

## COVID-19 restrictions and hygiene measures reduce the rates of respiratory infections and wheezing among preterm infants

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**Abstract.** *Background and aim:* During the 2020 and 2021 Italian COVID-19 pandemic social restrictions and strict hygiene measures were recommended to limit the spread of SARS-CoV-2. We aimed to assess whether rates of respiratory infections and wheezing in preterm infants have changed during the pandemic. *Methods:* Single center, retrospective study. Preterm infants in the first 6 months of life discharged home prior to (Period 1, January 2017 - December 2019) or during the pandemic (Period 2, January 2020 - March 2021) were compared. Rates of respiratory infection and wheezing in preterm infants with or without bronchopulmonary dysplasia (BPD) were assessed. *Results:* During period 2 premature infants had lower rates of respiratory infections (36 out of 55 in Period 1 vs 11 out of 28 in Period 2,  $P=0.023$ ) and wheezing (20 out of 55 in Period 1 vs 1 out of 28 in Period 2,  $P=0.001$ ). This difference remained significant when infants with BPD (all grades) were analyzed separately (respiratory infections 26 out of 40 in Period 1 vs 7 out of 24 in Period 2,  $P=0.005$ ; wheezing 16 out of 40 in Period 1 vs 1 out of 24 in Period 2,  $P=0.001$ ). In contrast, respiratory infections and wheezing in preterm infants without BPD did not change after pandemic. *Conclusions:* Episodes of respiratory infections and wheezing among preterm infants were reduced during pandemic. We highlight the importance of proper family education for preventing respiratory tract infections in preterm infants with BPD, beyond the extraordinary conditions of the COVID-19 pandemic. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** preterm birth, COVID-19, bronchopulmonary dysplasia, respiratory infections, wheezing

### Introduction

Coronavirus disease (COVID-19), which is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to an unprecedented global pandemic that affects individuals across all age groups. The World Health Organization (WHO) declared the outbreak a Public Health

Emergency of International Concern on January 30th 2020 and declared it a pandemic on March 11th. In February 2020 Italy was the first European country affected by SARS-CoV-2 and the Italian government imposed a national lockdown. The restriction of social relations and the implementation of hygiene measures were not specific to SARS-CoV-2 and were apparently effective in preventing the transmission of

additional respiratory viruses (1) and consequently the rates of childhood respiratory infections and hospitalization (2).

Bronchopulmonary dysplasia (BPD) is the major cause of chronic pulmonary disease of infancy. Both fetal and neonatal life are critical for proper anatomical and functional development of the respiratory system. Preterm infants complete their growth outside the womb in a non-physiological environment, therefore they have increased risks of developing BPD and respiratory long term sequelae (3). During their first 2 years of life, infants suffering from BPD are more likely to present with recurrent wheezing and respiratory infections. Infants with BPD frequently receive antibiotics, bronchodilators or corticosteroids (4, 5) and are often readmitted to hospital after respiratory infections, particularly during their first 6 months of life (6, 7). We aimed to assess the impact of COVID-19 social restrictions and hygiene measures on the rates of respiratory morbidity and hospital readmission of preterm neonates in the first six months of life.

## Patients and methods

This is a single-center, retrospective cohort study carried out at the Policlinico University Hospital of Modena (Italy). Very low birth weight neonates (VLBW, birth weight under 1500 g) and/or preterm infants under 30 weeks' gestation were included in the study.

Infants discharged from NICU from January 2017 to December 2019 (Period 1, prior to pandemic) and from January 2020 to March 2021 (Period 2, during pandemic) were compared. The first lockdown due to the SARS-CoV-2 pandemic, started in Italy in March 2020 and was followed by periods where more or less stringent restrictions were applied. Infants discharged home in the first two months of 2020 were included in Period 2 because they actually experienced the consequences of lockdown health policies during their first 6 months of life.

