorbidities, duration of hospitalization, use of oxygen therapy, and mechanical ventilation were found. There was a significant reduction in the use of antibiotics in the post-COVID group ($p=0.0173$), and a significant increase in the use of aminophylline and inhalation therapy drugs in the post-COVID group. There was a significantly higher number of isolated respiratory syncytial virus (RSV) cases in the post-COVID group, 32 (42.7%). Prevalence of fully vaccinated children was significantly higher in the pre-COVID period compared to the post-COVID period, 34 (74.4%) and 29 (45.3%), respectively.

Conclusion This study reveals a significant increase in the severity of bronchiolitis and an increase in RSV cases after the COVID-19 pandemic.

Keywords: anti-bacterial agents, coinfection, oxygen inhalation therapy, respiratory syncytial virus infections, vaccination

INTRODUCTION

Acute respiratory infections caused by viral pathogens are the most common reason for the hospitalization of children. Clinically, they are presented as croup, bronchiolitis, pneumonia, and exacerbation of asthma, and sometimes in the most severe form - acute respiratory distress syndrome (1). Bronchiolitis is an acute inflammatory disease of the bronchioles, characterized by pronounced mucosal edema, peribronchial lymphocytic infiltration, necrosis, intraluminal desquamation of ciliary epithelial cells, and increased mucus production (2). All these factors pathophysiologically lead to narrowing or obstruction of the small airways (1,2). Signs and symptoms usually begin with rhinitis and cough, which may progress to tachypnoea, wheezing, rales, use of accessory respiratory muscles, and flaring of the

nostrils (3). In some cases, respiratory distress syndrome may develop. In infants, particularly those born prematurely, episodes of apnoea may be the first sign of the disease (4). Most, but not all, children are febrile (5). Risk factors for severe or complicated bronchiolitis include: prematurity (gestational age under 36 weeks), low birth weight, age under 12 weeks, chronic lung disease (bronchopulmonary dysplasia), anatomical anomalies of the airways, hemodynamic congenital heart defects, immunodeficiencies, and neurological disorders (6).

There is evidence that bronchiolitis leads to bronchitis and bronchial asthma later in life (7). Annually, 150 million infants worldwide are diagnosed with bronchiolitis, and 2-3% of them are hospitalized. It is usually caused by a virus, whether due to a primary infection or reinfection with a viral pathogen (8). Although the proportion of infections caused by specific viruses varies by season, respiratory syncytial virus (RSV) remains the leading cause, accounting for up to 80% of cases (9). It has a seasonal character, with the highest incidence occurring between November and April (9,10). RSV infection does not provide lasting immunity, and reinfections are common (10). Less common causative agents include the influenza virus, parainfluenza virus, adenovirus, coronavirus, and human bocavirus (11).

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Molecular diagnostics can confirm viral etiology in more than 95% of cases (11,12). Two or more viruses have been detected in approximately one-third of hospitalized children (13). In rare cases, lower respiratory tract infections and wheezing episodes in infants are caused by the bacteria *Mycoplasma pneumoniae* and *Bordetella pertussis* (12,13). Bronchiolitis caused by non-RSV viral infections has a shorter clinical course (14,15). Respiratory syncytial virus (RSV) and the influenza virus are associated with the highest mortality rates in children (16).

The world has lived with the COVID-19 pandemic for more than three years. Since the COVID-19 pandemic, the SARS-CoV-2 coronavirus has been recognized as another significant cause of mortality in children (17). As SARS-CoV-2 transitions from the pandemic phase to the endemic/epidemic phase, there is potential for the virus to adopt a seasonal pattern, resulting in concurrent circulation with RSV and influenza during the winter months (18). The stringency of preventive measures implemented since the beginning of the pandemic has changed over time. Preventive measures were relaxed in 2022, leading to an increase in the number of cases of RSV, influenza, and COVID-19 during the seasonal period, which poses a major challenge for paediatricians (19).

Prevention of RSV infection in pregnant women and infants includes several strategies: passive immunization, active vaccination, as well as general preventive measures. The World Health Organization (WHO) and other health authorities recommend that pregnant women receive a single dose of the RSV vaccine, specifically Pfizer's Abrysvo, between 28 and 36 weeks of gestation. Passive immunization with Nirsevimab (Beyfortus) for infants is conducted with a single dose just before or at the beginning of RSV season (20).

