

Bronchiolitis and Severe Acute Respiratory Syndrome Coronavirus-2

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Keywords: bronchiolitis, SARS-CoV-2, COVID-19, coronavirus, infants.

Abstract

Background It has been speculated that the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) was already widespread in Western Countries before February 2020.

Methods We gauged this hypothesis by analyzing the nasal swab of infants with either bronchiolitis or a non-infectious disease admitted to the Ospedale Maggiore, Milan (one of the first epicenters of SARS-CoV-2 outbreak in Europe) from November 2019.

Results The SARS-CoV-2 RNA was never detected in 218 infants with bronchiolitis (95 females, median age 4.9 months) and 49 infants (22 females, median age 5.6 months) with a non-infectious disease between November 2019 and February 2020. On the contrary, two infants hospitalized for bronchiolitis between March and April 2020 tested positive for SARS-CoV-2.

Conclusions This study does not support the hypothesis that SARS-CoV-2 was already circulating among infants before the official outbreak of SARS-CoV-2 infection. However, it shows for the first time that SARS-CoV-2 might cause bronchiolitis requiring hospitalization.

INTRODUCTION

In December 2019, the first cluster of pneumonia of unknown etiology was reported by Chinese health authorities in Wuhan. The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) was then detected and its diffusion among the population in Europe was described in Northern Italy from February 21, 2020. However, it has been hypothesized that SARS-CoV-2 could have been present in Italy in the preceding months.¹ It has also been speculated that this virus was already widespread among children because infectious outbreaks tend to disseminate first among infants.² Yet, these hypotheses have not been tested so far. The main aim of this study was to verify if SARS-CoV-2 was already circulating among infants affected by bronchiolitis and asymptomatic infants from November 2019. The secondary aim was to verify if SARS-CoV-2 was associated with bronchiolitis.

METHODS

At the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, the diagnosis of bronchiolitis is established in infants with acute onset of worsening respiratory distress, cough and diffuse crackles on auscultation.³ Moreover, the bronchiolitis severity score (mild, moderate or severe) is calculated according to a standardized protocol on the basis of the respiratory rate, saturation in room air, presence of nasal or thoracic retractions, and ability to feed.³ In the context of a prospective case-control epidemiological study, all infants ≤ 12 months of life admitted for bronchiolitis to the Pediatric Emergency Department (PED) and the regular ward from November 1, 2019 to April 31, 2020, underwent a mid-turbinate nasal swab to investigate the presence of viral agents. In the same timeframe, infants admitted to the PED without signs or symptoms of infectious diseases (controls) were also invited to undergo a nasal swab to determine the circulation of respiratory syncytial virus (RSV) in the asymptomatic population of infants. Once collected by a trained researcher, the nasal swabs were stored at -80°C until nucleic acids extraction. The analysis of respiratory infectious agents in the nasal swab was performed by means of real-time polymerase chain reaction (PCR). SARS-CoV-2 RNA extraction was performed using the Mirneasy Mini Kit (Qiagen, Hilden, Germany), according to the manufacturer's instructions. To detect SARS-CoV-2 RNA a multiplex real time RT-PCR test (TaqPathTM Covid-19 CE-IVD RT-PCR kit, ThermoFisher Scientific) was applied.

For study purposes, data on the need for hospitalization and intensive care admission were also collected. Continuous data are presented as median and interquartile range and categorical data as frequency and percentage. The study was approved by the ethical committee of the Hospital (approval number 326_2020bis, 2017HWPZZZ) and all parents or caregivers signed an informed consent.

RESULTS

A total of 237 infants were diagnosed with bronchiolitis from November 2019 to April 2020 as shown in Figure 1. The consent to participate in the study was provided by parents or caregivers of 230 (123 males) infants (median age 4.9, IQR 2.5 – 9.2, months). The bronchiolitis severity score was mild in 103, moderate in 116 and severe in 18 infants. A total of 106 were admitted to the regular ward and 14 to the intensive care unit.

In infants with bronchiolitis, the most common infectious agent was the RSV (N= 127, 55%). Between November 2019 and February 2020, among the 218 infants with bronchiolitis, the SARS-CoV-2 was never detected. On the contrary, among the 12 infants enrolled between March and April 2020, two (16%) males tested positive for SARS-CoV-2. Their clinical characteristics are given in Table 1. They presented with moderate (N=1) or severe (N=1) bronchiolitis which required hospitalization, but not intensive care. No other micro-organism was detected in these two patients.

A total of 49 (27 males) infants (median age 5.6, IQR 2.6 – 9.4, months) without signs or symptoms of infectious diseases were enrolled: among these subjects, no positive nasal swab for SARS-CoV-2 was detected.

DISCUSSION

This study, conducted in the main pediatric emergency department of Lombardy, the epicenter of the first outbreak of SARS-CoV-2 in Western Countries, points out that SARS-CoV-2 was not responsible of any case of bronchiolitis between November 2019 to February 2020. This study also showed that SARS-CoV-2 was found in two patients with bronchiolitis requiring hospitalization after the official outbreak of this virus in Lombardy. Finally, this study failed to identify any infant without signs or symptoms of infectious diseases infected by the SARS-CoV-2.

