

## A Comparative Analysis of the Occurrence of Lower Respiratory Tract Infections Caused by Respiratory Syncytial Virus among Newborns in the Years before and during Covid-19 Pandemic at a Tertiary Referral Hospital in Slovenia

Sandra Cerar, Vesna Pirnovar

University Medical Centre Ljubljana, Division of Pediatrics, Department of Neonatology, Ljubljana, Slovenia

**Correspondence:** sandra.cerar@kclj.si; Tel. + 3865229278; Fax.: + 3865224035

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### Abstract

**Objective** – In this study we aimed to compare the occurrence of lower respiratory tract infections caused by respiratory syncytial virus in the neonatal population in the years before and during the COVID-19 pandemic. **Methods** – Cases of newborns, hospitalized due to viral lower respiratory tract infection from 2015 to 2020, were analyzed retrospectively, and compared according to cause (respiratory syncytial virus, non-respiratory syncytial virus) and treatment requirements before (2015–2019) and after (2020) the outbreak of the COVID-19 pandemic. **Results** – The number of newborns with lower respiratory tract infections and newborns contracting respiratory syncytial virus declined significantly during the COVID-19 pandemic. Respiratory syncytial virus was the major causative agent before the pandemic, while after the lockdown no more cases were reported. There were no significant differences between the two periods regarding the number of patients requiring treatment with oxygen ( $P=0.705$ ), non-invasive ( $P=0.842$ ) and invasive ventilation ( $P=0.574$ ), or in terms of median hospital stay ( $P=0.670$ ) and the duration of non-invasive ( $P=0.350$ ) and invasive ventilation ( $P=0.556$ ), while the difference in the duration of treatment with oxygen was statistically significant ( $P=0.048$ ). **Conclusions** – A decline was found in the number of newborns hospitalized due to respiratory syncytial virus and non-respiratory syncytial virus lower respiratory tract infections during the COVID-19. Our results strongly suggest that social distancing and other lockdown strategies were effective in slowing down the spread of respiratory syncytial virus and decreasing the need for hospitalization among newborns, but may be not equally effective for all agents causing lower respiratory tract infections.

**Key Words:** Newborn ■ Coronavirus Disease 19 ■ Covid-19 ■ Respiratory Syncytial Virus ■ Lower Respiratory Tract Infection.

### Introduction

Respiratory syncytial virus (RSV) is one of the most common causes of respiratory tract infections during infancy. The most common route of its transmission is by droplet spread from an infected person or by direct contact. It typically occurs in winter. Due to infections with RSV high hospitalization and mortality rates are observed in the first year of life worldwide. Clinical manifestations range from a mild upper respiratory tract illness, to severe and potentially life-threatening lower respiratory tract involvement. The most common clinical course

of RSV infection is acute bronchiolitis and pneumonia. Apnea may be observed in very young and premature infants as the first manifestation of infection (1). Extra-pulmonary complications caused by RSV infection may occur: myocarditis, brain convulsions, hepatitis being the most common.

A severe course of RSV infections is expected in high-risk populations: preterm newborns, individuals with bronchopulmonary dysplasia, chronic lung disease, hemodynamically important congenital heart disease, nerve and muscle system diseases, and immune deficiencies (1). Besides standard

prevention methods, using hand hygiene and social distancing, immunoprophylaxis with monoclonal antibodies is available for high-risk individuals (1).

In early 2020, the coronavirus 2019 disease pandemic (COVID-19) began and public health measures were gradually implemented from the beginning of 2020 on. After preventive measures (restrictions on public gatherings, restriction of teaching in colleges, and facial mask wearing), additional control measures, including social distancing, stay-at-home orders, quarantine, school closures, travel restrictions and border closures were adopted due to the progression of the epidemic. The first case of COVID-19 disease was recorded in Slovenia on 4<sup>th</sup> March 2020. On 16<sup>th</sup> March 2020 total lockdown of the country was implemented in Slovenia. Due to the impact of these measures on the transmission of other respiratory viruses, a decline in hospital admissions for acute respiratory illness was reported.

The aim of this study was to compare the occurrence of lower respiratory tract infections (LRTI) caused by RSV and other agents among newborns in the period before (2015 to 2019) and after (2020) the outbreak of the COVID-19 pandemic.

## Methods

A cross-sectional study was conducted at the Department of Neonatology, University Children's Hospital, Ljubljana, between January 2015 and December 2020. Two periods were defined and compared: pre-COVID-19 pandemic (2015 to 2019) and after (2020) the outbreak of the COVID-19 pandemic.

