SARS-CoV-2-related bronchiolitis: a multicentre international study

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ABSTRACT

Background Bronchiolitis is the main acute lower respiratory tract infection in infants. Data regarding SARS-CoV-2-related bronchiolitis are limited.

Objective To describe the main clinical characteristics of infants with SARS-CoV-2-related bronchiolitis in comparison with infants with bronchiolitis associated with other viruses.

Setting, patients, interventions A multicentre retrospective study was conducted in 22 paediatric emergency departments (PED) in Europe and Israel. Infants diagnosed with bronchiolitis, who had a test for SARS-CoV-2 and were kept in clinical observation in the PED or admitted to hospital from 1 May 2021 to 28 February 2022 were considered eligible for participation. Demographic and clinical data, diagnostic tests, treatments and outcomes were collected.

Main outcome measures The main outcome was the need for respiratory support in infants testing positive for SARS-CoV-2 compared with infants testing negative.

Results 2004 infants with bronchiolitis were enrolled. Of these, 95 (4.7%) tested positive for SARS-CoV-2. Median age, gender, weight, history of prematurity and presence of comorbidities did not differ between the SARS-CoV-2-positive and SARS-CoV-2-negative infants. Human metapneumovirus and respiratory syncytial virus were the viruses most frequently detected in the group of infants negative for SARS-CoV-2.

Infants testing positive for SARS-CoV-2 received oxygen supplementation less frequently compared with SARS-CoV-2-negative patients, 37 (39%) vs 1076 (56.4%), p=0.001, OR 0.49 (95% CI 0.32 to 0.75). They received less ventilatory support: 12 (12.6%) high flow nasal cannulae vs 468 (24.5%), p=0.01; 1 (1.0%) continuous positive airway pressure vs 125 (6.6%), p=0.03, OR 0.48 (95% CI 0.27 to 0.85).

Conclusions SARS-CoV-2 rarely causes bronchiolitis in infants. SARS-CoV-2-related bronchiolitis mostly has a mild clinical course.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Bronchiolitis is one of the most common viral acute lower respiratory tract infections in infants and among the leading causes of hospitalisation in this age group.
⇒ Respiratory syncytial virus (RSV) causes most bronchiolitis requiring hospital admission, but other respiratory viruses can be involved.
⇒ To date, data about SARS-CoV-2-related bronchiolitis are limited.

WHAT THIS STUDY ADDS

⇒ This multicentre international study finds that SARS-CoV-2 rarely causes bronchiolitis in infants requiring hospitalisation.
⇒ SARS-CoV-2-related bronchiolitis had a mild clinical course, with only a minority of patients needing oxygen supplementation or ventilatory support.
⇒ SARS-CoV-2-positive infants had a lower risk of requiring oxygen supplementation or ventilatory support compared with RSV-positive infants.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The impact of bronchiolitis on healthcare systems makes the description of the clinical course of forms related to new aetiological agents crucial.
⇒ The results of this multicentre international study add to the knowledge of the natural history of the respiratory involvement sustained by SARS-CoV-2 in infants.

INTRODUCTION

The social distancing measures adopted in most countries since 2020 to control the spread of SARS-CoV-2 had a significant impact on the seasonal epidemics of winter respiratory infections in the paediatric population. During the 2020–2021 winter season, social distancing and face mask wearing dramatically decreased the circulation of several respiratory viruses, mainly respiratory syncytial virus (RSV) and influenza virus, leading to the disappearance of seasonal epidemics in young children.[1] This led to a drop in the number of

infants hospitalised for bronchiolitis, the most common acute lower respiratory tract infection in infants, mainly caused by viral infections.[2–5]

Following the relaxation of social distancing measures, an out-of-season rebound of RSV infections has been reported in several countries worldwide.[6 7] An epidemic of RSV infection took place in Europe during autumn 2021.[8–11]

Data on SARS-CoV-2 infection in infants suggest that in most cases it presents as a mild disease.[12] In particular, a multicentre international study showed that only 3% of infants testing positive for SARS-CoV-2 developed symptoms consistent with bronchiolitis.[3] In the same study, SARS-CoV-2-related bronchiolitis mostly had a mild clinical course, but the number of affected infants was considerably limited.