Infants were evaluated at the outpatient clinic for respiratory diseases at 6-month corrected age. Infants with major malformations and/or severe

disabilities were excluded from the study. The respiratory follow-up program included clinical evaluations and collection of medical history (family history, environmental risk factors, present and past respiratory morbidities) at 6, 12, 24, 36, 48 months (corrected age), and subsequent evaluations at school age. Infants were diagnosed with mild, moderate or severe BPD according to NICHD 2001 definition (8). According to such a definition, the severity of BPD is based on the use of O<sub>2</sub> and mode of respiratory support at 36 weeks post-menstrual age (mild, breathing room air; moderate, need for < 30% O<sub>2</sub>; severe, need for ≥ 30% oxygen and/or positive pressure such as positive pressure ventilation or nasal continuous positive airway pressure). Because of the relatively few patients in study, comparisons were made by grouping all grades of BPD. Episodes of suspected or confirmed respiratory infection (defined as the presence of clinical signs or symptoms of upper or lower respiratory tract inflammation, with or without microbiological testing confirmation) or wheezing (defined by the presence of signs or symptoms of lower airway obstruction) were diagnosed and recorded by the general pediatrician. Data were collected from inpatient and outpatient medical records.

To maintain patient confidentiality, spreadsheets submitted to the principal investigator were fully anonymous and did not include any identifiable data of patients or caregivers. Therefore, according to the policy of our ethics committee review board patient consent was exempted. The local ethics committee Comitato Etico Area Vasta Emilia Nord approved the project on the 10<sup>th</sup> of February 2021 (Prot. N° 11/2021).

Statistical analyses: The respiratory morbidity of the entire population was analyzed, and rates of respiratory infections and wheezing between the two groups were compared. In descriptive analysis, continuous variables were reported as medians and ranges; categorical variables were reported as numbers and percentages. Categorical type data were analyzed with the chi-square test or Fisher's exact test, and continuous type data with parametric (t test) or nonparametric (Mann-Whitney U test). Differences with  $P < 0.05$  were considered significant. The STATA vers 13 for MAC program was used for data analysis.

## Results

We enrolled 83 infants discharged home during study periods (Period 1, n=55; Period 2, n=28). Infants did not differ for gestational age, birth weight, gender, diagnosis of any grade BPD, days of mechanical ventilation or oxygen supplementation, prenatal and postnatal steroids, maternal chorioamnionitis, presence of siblings (Table 1).

Among 64 infants diagnosed with BPD (data not shown), 39 (60.9%) had mild, 16 (25%) had moderate and 9 (14.1%) had severe BPD.

When assessed at the 6-month follow-up visit, infants in Period 2 had significantly lower rates of episodes of respiratory infection and wheezing (Table 2).

Furthermore, in Period 2 infants with BPD (data not shown) had significantly lower rates of respiratory

infection and wheezing when assessed at age 6 months (respiratory infections 26 out of 40 in Period 1 vs 7 out of 24 in Period 2,  $P=0.005$ ; wheezing episodes 16 out of 40 in Period 1 vs 1 out of 24 in Period 2,  $P=0.001$ ). In contrast, no significant differences were found in the preterm infants without BPD (rates of respiratory infections 10 out of 15 in Period 1 vs 4 out of 4 in Period 2,  $P=0.179$ ; rates of wheezing episodes 4 out of 15 in Period 1 vs 0 out of 4 in Period 2,  $P=0.245$ ). In Period 2, rates of hospital readmission were lower but did not reach statistical significance.

## Conclusions

Preterm infants often have high respiratory morbidity after discharge from the NICU. In one recent

**Table 1.** Demographics and characteristics of the study population enrolled prior to (Period 1) or during the COVID-19 pandemic (Period 2).

	Period 1 n = 55	Period 2 n = 28	P
Gestational age, median (IQR), weeks	28 (26 – 30)	28 (26 – 29)	0.403
Birth weight, median (IQR), g	980 (823 – 1208)	929.5 (828.5 – 1167.5)	0.644
Male gender, n (%)	29 (52.7)	15 (53.6)	0.942
BPD all grades, n (%)	40 (72.7)	24 (85.7)	0.183
Mild BPD, n (%)	25 (62.5)	14 (58.3)	0.084
Moderate BPD, n (%)	7 (17.5)	9 (37.5)	
Severe BPD, n (%)	8 (20.0)	1 (4.2)	
Days of mechanical ventilation, median (IQR), d	1 (0 – 6)	2 (0 – 7)	0.599
Days of oxygen supplementation during hospitalization, median (IQR), d	45 (20 – 76)	57.5 (40 – 72.5)	0.206
Maternal chorioamnionitis, n (%)	5 (9.1)	7 (25.0)	0.051
Prenatal steroids, n (%)	40 (72.7)	21 (75.0)	0.824
Postnatal steroids, n (%)	10 (18.2)	8 (28.6)	0.278
Presence of siblings, n (%)	30 (54.6)	16 (57.1)	0.278

BPD, Bronchopulmonary dysplasia

**Table 2.** Rates of respiratory infection, wheezing and hospital readmissions assessed at the 6-month follow-up visit in preterm infants (with or without BPD).