The study included infants aged up to 44 post-conceptual weeks with acute viral LRTI. The diagnosis of LRTI was based on all the available clinical information (determined by breathing rate, retractions, auscultatory findings, general appearance, accompanied by tachycardia, cyanosis, lethargy, or hypoxemia), or radiographic evidence. Respiratory viruses were detected in nasopharyngeal swabs or tracheal aspirates using the RT-PCR method. All the samples were tested for the presence of RSV, rhinovirus (hRV), human bocavirus (hBoV), human metapneumovirus (hMPV), parainfluenza virus

(PIV), influenza virus type A and B (InfV), human coronavirus (hCoV) and adenovirus (AdV).

The following data were collected: the number of hospitalized patients, the number of acute viral LRTIs caused by RSV and other respiratory viruses, average hospitalization time due to LRTI, the number of patients with LRTI requiring respiratory support with additional oxygen, delivered by binasal prongs, or invasive or non-invasive ventilation (nasal continuous positive airway pressure – CPAP and nasal bi-level positive airway pressure – BiPAP), and the duration of these therapeutic requirements.

## Ethics Statement

No request for the approval of the ethics committee was sought as this was a clinical study, involving information available in medical datasets. Furthermore, informed consent was obtained at the time of the original data collection, and the data were properly anonymised.

## Statistical Analyses

Numerical data were presented as mean and standard deviation (SD), and categorical data as frequencies. The differences in numerical variables were tested using the Kruskal Wallis H test. The differences in categorical variables were tested using the Mann-Whitney U test. In the ORs presented in Table 3 the dependent variables were: RSV/non-RSV, O<sub>2</sub> treatment required/not required, non-invasive ventilation (NIV)/non-NIV, invasive ventilation (IV)/non-IV. For each dependent variable, ORs were calculated with the year under consideration as the independent variable (i.e., 2015-2019 vs 2020 were used as the reference years). The level of significance for statistical testing was set at 0.05. IBM SPSS 26 was used to calculate frequencies, the Saphiro Wilk test to assess the normality of the distribution, the Kruskal Wallis test, Mann-Whitney U test, and the binomial test for sample proportions. Medcalc's OR calculator was used to calculate the odds ratio (OR) and the corresponding confidence interval (CI) and probability (<https://>

www.medcalc.org/calc/odds\_ratio.php). Fig. 1 was created using MS Excel (Office 365).

## Results

During the whole study period, 208 newborns with acute viral LRTI were admitted. A slight male predominance was present. Approximately one-quarter of them (53 newborns, 25.5%) were born prematurely. Among all hospitalized newborns, the proportion of preterm newborns with LRTI was 5.4-10.8%. The newborns were admitted to the hospital at the mean age of 26 days; however, their respiratory disease began two to three days prior to that. A high proportion of the newborns had positive epidemiological history.

As shown in Table 1, the annual numbers of hospitalizations for LRTI in 2015–2019 varied from 30 to 43 per year, which accounted for 4.4-6.3% of all hospitalized patients. In a large majority of cases,

RSV was the causative agent (23-30 patients yearly, or 62.2-80.6% of all LRTIs). A similar percentage was observed among preterm newborns with LRTI: RSV was the causative agent in 3-8 cases (50-77%) (Table 1; Fig. 1). Other respiratory viruses detected were: rhinovirus, human metapneumovirus, parainfluenza virus, influenza, human bocavirus and human coronavirus. Two respiratory viruses were detected in 5 (2.2%) newborns with LRTI.