Therefore, the aim of this study was to further describe the clinical characteristics of infants with SARS-CoV-2-related bronchiolitis, and in particular the need for ventilatory support and the need for oxygen supplementation, in comparison with bronchiolitis associated with other viruses.

PATIENTS AND METHODS

A multicentre international retrospective cross-sectional study was conducted involving 22 centres, 13 in Italy, 4 in Switzerland, 1 in the UK, 1 in Slovenia, 1 in Serbia, 1 in Greece and 1 in Israel.

Enrolment took place from 1 May 2021 to 28 February 2022.

Eligible patients were infants who received a diagnosis of bronchiolitis at the paediatric emergency department (PED).

Inclusion criteria were: age between 0 and 11 months, clinical diagnosis of bronchiolitis based on the current international guidelines,[13–15] clinical observation in the PED or admission to the hospital and the availability of a SARS-CoV-2 antigen or molecular test result.

Clinical criteria for the diagnosis of bronchiolitis were the presence of rhinorrhoea, cough, fever and signs of respiratory distress, such as high respiratory rate for age, use of accessory respiratory muscles, intercostal retractions, nasal flaring, crackles or wheeze and eventual low oxygen saturation levels.

Exclusion criteria were: age older than 11 months, discharge from the PED without clinical observation and the unavailability of a SARS-CoV-2 test result. Infants previously enrolled in the study were excluded from participation if they presented with a further episode of bronchiolitis.

The medical electronic database of each centre was searched for the International Classification of Diseases ninth revision (ICD-9) codes 466.11 and 466.19 or ICD-10 codes J21.0 and J21.9.

Data were recorded within an electronic database through the Research Electronic Data Capture tools based at the Institute for Maternal and Child Health IRCCS Burlo Garofolo.[16 17]

For each enrolled patient, the following data were collected: age, gender, presence of comorbidities; diagnostic tests performed such as blood tests, chest X-ray, chest CT and nasal or nasopharyngeal swab; treatments provided including nutritional support (feeding and/or hydration), drugs administration, oxygen supplementation and respiratory support, such as high flow nasal cannulae (HFNC), continuous positive airway pressure (CPAP), non-invasive ventilation (NIV) and mechanical ventilation; admission status and length of hospitalisation.

The participating centres provided data about the overall number of attendances, of attending infants and of infants tested positive for SARS-CoV-2 at the PED during the study period.

SARS-CoV-2 positivity was detected through an antigen or molecular test, performed on a nasal or nasopharyngeal swab at the PED or during hospitalisation.

The primary study outcome was the need for respiratory support in infants positive for SARS-CoV-2 compared with infants who were negative. Secondary outcomes were: need for oxygen supplementation, nutritional support, rate of hospitalisation, admission to intensive care unit (ICU) facilities, either neonatal (NICU) or paediatric (PICU), length of hospitalisation and death in the two groups of patients.

Statistical analysis

The main characteristics of the study population were analysed with frequency and percentage for categorical variables and with median and IQR for continuous variables. Differences between SARS-CoV-2-positive bronchiolitis and bronchiolitis unrelated to SARS-CoV-2 were analysed by the χ^2 test or the Fisher's exact test, when appropriate for categorical variables, and by the non-parametric Mann-Whitney U test for continuous variables. Univariate and multivariate logistic regression models were constructed using oxygen supplementation or ventilatory support as dependent variables while SARS-CoV-2, RSV, human metapneumovirus and rhinovirus positivity were included as independent variables. All analyses were conducted using SAS software, V.9.4 (SAS Institute, Cary, North Carolina, USA), and a p value <0.05 was considered statistically significant.