As the pandemic has only recently subsided, current studies are just beginning to assess its long-term consequences on paediatric respiratory health, the burden of disease, and the effectiveness of preventive interventions. Despite the global interest in post-pandemic trends of bronchiolitis, data from Southeastern Europe, particularly Bosnia and Herzegovina, remain scarce. To the best of our knowledge, no studies from the region have directly compared clinical and etiological characteristics of bronchiolitis before and after the COVID-19 pandemic.

The aim of this study was to examine bronchiolitis severity before and after the COVID-19 pandemic.

PATIENTS AND METHODS

Patients and study design

This retrospective study involved 129 patients of both genders of the age <2 years with bronchiolitis hospitalized at the Pulmonology and Cardiology Department, Clinic for Paediatric Diseases at the University Clinical Centre (UCC) Tuzla (Bosnia and Herzegovina).

Clinical and laboratory data were collected from the Information Database System (BIS) and covered the analysis of stored patient data diagnosed, treated, and monitored between 1 November 2018 and 30 April 2019 (pre-COVID group), as well as from 1 November 2023 to 30 April 2024 (post-COVID group). The inclusion criteria were: all patients aged <2 years diagnosed with bronchiolitis, patients who underwent a triple test for RSV, Influenza A, and Influenza B. The exclusion criteria were: the patients who, upon discharge, did not have a confirmed diagnosis of bronchiolitis, patients who did not undergo

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the triple test for RSV, Influenza A, and Influenza B, patients >2 years, patients with incomplete documentation of the monitored parameters. In the pre-COVID period, patients were not tested for SARS-CoV-2.

The study was conducted in accordance with the basic principles of the Declaration of Helsinki (latest revision, 2008) on the rights of patients involved in biomedical research. During the implementation of this study, the identity and all personal data of patients were permanently protected in accordance with data protection regulations. The study was approved by the Ethics Committee of UCC Tuzla reference no: 02-09/2-70-3/25.

Methods

The diagnosis of bronchiolitis was established based on the criteria of the American Academy of Pediatrics (AAP), 2014 (21). Risk factors such as premature birth, bronchopulmonary dysplasia, congenital heart disease, and immunodeficiency, which may influence the disease progression, were obtained through anamnesis (parents).

The following parameters were monitored and analysed: age, body weight, birth weight, clinical symptoms of bronchiolitis (cough, difficulty breathing, fever, nasal discharge), length of hospital stay, antibiotic, systemic corticosteroids, aminophylline, and oxygen therapy, C-reactive protein (CRP) (reference value <0.5 mg/L), complete blood count (CBC), PCR testing for RSV, PCR testing for influenza A and influenza B, IgM and IgG serology for *Bordetella pertussis*. The CBC included: white blood cells (WBC) (reference value 6.60-16.00x10⁹/L), red blood cell (RBC) (reference value 4.00-5.00x10⁹/L), thrombocytes (PLT) (reference value 150-450x10⁹/L), neutrophils (Neu) (reference value 30-72%), lymphocytes (Lym) (reference value 30-72%), monocytes (Mono) (reference value 15-55%), eosinophils (Eos) (reference value 0-6%).

Nasopharyngeal swabs were collected from each patient for molecular detection of respiratory viruses. The presence of RSV, Influenza A and B, and SARS-CoV-2 was confirmed using real-time reverse transcription polymerase chain reaction (RT-PCR) on the Xpert Xpress CoV-2/Flu/RSV plus test (Cepheid, USA), performed on the GeneXpert automated system (22).

Serological testing for *Bordetella pertussis* was conducted on serum obtained from venous blood samples, using the automated ELISA system Alegria (Orgentec, Mainz, Germany), which detects Anti-*B pertussis* toxin IgA and Toxin G antibodies (23).

Statistical analysis

All values are expressed as mean±SD and in percentages. Statistical differences were determined using an unpaired T-test for comparisons between two groups. Proportional values were tested using the inverse proportion test. A p<0.05 was considered statistically significant.

RESULTS

The total number of 129 patients were hospitalized during the periods from 1 November 2018 to 30 April 2019 (pre-COVID group), and from 1 November 2023 to 30 April 2024 (post-COVID group). The mean age of patients was 7.6 months in the pre-COVID period and 6.5 months in the post-COVID period. The average length of hospital stay was 7.7 days in the pre-COVID period and 7.6 days in the post-COVID period. No significant difference between the groups in terms

of age, body weight, comorbidities, length of hospitalization, use of oxygen therapy, and mechanical ventilation was found ($p=0.6266$). The prevalence of recovered patients did not differ significantly between the observed groups ($p=0.3839$). However, there was a significant reduction in the antibiotic use in the post-COVID group comparing to the pre-COVID group (94.9% vs. 77.3%; $p=0.0173$). A significant increase in the use of aminophylline (15.4% vs. 65.3%; $p<0.0001$) and inhalation therapy drugs (1.7 vs. 2.2; $p=0.001$) in the post-COVID group was found comparing to the pre-COVID group. The number of symptoms was significantly lower in the post-COVID group (2.54 vs. 2.1; $p=0.0069$) (Table 1).

