

LETTER TO THE EDITOR

Unexpected peak of bronchiolitis requiring oxygen therapy in February 2020: Could an undetected SARS-CoV2-RSV co-infection be the cause?

To the Editor,

In the current winter season, children's hospitals may have to face the seasonal outbreak of bronchiolitis in a never seen context of coronavirus disease 2019 (COVID-19) pandemic. Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis among infants less than 12 months, presenting with a seasonal pattern with greater prevalence in the winter and spring months.¹ Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) officially appeared in Italy just as the RSV-bronchiolitis season was winding down. As a result, there was never a real overlap between SARS-CoV2 and RSV.

However, several authors hypothesized that SARS-CoV2 was present in northern Italy some weeks before the first Italian confirmed case on February 20, 2020.²⁻⁵ As a result, we suspected that this virus, circulating as early as 2020, may have aggravated the course of some infants with bronchiolitis.

We performed a retrospective study to evaluate the frequency and severity of infants presenting with a clinical picture of bronchiolitis to the Pediatric Emergency Department (ED) of Giannina Gaslini Institute, the largest children hospital in northern Italy, in the period between the first identification of COVID-19 in the polluted water of the city of Milan² and the start of Italian lockdown (December 1, 2019–March 9, 2020).

Results were compared with the same time frame in 2017–18 and 2018–19 seasons.

The Kruskal–Wallis test was used to determine if there are statistically significant differences between groups. A *p* value less than .05 was considered as statistically significant. All data analyses were done with Stata® version 13 software (StataCorp LLP).

A total of 125, 244, and 211 patients with a clinical picture of bronchiolitis were observed in 2019–2020, 2018–2019, and 2017–2018 group, respectively.

No statistically significant differences in age, pre-existing medical conditions (including prematurity), triage severity score at ED presentation, hospitalization rate, and length of stay were noted between groups (Table 1).

Figure 1 reports the proportion of severe bronchiolitis observed in the three time periods. From February 2nd to March 9th, 2020, (weeks 10–14), 55.1% of the patients admitted with a clinical picture of bronchiolitis required oxygen therapy (given when oxygen saturation

< 92%) compared with the 18% and 14.5% observed in the same period in 2017–2018 and 2018–2019, respectively (*p* < .0001) (Table 1).

We found no differences between groups in the type of respiratory support. High flow nasal cannulae (HFNC) were used in 45.5%, 55%, and 39% of cases in groups 2019–2020, 2018–2019, and 2017–2018, respectively.

No significant difference in HFNC was observed between the three groups (26.6%, 60%, and 40%, respectively) even in the period from week 10–14.

Continuous positive airway pressure (CPAP) was used in only one case in each period. Mechanical ventilation was required in only one child, in the 2018–2019 group.

Although not statistically significant we observed an increase in the length of oxygen therapy in the 2019–2020 (median: 96 h; IQR: 72–144) and 2018–2019 (96 h; IQR: 48–120) groups as compared with the 2017–2018 group (48 h; IQR 24–108).

Among inpatients, 55/71(77%), 100/140 (71%), and 86/118 (73%) were tested with multiplex polymerase chain reaction (PCR) in the 2019–2020, 2018–2019, and 2017–2018 groups, respectively.

In the 2019–2020 group, 97% (32/33) of oxygen-treated patients were tested with at least one pathogen detected in all cases.

Specifically, in weeks 10–14, among the sixteen patients who required oxygen therapy, ten were diagnosed as RSV bronchiolitis and six were diagnosed as bronchiolitis caused by coinfection between RSV and other viruses including influenza,² bocavirus, rhinovirus, human metapneumovirus-coronavirus, or enterovirus.

In the same weeks of the 2018–2019 season, the germs detected for patients with bronchiolitis requiring oxygen were RSV in 10 cases, influenza in one, and viral coinfections in four patients (RSV–coronavirus, RSV–rhinovirus,² and bocavirus–rhinovirus–parainfluenza), whereas multiplex PCR was not performed in three patients.

In the 2017–2018 season, weeks 10–14, the causes of severe bronchiolitis were RSV in nine cases, RSV–rhinovirus in three, and RSV–bocavirus in one, while two tests were negative and two not performed.

Our results showed no significant differences in the number of patients with viral co-infections between the three seasons either in the entire study period or in the weeks from February 2 to March 9 (Table 1).