RESULTS

From May 2021 to February 2022, 366 700 children were assessed at the PED of the participating centres, including 59 737 infants. Among infants, 2004 received a diagnosis of bronchiolitis, and were either observed in the PED or hospitalised. During the same period, 2801 infants who attended the PED tested positive for SARS-CoV-2. Among infants positive for SARS-CoV-2, 95 (3.3%) received a diagnosis of bronchiolitis. These 95 infants represented the 4.7% of the overall number of infants diagnosed with bronchiolitis.

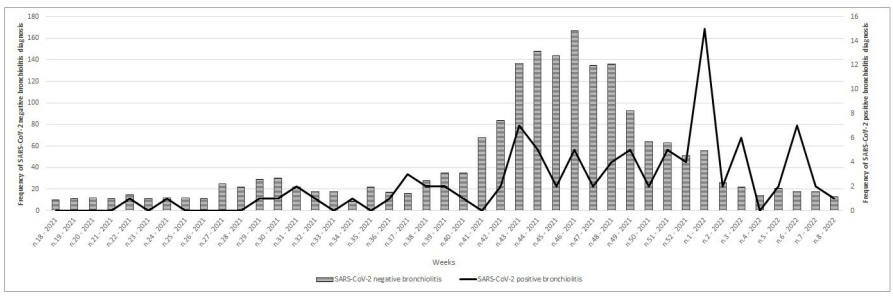

Figure 1 Distribution of the cases of bronchiolitis testing positive and negative for SARS-CoV-2 during the study period.

Table 1 Main demographic and clinical characteristics of the enrolled infants with bronchiolitis

	SARS-CoV-2-positive bronchiolitis (n=95)	SARS-CoV-2-negative bronchiolitis (n=1909)	P value
Age in months, median (IQR)	3 (1.5–4.5)	2.1 (1–5)	0.44
Male sex, n (%)	60 (63.2)	1107 (58.0)	0.32
Weight in kg, median (IQR)	5.1 (4.3–6.9)	5.4 (4.3–7)	0.21
Ethnicity, n (%)			0.02*
Caucasian	84 (88.4)	1576 (82.6)	
Asian	3 (3.2)	217 (11.4)	
African	6 (6.3)	98 (5.1)	
Other	2 (2.1)	18 (0.9)	
History of prematurity, n (%)	14 (14.7)	217 (14.7)	0.32
Presence of at least one comorbidity, n (%)	12 (12.6)	216 (11.3)	0.69
Congenital heart disease	3 (3.2)	83 (4.3)	0.80*
Chronic pulmonary disease	3 (3.2)	34 (1.8)	0.26*
Genetic syndrome	2 (2.1)	37 (1.9)	0.71*
Other comorbidities	8 (8.4)	120 (6.3)	0.41
Positivity for viruses other than SARS-CoV-2, n (%)	7 (7.4)	154 (8.1)	–
Human metapneumovirus	1 (14.3)	57 (37.0)	
Respiratory syncytial virus	1 (14.3)	56 (36.4)	
Rhinovirus	1 (14.3)	50 (33.3)	
Enterovirus	1 (14.3)	34 (22.7)	
Parainfluenza viruses 1–4	1 (14.3)	30 (20.0)	
Other coronaviruses	1 (14.3)	17 (11.3)	
Bocavirus	1 (14.3)	13 (8.7)	
Adenovirus	0	8 (5.3)	
Influenza A	0	2 (1.3)	

*Fisher's exact test.