Table 1. Baseline characteristics of 129 patients with bronchiolitis

Variables	Pre COVID	Post COVID	P
	Mean±SD		
Age (mean±SD) (months)	7.7±5.1	6.5±6.5	0.3396
Gender (M/F)	27/12	48/27	0.5782
Body weight (g)	7850±2527	6985±2831	0.1123
Hospitalization (mean±SD) (days)	7.2±5.0	7.7±4.1	0.5382
Number of symptoms (mean±SD)	2.54±0.9	2.1±0.7	0.0069
	No (%) of patients		
Number of comorbidities			0.1565
0	10 (25.6)	34 (45.3)	
1	21 (53.8)	28 (37.3)	
2	5 (12.8)	11 (14.7)	
3	2 (5.1)	2 (2.7)	
4	1 (2.6)	0 (0)	
Number of antibiotics			
0	2 (5.1)	17 (22.7)	
1	33 (84.6)	43 (57.3)	
2	3 (7.7)	11 (14.7)	
3	1 (2.6)	4 (5.3)	
Antibiotic therapy	37 (94.9)	58 (77.3)	0.0173
Aminophylline	6 (15.4)	49 (65.3)	<0.0001
Oxygen therapy	12 (30.8)	30 (40.0)	0.3256
Mechanical ventilation	1 (2.6)	1 (1.3)	0.6266
Outcome - recovered patients	20 (51.3)	32 (42.7)	0.001

A significantly higher number of isolated RSV cases (2.6% vs. 42.7%; $p<0.0001$) as well as isolated *Bordetella pertussis* cases in the post-COVID group was found comparing to the pre-COVID group (0% vs. 17.3%; $p=0.006$) (Table 2).

Table 2. Distribution of bronchiolitis pathogens in hospitalized children

Pathogen	No (%) of patients		p
	Pre COVID	Post COVID	
RSV	1 (2.6)	32 (42.7)	<0.0001
Influenza A	2 (5.1)	1 (1.3)	0.2285
Influenza B	1 (2.6)	0	0.1626
COVID	n/a	10 (13.3)	-
<i>Bordetella pertussis</i>	0	13 (17.3)	0.006

RSV, respiratory syncytial virus, n/a, not available

There was no statistically significant difference in the prevalence of Influenza A and B cases. COVID-positive cases were not considered because testing was not conducted in the pre-COVID period. Analysis of laboratory blood parameters revealed significant differences in the frequency of Ne, Lym, and Eos (50.5% vs. 41.1%; $p=0.0257$; 34% vs. 43.7%; $p=0.0239$; and 0.6% vs. 3.1%; $p=0.0039$) (Table 3).

Table 3. Characteristics of X-ray and laboratory parameters

Parameter (reference value)	Pre-COVID	Post-COVID	P
	Mean±SD		
CRP <0.5 mg/L)	7±9.2	13.4± 29.3	0.1870
RBC (4.00-5.00x10 ⁹ /L)	4.2±0.6	4.8 ±4.6	0.4256
Hb (109-138 g/L)	111.5±14.3	115.6±18.4	0.2235
PLT (150-450x10 ⁹ /L)	462.1±173.4	464±179.9	0.9568
WBC (6.60-16.00x10 ⁹ /L)	13.6±6.3	13.3±9.8	0.8885
Neu (30-72%)	50.7±22.3	41.1±20.7	0.0257
Lym (15-55%)	34±20.1	43.7±21.8	0.0239
Eo (0-6%)	0.6±1.2	3.1±5.1	0.0039
	No (%) of patients with pneumonia		
X-ray	21 (54.0)	54 (72.0)	0.0556

CRP, C-reactive protein; RBC, red blood cells; Hb, haemoglobin; PLT, platelets; WBC, white blood cells; Neu, neutrophils; Lym, lymphocytes; Eo, eosinophils

The prevalence of fully vaccinated children was significantly higher in the pre-COVID period compared to the post-COVID period (74.4% vs. 45.3%; $p=0.0032$) (Table 4).