TABLE 1 Characteristics of patients with bronchiolitis admitted to Gaslini Emergency Department during the study period

	December 1, 2017–March 9, 2018	December 1, 2018–March 9, 2019	December 1, 2019–March 9, 2020	p value
Total number	211	244	125	–
Sex (M)	139 (65.9%)	127 (52%)	76 (60.8%)	.01
Age (days) median (IQR)	96 (65–172)	110 (63–174)	108 (49–183)	NS
Preterm children	2 (0.9%)	3 (1.2%)	5 (4%)	.1
Comorbidity	4 (1.9%)	13 (3%)	8 (6.4%)	.09
Emergency consultations (Red code)	2 (0.9%)	2 (0.8%)	3 (2.4%)	.4
High priority consultations (Yellow code)	143 (67.8%)	153 (63%)	86 (68.8%)	.4
Low priority consultations (Green code)	66 (31.2%)	88 (36%)	36 (28.8%)	.3
Hospitalization	118 (55.9%)	140 (57.4%)	71 (56.8%)	.9
Oxygen therapy				
December 1–March 9				.09
Patients treated/observed (%; CI 95%)	36/211 (17%) (12.6–22.7)	49/244 (20%) (15.5–25.5)	33/125 (26.4%) (19.4–34.7)	
December 1–February 1				0.14
Patients treated/observed (%; CI 95%)	19/117 (16.2%) (10.6–24)	31/120 (25.8%) (18.8–34.3)	17/96 (17.7%) (11.3–26.5)	
February 2–March 9				<.0001
Patients treated/observed (%; CI 95%)	17/94 (18%) (11.6–27)	18/124 (14.5%) (9.3–21.7)	16/29 (55.1%) (37.5–71.6)	
Length of oxygen therapy (hours, median and IQR)	48 (24–108)	96 (48–120)	96 (72–144)	.07
Etiology				
Multiplex PCR performed	86 (41%)	100 (41%)	55 (44%)	NS
Multiplex PCR performed in hospitalized patients	86/118 (73%)	99/140 (71%)	54/71 (76%)	NS
Positive multiplex PCR test	78/86 (91%)	98/100 (98%)	55/55 (100%)	.01
RSV	66/86 (76.7%)	74/100 (74%)	52/55 (95%)	.007
Viral coinfections	15/86 (17.4%)	27/100 (27%)	15/55 (27%)	.2
RSV (February 2–March 9)	32/40 (80%)	28/38 (74%)	26/28 (93%)	.1
Viral coinfections (February 2–March 9)	5/40 (12.5%)	10/38 (26.3%)	6/28 (21.5%)	.9

Abbreviations: CI, confidence interval; IQR, interquartile range; PCR, polymerase chain reaction; RSV, respiratory syncytial virus.

Besides, metapneumovirus, an important cause of seasonal bronchiolitis, was found in only one case in the 2019–2020 group.

In the period of 2020 covered by our analysis real-time polymerase chain reaction (RT-PCR) test for SARS-CoV-2 detection in the respiratory tract was not available.

RSV is the leading cause of bronchiolitis and has a seasonal epidemiology with a peak in the period December–March, when frequently co-circulate with coronaviruses.¹

Our data show the presence of an unexpected proportion of infants with a clinical picture of severe bronchiolitis requiring oxygen therapy in the season 2019–2020, just in the weeks preceding the declaration of COVID-19 pandemic in Italy. Co-infections of SARS-CoV-2 and other viruses has been described in children.⁶ However the description of cases of RSV bronchiolitis with severe respiratory distress who tested positive also for SARS-CoV2 is rare.⁷

With this letter we propose the suggestion of a co-circulation of these two viruses that may have led to an increase of severity of

bronchiolitis in 2019–2020 compared with the two previous years. Unfortunately, because of the lack of RT-PCR test in that period this remains an epidemiology-driven hypothesis.

Although COVID-19 appears less severe in children than in adults, the pandemic has taught us that novel, peculiar, and sometimes severe clinical pictures can occur in children. The spike in severe bronchiolitis that we found in February 2020 seems to have no significant epidemiological explanation. We could hypothesize that an undetected SARS-CoV2 (co)-infection might have played some role.

Anyway, we want to stress the need of continuous epidemiological surveillance for the occurrence of new and unexpected clinical conditions.

Because several co-infections of SARS-CoV2 with other airborne pathogens are known,⁶ we recommend that great caution must be used in the management of childhood respiratory infections to promptly isolate and treat suspected cases and prevent transmission among healthcare workers.