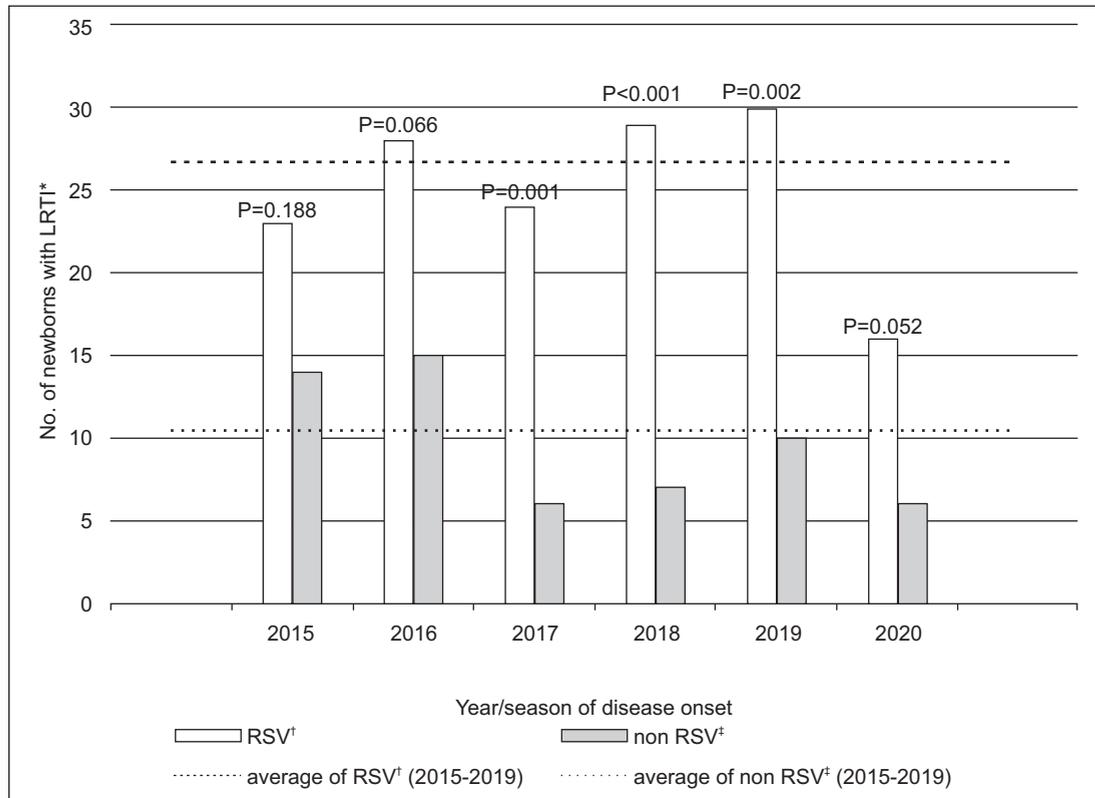
The differences between the proportion of RSV and non-RSV cases for each year were statistically significant in 2017, 2018 and 2019 (Fig. 1).

A characteristic winter peak in hospitalizations occurred between December and March. The overall number of admissions declined in 2020, and the proportion of patients admitted due to LRTI was also lower (3.48% of all hospitalized newborns). Concomitantly, a decline was observed in neonatal admissions due to LRTI caused by RSV (Table 1). All newborns that contracted RSV in 2020 were

Table 1. Admission Rates, Proportion of Lower Respiratory Tract Infections Caused by Respiratory Syncytial Virus and Respiratory Support Requirements in Hospitalized Newborns, 2015–2020

Numbers and proportions of patients	Observed period (Year)					
	2015	2016	2017	2018	2019	2020
Total number of patients hospitalized per year (number and % premature of all admissions)	723 (143; 19.7)	688 (129; 18.8)	690 (120; 17.4)	641 (99; 15.4)	696 (109; 15.6)	633 (112; 17.7)
Number and % of all admissions of patients with LRTI <sup>†</sup>	37 (5.1)	43 (6.3)	30 (4.4)	36 (5.6)	40 (5.8)	22 (3.5)
Number and % of newborns with RSV <sup>†</sup> of all LRTI <sup>†</sup>	23 (62.2)	28 (65.1)	24 (80.0)	29 (80.6)	30 (75.0)	16 (72.7)
Number of newborns with RSV <sup>†</sup> per 1000 hospitalized	31.8	40.7	34.8	45.2	43.1	25
Number of preterm newborns with LRTI (% of all newborns with LRTI <sup>†</sup> )	13 (35%)	14 (32.6)	7 (23.3)	4 (13.8)	9 (30)	6 (37.5)
Number and % of preterm newborns with RSV <sup>†</sup> of newborns with LRTI <sup>†</sup>	7 (53.8)	8 (57.1)	5 (71.4)	3 (75.0)	7 (77.8)	3 (50.0)
Number of preterm newborns with RSV <sup>†</sup> per 1000 hospitalized	49.0	62.0	41.7	30.3	64.2	26.8
Number and % of all LRTI <sup>†</sup> of patients requiring oxygen treatment	36 (97.3)	42 (97.7)	29 (96.7)	29 (80.6)	28 (70.0)	20 (90.9)
Number and % of patients requiring NIV <sup>‡</sup> of all LRTI <sup>†</sup>	15 (40.5)	12 (27.9)	14 (46.7)	14 (38.9)	17 (42.5)	9 (40.9)
Number and % of patients requiring IV <sup>§</sup> , of all LRTI <sup>†</sup>	12 (32.4)	15 (34.9)	7 (23.3)	3 (8.3)	7 (17.5)	4 (18.2)

<sup>†</sup>Lower respiratory tract infection; <sup>‡</sup>Respiratory syncytial virus; <sup>‡</sup>Non-invasive ventilation; <sup>§</sup>Invasive ventilation.