	Period 1 n = 55	Period 2 n = 28	P
At least one episode of suspected or confirmed respiratory infection at the follow-up visit, n (%)	36 (65.5)	11 (39.3)	0.023
At least one episode of wheezing at the follow-up visit, n (%)	20 (36.3)	1 (3.6)	0.001
Hospital readmission, n (%)	9 (16.3)	2 (7.1)	0.241

study the estimated incidence of acute respiratory infections during the first year of life in infants born before 32 weeks' gestation was 52.2% (9). Moreover, compared to preterm without BPD and full-term infants, respiratory infections affecting infants with BPD are often more severe (10 - 13). Risk of rehospitalization in the first year of life in infants with BPD can exceed 50% (6, 7), and episodes of wheezing are at least twice as likely (7). Globally, acute respiratory infections remain one of the leading causes of morbidity and mortality in children younger than 5 years of age (14). Viruses represent approximately 90% of all respiratory tract infections (15). The most common causative agent of bronchiolitis during infancy is respiratory syncytial virus (detected in 50-80% of bronchiolitis admitted to hospital), followed by rhinovirus, bocavirus, metapneumovirus, parainfluenza virus, adenovirus, coronavirus and influenza virus (16). Exposure to infected respiratory fluids is one of the main transmission routes of SARS-CoV-2 (17) or other respiratory viruses. Preventive strategies to contain the SARS-CoV-2 pandemic have also determined drastic reductions in respiratory diseases during the pandemic period (1).

Our study investigates a population at high risk of respiratory disease after hospital discharge. Interestingly, we found a significant decrease in the incidence of respiratory infections and episodes of wheezing in infants born during or immediately prior to pandemic. The effects of social restrictions were even more pronounced when only infants with BPD were evaluated. However, the small number of non-BPD infants enrolled in the study prevented us from detecting significant differences between the two periods. We showed that vulnerable premature infants benefited from the COVID-19 restrictions period during their first 6 months of life. The use of the mask reduced contacts with adults or children suffering from respiratory symptoms and limited the spread of viruses other than SARS-CoV-2.

We highlight the need to promote behavior and educational strategies to prevent respiratory tract infections within family members, even beyond the pandemic period. In our outpatient clinic for respiratory diseases we recommend using the mask in case of respiratory symptoms, avoiding contact with people with respiratory symptoms, and limiting the stay in

crowded places. In addition, it is crucial to avoid the infant's exposure to smoke and other environmental contaminants (18, 19).

Our study has several potential limitations. Firstly, the sample size of infants in study is small, and particularly during the pandemic period some follow up visits were missing. Furthermore, grades of restrictions varied during the pandemic, perhaps affecting the burden of our results. Finally, the number of infants with confirmation of respiratory infection through a microbiologic diagnosis was relatively small. However, in the common practice of general pediatricians the diagnosis of respiratory tract infections is often based only on clinical findings, without further microbiological testing.

In conclusion, our study shows the additional benefits of strategies to prevent COVID-19 on respiratory morbidity in preterm infants with BPD. These results highlight the importance of family education to prevent respiratory tract infections. Attention to these preventive measures should be extended beyond the pandemic period.

**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.

**Ethics Approval:** The local ethics committee Comitato Etico Area Vasta Emilia Nord approved the project on the 10<sup>th</sup> of February 2021 (Prot. N° 11/2021).

**Availability of Data and Materials:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Authors' Contributions:** DS, LB, GMC, BMB and AB conceptualized and designed the study, coordinated and supervised data collection, drafted the initial manuscript, and reviewed and revised the manuscript. TZ, MDM, ES, KR and FM collected data and drafted the initial manuscript. FM, LL and LI critically analyzed and interpreted data, and reviewed the manuscript. AB is the corresponding author. All authors read and approved the final manuscript.

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