Table 2 Diagnostic tests, treatment and outcomes of infants with bronchiolitis

	SARS-CoV-2-positive bronchiolitis (n=95)	SARS-CoV-2-negative bronchiolitis (n=1909)	P value
Diagnostic tests, n (%)			
Blood tests	64 (67.4)	1416 (74.2)	0.14
Chest X-ray	29 (30.5)	562 (29.4)	0.82
Chest CT scan	0 (0.0)	2 (0.1)	1.0*
Treatment received, n (%)			
Oxygen supplementation	37 (39.0)	1076 (56.4)	0.001
Any non-invasive respiratory support	13 (13.7)	509 (26.7)	0.01
HFNC	12 (12.6)	468 (24.5)	0.01
CPAP	1 (1.0)	125 (6.6)	0.03*
NIV	0 (0.0)	19 (1.0)	1.0*
Mechanical ventilation	0 (0.0)	31 (1.6)	0.40*
Nutritional support	47 (49.5)	897 (47.0)	0.64
Pharmacological therapies, n (%)			
Inhaled albuterol	26 (27.4)	676 (35.4)	0.11
Inhaled epinephrine	20 (21.0)	286 (15.0)	0.11
Antibiotic	19 (20.0)	462 (24.2)	0.35
Inhaled hypertonic solution	18 (19.0)	401 (21.0)	0.63
Systemic steroids	10 (10.5)	400 (20.9)	0.01
Inhaled steroids	7 (7.4)	127 (6.7)	0.79
Other drugs	10 (10.5)	181 (9.5)	0.74
Outcome, n (%)			
Short observation in the PED	28 (29.5)	490 (25.7)	0.41
Admission to the paediatric ward	54 (56.9)	1215 (63.7)	0.18
Admission to NICU or PICU	5 (5.3)	140 (7.3)	0.45
Other	8 (8.4)	64 (3.4)	0.01
Death	0 (0.0)	1 (0.1)	1.0*
Days of hospitalisation, median (IQR)	3 (1–5)	4 (2–6)	0.2

*Fisher's exact test.
CPAP, continuous positive airway pressure; HFNC, high flow nasal cannulae; NICU, neonatal intensive care unit; NIV, non-invasive ventilation; PED, paediatric emergency departments; PICU, paediatric intensive care unit.

Figure 1 shows the distribution of the cases of bronchiolitis testing positive and negative for SARS-CoV-2 during the study period.

Table 1 describes the main demographic and clinical characteristics of the infants with bronchiolitis.

The main clinical characteristics of infants with bronchiolitis who tested positive and negative for SARS-CoV-2 were statistically similar. The median age was 3 months (IQR 1.5–4.5) and 2.1 months (IQR 1–5), respectively, p=0.44. Gender, weight, history of prematurity and presence of comorbidities did not differ between the two groups. Seven co-infections with an additional respiratory virus were found in five infants in the SARS-CoV-2 group. In infants negative for SARS-CoV-2, the respiratory viruses detected most frequently were: human metapneumovirus (HMPV) (37.0%), RSV (36.4%) and rhinovirus (33.3%).

Table 2 summarises the diagnostic tests performed, the treatments received and the outcome of the infants with bronchiolitis who tested positive and negative for SARS-CoV-2.

Infants with bronchiolitis positive for SARS-CoV-2 were provided significantly less oxygen supplementation compared with SARS-CoV-2-negative patients, 37 (39%) vs 1076 (56.4%), respectively, p=0.001. Similarly, they received less non-invasive respiratory support: specifically 12 (12.6%) were provided HFNC vs 468 (24.5%), p=0.01, while 1 infant (1.0%) positive for SARS-CoV-2 had CPAP vs 125 (6.6%), p=0.03. Notably, the infant who received CPAP support in the SARS-CoV-2 group was coinfected with RSV.

SARS-CoV-2-positive infants had a lower probability of requiring oxygen supplementation compared with infants with bronchiolitis related to other viruses, OR 0.49 (95% CI 0.32 to 0.75). In the same way, they had a lower probability of requiring ventilatory support, OR 0.48 (95% CI 0.27 to 0.85). Among infants who were positive for other viruses, the multivariate analysis showed that infants positive for RSV had a higher risk to receive oxygen supplementation and ventilatory support (table 3).

Nutritional support was provided to 47 (49.5%) SARS-CoV-2-positive infants and 897 (47%) patients in the negative group, p=0.64.

Infants positive for SARS-CoV-2 did not have diagnostic tests and/or pharmacological therapies more frequently, than SARS-CoV-2-negative patients.

