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Influence of the COVID outbreak on infants' hospitalization for acute bronchiolitis

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Abstract

Objective. Acute bronchiolitis is a major public health issue with high number of infants hospitalized worldwide each year. In France, hospitalizations mostly occur between October and March, and peak in December. A reduction of emergency visits for bronchiolitis has been observed at onset of the COVID outbreak. We aimed to assess the pandemic effects on the hospitalizations for bronchiolitis during the 2020-2021 winter (COVID-period) compared to 3 previous winters (pre-COVID).

Study design. We reviewed the medical records of all infants aged under 12-months, hospitalized for acute bronchiolitis in our pediatric hospital in Paris during the autumn/winter seasons (October 1-March 31) from 2017 to 2021. Clinical and laboratory data were collected using standardized forms.

Results. During the COVID-period was observed a 54.3% reduction in hospitalizations for bronchiolitis associated with a delayed peak (February instead of November-December). Clinical characteristics and hospitalization courses were substantially similar. The differences during the COVID period were: smaller proportion of infants with comorbidities, lower need for oxygen, higher proportions of Metapneumovirus, Parainfluenzae 3, Bocavirus, Coronavirus NL63 and OC43, and no Influenza. The three infants positive for SARS-CoV-2 were also positive for RSV, suggesting that SARS-CoV-2 alone does not cause bronchiolitis, despite previous assumptions.

Conclusions. The dramatic reduction in infants' hospitalizations for acute bronchiolitis is an opportunity to change our future habits: advising the population to wear masks and apply additional hygiene measures in case of respiratory tract infections. This may drastically change the worldwide bronchiolitis burden and improve children outcomes, as severe broncholitis in early childhood is associated with long-term morbidities.

Article Summary

Strengths and limitations of this study

- The vast majority of infants admitted to our pediatric hospital between 2017 and 2021 for acute bronchiolitis in their first year after birth will have been identified.
- The clinical and viral characteristics of these infants hospitalized during the COVID-epidemic season 2020-2021 were compared to those of 3 previous winters.
- Three physicians independently reviewed the medical records to collect clinical data and laboratory tests results using a standardized specific form.
- The decrease in the number of hospitalizations may have been partly the consequence of a decrease in the overall number of emergency room visits at the start of the COVID-19 pandemic.

Introduction

In autumn and winter in the northern hemisphere, community medicine (pediatricians and general practitioners), as well as emergency and general pediatric departments, are usually overwhelmed by children, especially infants, with acute bronchiolitis (1, 2). Hospital pediatric inpatient departments have to reorganize every winter to handle the high number of infants with this acute lower respiratory infection (ALRI), mostly due to the respiratory syncytial virus (RSV) (1-5). Neonates and young infants often require hospitalization in general wards, and some even require ICU care (2, 6). Moreover, RSV is the third leading cause of death in children aged below 5 years (from ALRI, after pneumonia), secondary to *Streptococcus pneumonia* and *Haemophilus influenzae* type b (2). Acute bronchiolitis is thus a yearly worldwide public health issue. In France, similar epidemic patterns are seen each year with a large majority of hospitalizations between October and March, with a peak in December (7). Management is largely supportive, focusing on maintaining oxygenation and hydration.

The emergence of the coronavirus disease 2019 (COVID-19) pandemic and the global public health responses related to this pandemic have influenced the viruses' epidemiology. A striking reduction of admission for ALRIs in pediatric ICUs was observed during the winter 2020 in the southern hemisphere (8). In France, collective measures to contain the pandemic have been implemented since mid-March 2020, namely lockdowns, curfews, social distancing, requirement of masks, strict hand hygiene, and restriction of commerce activities. We observed a reduction in the visits to the pediatric emergency department of our hospital for bronchiolitis in the autumn 2020 (9). Here, we aimed to assess the effects of the COVID-19 pandemic on the clinical and viral characteristics of infants hospitalized for bronchiolitis during the epidemic season 2020-2021 (COVID period) compared to previous winters (pre-COVID period).