Lower respiratory tract infection; <sup>†</sup>Respiratory syncytial virus; <sup>‡</sup>Non-respiratory syncytial virus.

**Fig. 1.** The number of newborns with lower respiratory tract infections admitted in 2015-2020 by causative agent (respiratory syncytial virus and non-respiratory syncytial virus).

admitted before March (12<sup>th</sup> week), but 3 more newborns with non-RSV infections were admitted by the end of 2020 (one subject contracted metapneumovirus at the end of March, 2 subjects contracted rhinovirus in July and September 2020). RSV was the most common cause of LRTI in both periods observed and the proportion of patients with RSV infection among the LRTIs was similar in the pre-COVID-19 period (2015–2019) and in 2020. None of the hospitalized newborns was positive for severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), and none of them died due to the LRTI- or RSV-related complications.

The analysis of the course of the disease revealed that before the COVID-19 pandemic 28-42 (70.0-97.7%) newborns with LRTI were treated per year with oxygen, 12-17 (27.9–46.7%) with non-invasive and 3-12 (8.3–34.9%) with invasive ventilation. Data regarding the duration of hospitalization

and treatment requirements in newborns are presented in Table 2.

In the periods observed there were no significant differences regarding the percentage of patients treated with oxygen (88.2% vs. 90.9%,  $P=0.705$ ), non-invasive (38.7% vs. 40.9%,  $P=0.842$ ) or invasive ventilation (23.7% vs. 18.2%,  $P=0.574$ ) (Table 3).

The comparison of the duration of therapeutic requirements in patients hospitalized in the two periods analyzed are presented in Table 4. The median duration of the hospital stay of the newborns did not differ significantly (8.7 days vs. 7.7 days,  $P=0.670$ ). The duration of treatment with oxygen was longer in the pre-COVID-19 era (4.1 day vs. 2.1 day,  $P=0.048$ ) while there were no significant differences regarding the duration of treatment with non-invasive (1.2 days vs. 1.9 day,  $P=0.350$ ) or invasive ventilation (1.7 days vs. 0.8 days,  $P=0.556$ ).

**Table 2. Duration of Hospitalization and Respiratory Support with Oxygen, Non-invasive and Invasive Ventilation in Newborns Hospitalized due to Lower Respiratory Tract Infections in 2015–2020**

Parameter		Observed period (Year)					
		2015	2016	2017	2018	2019	2020
Duration of hospitalization	Average (days)	10.4	8.49	8.63	8.06	7.4	7.4
	Interval (days)	(1-62)	(2-30)	(2-21)	(1-22)	(2-27)	(2-17)
	U*	775.5	610.5	505.5	660.5	427.5	
	P†	0.846	0.698	0.656	0.534	0.853	
Duration of treatment with oxygen	Average (days)	6.2	4.7	5.45	4.3	2.43	2.33
	Interval	(0-45)	(0-14)	(0-20)	(0-11)	(0-8)	(0-8)
	U*	766.5	556.0	300.0	568.5	377.0	
	P†	0.941	0.316	0.002	0.099	0.328	
Duration of treatment with non-invasive ventilation	Average (days)	2.6	2.04	2.89	3.43	4.06	4.56
	Interval	(0-12)	(0-6)	(0-7)	(0-9)	(0-10)	(0-8)
	U*	700.0	521.5	538.5	683.5	434.5	
	P†	0.363	0.092	0.982	0.667	0.928	
Duration of treatment with invasive ventilation	Average (days)	8.83	6.86	8.43	5.17	5.79	4.75
	Interval	(0-28)	(0-11)	(0-16)	(0-5)	(0-9.5)	(0-6)
	U <sup>a</sup>	781.5	592.0	446.0	670.5	425.5	
	P†	0.872	0.470	0.072	0.400	0.757	

\*Comparison between the current and the following year - Mann-Whitney U test: U and P value.