Five infants (5.3%) positive for SARS-CoV-2 were admitted to NICU or PICU compared with 140 (7.3%) in the SARS-CoV-2-negative group, p=0.45.

Among admitted infants, the median length of hospitalisation was statistically similar between patients who tested positive and

Table 3 Multivariate analysis for the need of oxygen supplementation and ventilatory support related to viral aetiology

		Univariate			Multivariate		
			95% CI			95% CI	
Outcome	Viral aetiology	OR	Lower	Upper	OR	Lower	Upper
Oxygen supplementation	SARS-CoV-2	0.49	0.32	0.75			
	Rhinovirus*	0.85	0.41	1.76	0.81	0.38	1.70
	RSV*	2.06	0.95	4.49	2.48	1.02	6.03
	HMPV*	0.91	0.44	1.86	1.38	0.60	3.14
Ventilatory support	SARS-CoV-2	0.48	0.27	0.85			
	Rhinovirus*	0.91	0.46	1.82	0.87	0.43	1.74
	RSV*	1.74	0.89	3.41	1.73	0.78	3.84
	HMPV*	0.73	0.37	1.44	0.96	0.43	2.17

*OR calculated among the infants with viral positivity other than SARS-CoV-2.
HMPV, human metapneumovirus; RSV, respiratory syncytial virus.

negative for SARS-CoV-2, 3 days (IQR 1–5) and 4 days (IQR 2–6), respectively, p=0.2.

No infants positive for SARS-CoV-2 died. One infant negative for SARS-CoV-2, with prematurity and chronic pulmonary disease, died.

DISCUSSION

This multicentre international study shows that SARS-CoV-2 can cause bronchiolitis, but this is limited to a minority of infected infants. In the analysed population, only 4.7% of infants with bronchiolitis tested positive for SARS-CoV-2 and only 3.3% of infants positive for SARS-CoV-2 developed bronchiolitis, confirming the data of a previous study, showing a prevalence of bronchiolitis in a population of SARS-CoV-2-positive infants of 3%.[3]

This study collected the largest sample of infants with SARS-CoV-2-related bronchiolitis available so far. Analysing a population of 59 737 infants attending the PED, with 2801 infants positive for SARS-CoV-2, 95 cases of SARS-CoV-2-related bronchiolitis were described, while previous case series were limited to a maximum of 16 patients.[3 18 19] Moreover, the analysis of 2004 cases of bronchiolitis overall, further strengthened the results.

Bronchiolitis is one of the most common viral acute lower respiratory tract infections in infants and among the leading causes of hospitalisation in this age group.[20 21] Its impact on healthcare systems during epidemics makes the description of the clinical course of bronchiolitis related to new aetiological agents crucial.

The results of the present study adds to the knowledge of the natural history of the respiratory involvement associated with SARS-CoV-2 in infants, which appears significantly milder than in adults.[22]

In this study, infants with SARS-CoV-2-related bronchiolitis had a milder clinical course compared with infants with bronchiolitis associated with other viruses, showing a lower risk of requiring oxygen supplementation and respiratory support. Only 39% of hospitalised infants with SARS-CoV-2-related bronchiolitis needed oxygen supplementation compared with 56.4% of infants with bronchiolitis negative for SARS-CoV-2. Notably, only 12.6% received HFNC and 1% CPAP, compared with 24.5% and 6.6%, respectively, in the group of children with bronchiolitis sustained by other viruses. Moreover, the only infant who received CPAP support in the SARS-CoV-2 group was co-infected with RSV, suggesting the influence of RSV on the outcome. These data confirm the mild clinical course of the disease in the context of the recent widespread use of HFNC in patients with bronchiolitis, and are consistent with a multicentre Italian study showing an additional increase of HFNC use from the beginning of the pandemic.[23] Moreover, in this study, infants with bronchiolitis testing positive for SARS-CoV-2 needed admission to ICU facilities significantly less frequently than infants negative for SARS-CoV-2, 5.3% vs 7.3%, respectively.