Based on serological studies, phylogenetic analyses of SARS-CoV-2 genome and anecdotal reports among adults, it has been speculated that SARS-CoV-2 was prevalent among the

population in the months preceding the official identification of SARS-CoV-2 in Europe. It is also known that most children do not develop any symptom or sign of SARS-CoV-2 infection. Therefore, children have been suggested to have facilitated the spread of the virus in the general population.⁴ The results of this study, which included both infants with bronchiolitis and infants without signs or symptoms of infectious diseases do not support these assumptions.

Bronchiolitis is the most common cause of admission among infants that typically occur during cold seasons. Although the main cause of bronchiolitis is the RSV, coronaviruses are also frequently detected in infants with bronchiolitis and often associated with co-infections.⁵ To the best of our knowledge, this is the first study documenting the association between SARS-CoV-2 and bronchiolitis. Our data suggest that SARS-CoV-2 might cause bronchiolitis in infants.

This study has limitations. Although it was conducted in one of the first epicenters of SARS-CoV-2 outbreak, this is a monocenter study. In addition, the number of asymptomatic subjects enrolled is rather limited. Furthermore, few cases of SARS-CoV-2 infection among infants with bronchiolitis were observed. Therefore, we cannot compare the characteristics of bronchiolitis associated with SARS-CoV-2 and with those associated with RSV or other viral agents.

In conclusion, this study does not support the hypothesis that SARS-CoV-2 was already circulating among infants with bronchiolitis and asymptomatic infants before the official outbreak of SARS-CoV-2 infection. However, it shows for the first time that SARS-CoV-2 might be associated with bronchiolitis. Further studies are needed to explore the association between SARS-CoV-2 and bronchiolitis.

Acknowledgements. None

Funding. The study was supported by a grant of the Italian ministry of Education and University (PRIN 2017 2017HWPZZZ) and one the Italian ministry of Health (Ricerca Corrente 2019).

Disclaimer. The funding agencies had no role in study design, data collection, analysis or interpretation, or writing of the report

Authors contribution. All authors contributed to the study design. GPM, LR, SB, RP contributed to data collection. GL, FR, LD, GL, AL contributed to data analysis, VB, CG, Cam PM contributed to data interpretation. GPM, VB, PM wrote the first draft of the manuscript. LR, SB, RP, FR, LD, GL, AL CA reviewed the first draft of the manuscript. All authors approved the manuscript as submitted.

Potential conflict of interest. none for all authors.

What is already known?

- In December 2019, the first cluster of pneumonia of unknown etiology was reported by Chinese health authorities in Wuhan
- It has been speculated that the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) was already spread in Western Countries before February 2020, especially among children

What this study adds?

- The hypothesis that SARS-CoV-2 was already circulating among infants with bronchiolitis and asymptomatic infants before the official outbreak of SARS-CoV-2 infection is not supported by this study
- For the first time, an association between SARS-CoV-2 and bronchiolitis is reported

References

1. Valenti L, Bergna A, Pelusi S, et al. SARS-CoV-2 seroprevalence trends in healthy blood donors during the COVID-19 Milan outbreak. *medRxiv* 2020: 2020.05.11.20098442.
2. Rabbat A, Huchon GJ. Nonbacterial Pneumonia. *Clinical Respiratory Medicine* 2008: 351-64.
3. Milani GP, Plebani AM, Arturi E, et al. Using a high-flow nasal cannula provided superior results to low-flow oxygen delivery in moderate to severe bronchiolitis. *Acta Paediatrica* 2016; **105**: E368-E72.
4. Kelvin AA, Halperin S. COVID-19 in children: the link in the transmission chain. *Lancet Infect Dis* 2020; **20**: 633-4.
5. Mansbach JM, Hasegawa K, Piedra PA, Sullivan AF, Camargo CA. Severe Coronavirus Bronchiolitis in the Pre-COVID-19 Era. *Pediatrics* 2020; **146**; e20201267

Table 1. Characteristics of infants with Severe Acute Respiratory Syndrome Coronavirus-2 and bronchiolitis on admission.

	Patient 1	Patient 2
Age (months)	5.0	3.5
Gender	male	male
Gestational age at birth (weeks)	39	41
Respiratory rate, frequency/min	64	55
O ₂ -saturation in room air	88%	89%
Thoracic retractions	present and associated with nasal flare	present
Ability to feed	reduced	reduced
Bronchiolitis severity score*	7 (severe)	5 (moderate)
Need for intensive care	No	No
Length of hospital stay (days)	9	4

*The bronchiolitis severity score at the admission includes the following parameters: respiratory rate (< 45/min = 0; 45–60/ min = 1; > 60/min = 2), O₂-saturation in room air (> 95% = 0; 95– 90% = 1; < 90% = 2), presence of thoracic retractions (none = 0; present = 1; present and associated with nasal flare = 2) and ability to feed (normal = 0; reduced = 1; strongly reduced = 2). A severity score ≤3 identifies a mild, 4 to 6 a moderate and 7 to 8 a severe bronchiolitis.³

FIGURE LEGEND

Figure 1. Flow chart of subject enrollment.