**Table 3. Treatment Requirements in Newborns with Lower Respiratory Tract Infections Hospitalized before COVID-19 (2015 to 2019) and during the COVID-19 Pandemic (2020)**

Number of patients	Observed period (Year)				
	2015 – 2019		2020	OR* (95% CI)	P
	N	ANPY† (%)	N (%)		
Total	186	37.2 (100)	22 (100)	-	-
Oxygen treatment	164	32.8 (88.2)	20 (90.9)	1.3415 (0.293, 6.135)	0.705
NIV‡	72	14.4 (38.7)	9 (40.9)	1.096 (0.446 – 2.670)	0.842
IV§	44	8.8 (23.7)	4 (18.2)	0.717 (0.231– 2.231)	0.574

\*Odds ratio; †Average number of patients per year; ‡Non-invasive ventilation; §Invasive ventilation.

**Table 4. Comparison of the Duration of Therapeutic Requirements in Patients Hospitalized due to Lower Respiratory Tract Infections before COVID-19 and during the COVID-19 Pandemic**

Variable	Period (Year)				Mann-Whitey U test	
	2015–2019		2020		U	P
	M (SD)	Me (Q1 - Q3)	M (SD)	Me (Q1 - Q3)		
Total duration of hospitalization (days)	8.7 (6.9)	7 (4 - 11)	7.7 (4.4)	7 (5 - 11)	1932.5	0.670
Duration of oxygen requirement (days)	4.1 (5.4)	3 (1 - 5)	2.1 (2.2)	2 (0 - 4)	1513.5	0.047
Duration of non-invasive ventilation requirements (days)	1.2 (2.2)	0 (0 - 2)	1.9 (2.6)	0 (0 - 4)	1822.5	0.350
Duration of invasive ventilation requirements (days)	1.7 (3.7)	0 (0 - 0)	0.8 (1.7)	0 (0 - 0)	1927.5	0.556

\* Mean value; †Median; ‡Standard deviation; §Percentile 25; ¶Percentile 75.

## Discussion

Our study is unique due to the fact that we analyzed the occurrence and clinical course of RSV LRTI during the COVID-19 pandemic exclusively in newborns, who represent the most vulnerable population for a difficult course of infection with RSV. We found a decline in the number of newborns admitted due to RSV and non-RSV LRTI soon after the lockdown in 2020, and after the 12<sup>th</sup> week of the year in March 2020 no newborns were identified with LRTI due to RSV.

Studies covering the incidence of RSV and other respiratory infections exclusively in the neonatal period are rare. According to a report from Slovenia, the average weekly hospitalizations in children aged 5 months or younger due to acute LRTI caused by RSV in five seasons from 2006 to 2011 was 120.1–272.9 per 100,000 (9). Our group of patients consisted of preterm and term infants, and in the pre-COVID-19 era LRTI accounted for 5.4% and RSV for 3.9% of all admissions. An estimation of the RSV infection hospitalization rate in our study in the pre-COVID-19 era was 36.6 per 1,000 term newborns per year. This was higher compared to reports from US pediatric hospitals, where it is described to be 25.1–25.9 per 1000 children aged 1 month (10, 11). When calculated exclusively for preterm newborns (49.4 cases per 1000 hospitalized preterm newborns aged up to 44 postconceptional weeks) the hospitalization rate was higher in this high-risk subgroup of newborns. Furthermore, according to a meta-analysis of 32 countries, among preterm babies less than 1 year of age where the hospitalization rate is described to be much higher (63.85/1000 infants) (12), the increased risk of a more severe course of RSV infection among premature newborns persists beyond the neonatal period.

The decline in LRTI due to RSV in 2020 appeared earlier than in previous years, when the season of RSV persisted until April with sporadic cases up until May. Our findings are closely aligned with reports from the National Institute of Public Health (13), where no more RSV cases were detected in the general population from the 16<sup>th</sup> week

of 2020 onwards. In the years before 2020, the annual winter peak of respiratory infections (flu-like infections) was reported from December to March. In 2020 a decline was observed in respiratory infections compared to previous years in the general Slovenian population, and the level of respiratory infections remained low throughout 2020, with the absence of a winter peak (14). According to reports by the Centre for Disease Control and Prevention (CDC), the situation was similar in the United States. Compared with previous years, RSV activity remained relatively low from May 2020 to March 2021 (15).