Patients with bronchiolitis requiring oxygen therapy

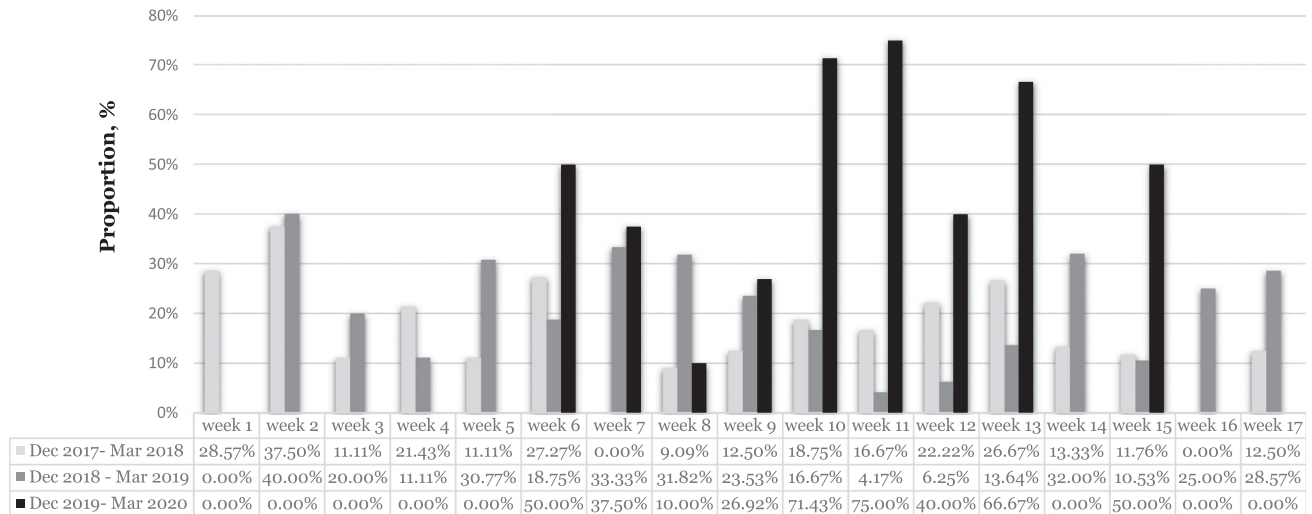


FIGURE 1 Proportion of patients with bronchiolitis requiring oxygen therapy in three observation periods

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AUTHOR CONTRIBUTIONS

Gioacchino Andrea Rotulo: conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); writing original draft (equal). **Emilio Casalini:** conceptualization (supporting); data curation (equal); writing original draft (equal). **Giacomo Brisca:** writing review & editing (equal). **Emanuela Piccotti:** writing review & editing (equal). **Elio Castagnola:** conceptualization (equal); supervision (equal); writing review & editing (equal).

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REFERENCES

1. Meissner HC. Viral bronchiolitis in Children. *N Engl J Med.* 2016; 374(1):62-72.
2. La Rosa G, Mancini P, Bonanno Ferraro G, et al. SARS-CoV-2 has been circulating in northern Italy since December 2019: evidence from environmental monitoring. *Sci Total Environ.* 2021;750: 141711.
3. Amendola A, Bianchi S, Gori M, et al. Evidence of SARS-CoV-2 RNA in an oropharyngeal swab specimen, Milan, Italy, early December 2019. *Emerg Infect Dis.* 2020;27(2):648-650.
4. Gianotti R, Barberis M, Fellegara G, Galván-Casas C, Gianotti E. COVID-19 related dermatosis in November 2019. Could this case be Italy's patient zero? *Br J Dermatol.* 2021:bjd.19804.
5. Apolone G, Montomoli E, Manenti A, et al. Unexpected detection of SARS-CoV-2 antibodies in the pre-pandemic period in Italy. *Tumori.* 2020.
6. Di Nardo M, Leeuwen G, Loreti A, et al. A literature review of 2019 novel coronavirus (SARS-CoV2) infection in neonates and children. *Pediatr Res.* 2020.
7. André MC, Pätzug K, Bielicki J, Gualco G, Busi I, Hammer J. Can SARS-CoV-2 cause life-threatening bronchiolitis in infants? *Pediatr Pulmonol.* 2020;55:2842-2843.