Table 4. Comparison of risk factors in children with bronchiolitis

Risk factor	Pre COVID	Post COVID	p
Natural feeding	17 (43.6)	33 (44.0)	0.9676
Regular vaccination	29 (74.4)	34 (45.3)	0.0032
Antirachitic prophylaxis	38 (97.4)	69 (92.0)	0.2571
Immunodeficiency	0	2 (2.7)	0.3026

DISCUSSION

Our study analysed patients hospitalized in the Pulmonology and Cardiology Department at the Clinic for Paediatric Diseases who were diagnosed with acute bronchiolitis before and after the most recent epidemic season (i.e., the post-COVID resurgence of RSV and other respiratory viruses). Interestingly, following COVID-19, the bronchiolitis season started earlier than usual (2023/2024) with an increase of hospitalization prevalence (24).

This study reveals a significant increase in bronchiolitis severity and a rise in RSV cases after the COVID-19 pandemic. Notably, during the post-COVID phase, there was a rise in the number of hospitalizations and an extended length of hospital stay, indicating an increase of disease severity among hospitalized patients (25). Our study confirmed that the clinical presentation of bronchiolitis in the post-COVID period was more severe compared to the pre-COVID period, which was reflected in longer hospital stay and a greater need for antibiotic, aminophylline, and oxygen therapy.

Although patients in the post-COVID period developed a more severe clinical presentation, the need for invasive mechani-

cal ventilation (IMV) was significantly lower compared to the pre-COVID period. However, the number of patients requiring non-invasive ventilation (NIV) increased. Some studies align with our findings (26) reporting an increased need for IMV (26). For example, a Spanish study described a severe bronchiolitis season in 2021, compared to the previous ten years, in terms of length of hospital stay and oxygen therapy requirements (27). The number of patients with comorbidities significantly increased compared to the pre-COVID pandemic period, which was also reported (28). In addition, we observed a significant increase in RSV prevalence during the post-COVID period, which was confirmed by other studies (29). Similarly, an Italian research team, comparing hospitalized patients with acute bronchiolitis in the year before COVID-19 and the post-COVID period (2021-2022), found that RSV-positive patients required longer oxygen therapy and had prolonged hospital stay. Our research indicates that, even several years later, the peak incidence of bronchiolitis remains high, despite these children being born after the pandemic. The higher incidence may be associated with new viral genetic patterns (30). During the SARS-CoV-2 pandemic, a genetic lineage shift in RSV associated with an outbreak of severe RSV disease in Minnesota was described (31). Another plausible explanation for the observed changes during the COVID-19 pandemic is the significant drop in air pollution associated with lockdown measures. This suggests that air pollution and climate factors may influence the transmission of RSV, as described in several studies (32). In one group of patients, no causative agent was isolated, which may be due to the timeframe in which the diagnostic tests were performed. PCR and rapid antigen tests should be conducted within the first three to five days after the symptom onset, as viral load in the nasal mucosa is highest during this period (33). It is essential to predict the real temporal trend of bronchiolitis not to leave high-risk children uncovered and to guide hospitals to maintain a high level of readiness (34). Considering this, the actual number of RSV-positive bronchi-

olitis cases may be much higher than reported. Following RSV, SARS-CoV-2 is also an important cause of bronchiolitis, especially during the winter respiratory infection season, as confirmed by numerous global studies (35).

In conclusion, this study highlights a significant surge in the prevalence of bronchiolitis after the COVID-19 pandemic. This increase is coupled with a prolonged duration of hospitalization and a heightened requirement for oxygen therapy compared to the pre-COVID-19 period. Importantly, there is a significant rise in the prevalence of cases attributed to RSV during the post-COVID-19 period. These findings underscore the lingering impact of the pandemic on respiratory health, necessitating ongoing attention and further investigation into the evolving dynamics of bronchiolitis in the post-COVID era.

The pandemic has caused an increase in the severity of bronchiolitis, changes in the number and types of circulating viruses, and shifts in therapeutic approach. This will be useful for paediatricians, public health services, and the scientific community, as it will enable better planning of preventive measures and treatment in the future, as well as better understanding of the pandemic's impact on the health of young children.

AUTHOR CONTRIBUTION

AP and AS conceived and designed the research. DŽK and NT conducted experiments. AH contributed to new reagents or analytical tools. AS and AL wrote the manuscript. AP analysed data, reviewed the manuscript and edited the submission. AS reviewed and funded publishing. All authors read and approved the manuscript.

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TRANSPARENCY DECLARATION

Conflicts of interest: None to declare.

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