Similar observations were also found in other parts of the world. At Philadelphia Children's Hospital there was a dramatic decrease in emergency pediatric department visits (16). In the 30-day window after the stay-at-home order in 2020, the mean number of daily visits was lower in 2020 compared to the same time period in 2017–2019 (16). In a Finnish study (17) a major decrease in the median rate of daily emergency pediatric visits was detected during the nationwide lockdown compared with the study period before the lockdown. The authors reported a shorter influenza season (8 weeks from peak to no cases), and a faster decrease in the weekly rate of new cases compared to the previous 4 influenza seasons (previously 15–20 weeks from peak to no cases). A similar decrease was also seen in RSV cases. They did not report any pediatric cases of COVID-19 during the study period (17) which is in accordance with our results, as in the observed period no COVID-19 was identified in our cohort. In an Australian study (5) a concurrent lower frequency of respiratory syncytial virus detection was observed (A and B), lower hospital admission rates for bronchiolitis, and lower emergency department attendance for acute respiratory illnesses in 2020 compared to preceding years. Similar findings were reported among infants under 2 years of age in New Zealand (7), where hospitalizations for LRTI due to RSV or influenza virus infection decreased dramatically.

The reduced inflow of pediatric patients to hospitals was also reflected in the number of

admissions to intensive care units. Reports from South America(18) claim that between January and August there were 83% fewer pediatric intensive care unit admissions for LRTI in 2020 compared to 2018/2019(18). Similar decreases were noted for pediatric intensive care unit admissions due to diseases caused by RSV and influenza (18).

Although the overall number of admissions to our department declined in 2020, the proportion of patients admitted due to LRTI was also lower. In the years observed, RSV was the most common causative agent of LRTI, although after the lockdown in March 2020 no newborns were found with LRTI due to RSV. Interestingly, the number of patients contracting a non-RSV agent also declined, but some more cases were also identified after the lock-down (rhinovirus, metapneumovirus). Similar findings were described in a study from New Zealand, in which the authors studied hospitalizations of children with non-RSV (adenovirus, rhinovirus/enterovirus) LRTI (7). As reported from Australia, the small uptick in emergency department attendances and bronchiolitis admissions in June 2020 was not associated with increased RSV detection, as the causative agent was found to be almost exclusively rhinovirus (5). The differences in the proportions of RSV and non-RSV cases for each year were present in years 2017, 2018 and 2019 due to lower proportion of non-RSV.

Several studies reported that the interventions, including social distancing, stay-at-home orders, school closures, travel restrictions and border closures, due to the outbreak of the novel coronavirus in December 2019, that were adopted in order to control the early phase of the COVID-19 pandemic, played an important role in preventing the spread of RSV and other LRTI (5,6). According to our results and the results of some other studies, we can speculate that public health measures to prevent the spread of SARS-Cov-2 appear to have been less effective in preventing the spread of non-RSV agents. Authors from Italy report a strong reduction in all viral respiratory infections in the 2020 season compared to the two previous seasons, with the invasion of rhinovirus to a lesser extent

(19). Australian authors, who reported an increase in admissions due to bronchiolitis caused by rhinovirus in 2020, concluded that rhinoviruses are more easily transmitted between children because they are non-enveloped, and are less susceptible to inactivation by handwashing (5).

In children under 12 months of age, RSV causes more severe LRTI than other respiratory viruses, and premature newborns are the most vulnerable subgroup of these children (20, 21). Therefore, in our study we also studied the course of RSV and non-RSV infections in the periods before and after the outbreak of the pandemic. When comparing the years 2015-2019 and 2020 in terms of the number of patients requiring respiratory support, we found no differences in the numbers of patients needing treatment with oxygen, non-invasive ventilation or invasive ventilation. The median duration of hospital stay did not differ significantly between the study periods, nor did the duration of respiratory support requirements.

Our study has several limitations. The main one is that it is a single center study with a relatively small number of cases, covering a narrow period of observation. However, it provides an overview of LRTI occurrence and clinical course in the most fragile population of patients, and can serve as a basis for a strategy to prevent these diseases in future.

## Conclusion

We found a decline in the number of newborns hospitalized due to RSV and non-RSV LRTI during the pandemic. Our results strongly suggest that social distancing and other lockdown strategies are effective in slowing down the spread of RSV, thus decreasing the need for hospitalization of newborns, but may be not be equally effective for all agents.

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**Conflict of Interest:** The authors declare that they have no conflict of interest.

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