In this study, the viral aetiology of bronchiolitis was defined only in a limited number of patients. The most frequently isolated viruses were HMPV, RSV and rhinovirus. Nevertheless, the study was conducted during a period of time in which the reduction of the measures aimed at containing the spread of SARS-CoV-2 in Europe, led to an unprecedented surge of RSV infections in infants.[8–11 24] Therefore, we can assume a considerable role of RSV in infants with bronchiolitis testing negative for SARS-CoV-2. Moreover, figure 1 clearly shows that, comparing the group of infants positive for SARS-CoV-2 and the group negative, the major amount of cases were collected in different weeks, suggesting a limited role of co-infections in the SARS-CoV-2 group. To our knowledge, this is the first study that compared the clinical course of SARS-CoV-2-related and unrelated bronchiolitis during an RSV epidemic. Previous studies[3 18] were conducted during the winter season 2020–2021, when a dramatic drop in respiratory infections in general, and in particular RSV, was observed. In the above winter season, respiratory infections in children were mainly associated with rhinovirus,[3 24] and therefore, comparisons were mainly possible with rhinovirus-related bronchiolitis. In our population, infants positive for RSV had a higher risk of requiring oxygen supplementation and ventilatory support compared both with SARS-CoV-2-positive and rhinovirus-positive infants.

Although the available international guidelines[13–15] state the treatment of bronchiolitis should be supportive, in this study, a significant number of patients received pharmacological therapies. This decision is often made on an individual basis and/or single-centre protocols, as previously reported.[25] However, the frequency of their administration did not appear to be affected by the viral tests result. Infants positive for SARS-CoV-2 did not undergo more diagnostic tests, nor receive more pharmacological therapies than patients with bronchiolitis associated with other viruses. Infants with SARS-CoV-2-related bronchiolitis were hospitalised a median 1 day less than patients with bronchiolitis unrelated to SARS-CoV-2, further suggesting a milder clinical course; however, this difference was not statistically significant.

This study has several limitations. Due to the study design, some cases may have been missed or mislabelled. Screening for SARS-CoV-2 was not homogeneous among centres, some centres using antigen tests and others molecular tests. Moreover, viral detection through nasal and nasopharyngeal swabs was performed in accordance with local practices, and no common diagnostic panels were used. Several centres did not routinely use a multiviral diagnostic panel for infants with bronchiolitis, so we were only able to identify the viral aetiology of bronchiolitis in a limited number of patients. Moreover, we did not collect data about the number of infants seen with viral infections other than SARS-CoV-2. Therefore, we cannot provide the total number of infants with viral infections during the study period. However, previous studies showed that viral swabs in children with bronchiolitis may not be able to identify all the potentially involved viral agents.[26] We cannot exclude that some patients testing positive for SARS-CoV-2 had an unidentified co-infection that may have influenced the clinical course, and on the other side we cannot exclude that some cases of SARS-CoV-2-related bronchiolitis were mislabelled. However, among infants who had a multiviral test which was positive for other viruses, the presence of a co-infection with SARS-CoV-2 was uncommon, as shown in table 1. Considering also, as already mentioned, the different peak of cases of bronchiolitis related to SARS-CoV-2 during the period, we can presume that the influence of co-infections on our results was limited. This study was performed during the spread of SARS-CoV-2 Delta and Omicron genetic variants through Europe. We can presume that the cases of SARS-CoV-2-related bronchiolitis in this study were sustained by those variants, but no genetic data were collected.

In conclusion, this large multicentre international study showed that SARS-CoV-2 in infants is uncommonly associated with the development of symptoms suggestive of bronchiolitis requiring hospital admission. Infants who developed a SARS-CoV-2-related bronchiolitis had a mild clinical course, with a minority of cases needing respiratory support and admission to intensive care. Nevertheless, continuous surveillance remains mandatory to describe the role of new SARS-CoV-2 variants in the development of this disease.

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