Methods

Study design and patients

We retrospectively reviewed the records of all infants aged less than 12 months, hospitalized for acute bronchiolitis in our tertiary university pediatric hospital in Paris (France) during the autumn/winter seasons (October 1 to March 31) from 2017 to 2021 (*i.e.,* 2017-2018; 2018-2019; 2019-2020; and 2020-2021). The study was approved by the local ethics committee of our institution, which waived the need for patient consent (study BronChioVID N°20201119185601).

Patient's selection was performed using the ICD10 code diagnoses of bronchiolitis (J21.0, J21.1, J21.8, and J21.9). Three physicians reviewed the medical records to collect clinical data and laboratory tests results using a standardized specific form. PCR in nasopharyngeal swabs or aspirates for virus identification were performed using Allplex™ Respiratory Panel Assays (Seegene), and/or Simplexa™ Flu A/B & RSV Direct Gen II Kit (Diasorin Molecular).

Statistical analysis

Patients' characteristics were described using means and percentages. We compared the patients' characteristics between the pre-COVID periods, defined as October 1 to March 31 2017-2018, 2018-2019, and 2019-2020, with those of the COVID period, defined as October 1, 2020 to March 31, 2021. This was done using chi2 and t-tests. The analyses were performed using STATA 14.2.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Number of hospitalizations

Over the pre-COVID period, 1,347 infants were hospitalized for bronchiolitis in our hospital, with a mean of 449 infants per year, compared to 205 infants during the COVID period; which corresponds to a 54.3% reduction in the number of hospitalizations (**Table 1**). As shown in **Figure 1**, the bronchiolitis outbreak was delayed during the COVID period, with a peak in the hospitalizations in February, compared to the usual peaks in November-December during the pre-COVID periods.

Characteristics of the patients

The clinical characteristics of the infants hospitalized for bronchiolitis are shown in **Table 1**. The age distribution and the sex ratio were not significantly different between the pre-COVID and the COVID periods ($p = 0.3$ and 0.5 respectively). During the pre-COVID periods, 14% of the infants presented with comorbidities (with 11% of preterm), whereas only 8% had comorbidities during the COVID period, ($p = 0.02$).

The number of infants who received oxygen therapy was significantly lower during the COVID period than during the pre-COVID period (45% vs 55% respectively, $p = 0.01$). There were no significant differences between the pre-COVID and the COVID periods regarding the length of hospitalization ($p = 0.8$), the number of patients transferred to a pediatric ICU ($p = 0.6$), and the need for non-invasive ($p = 0.9$) or invasive ventilation ($p = 0.6$).

Viral epidemiology

PCR in nasopharyngeal swabs for virus identification were performed increasingly across the years ($p < 0.01$) (**Table 2**). RSV remains the most common virus found (74%), followed by Rhinovirus and Adenovirus (**Table 2**). The RSV outbreak was significantly

delayed during the COVID period compared to the previous winters, with a plateau between January and March 2021, compared to peaks in November-December during the pre-COVID periods (**Figure 1**).

The proportion of the following viruses was significantly higher during the COVID period than during the pre-COVID period: Metapneumovirus ($p = 0.001$), Parainfluenzae 3 ($p < 0.01$), Bocavirus ($p = 0.001$), Coronavirus OC43 ($p < 0.01$) and NL63 ($p < 0.01$) (**Table 2**). No Influenza (A and B) was found during the COVID period. Only 3 infants with bronchiolitis had a PCR positive for SARS-CoV-2 in nasopharyngeal swabs during the COVID period, but all 3 were also positive for RSV.

Discussion

This study highlights the dramatic reduction in the number of infants who required a hospitalization for acute bronchiolitis during the COVID-19 outbreak compared to the three previous years. The outbreak of acute bronchiolitis was not only smaller, but also delayed by several weeks. The clinical characteristics of the infants hospitalized for acute bronchiolitis as well as the hospitalization courses were substantially similar during pre-COVID and COVID periods. While the proportions of RSV and Rhinovirus were similar between both periods, those of Metapneumovirus, Parainfluenzae 3, Bocavirus, Coronavirus NL63 and Coronavirus OC43 increased during the COVID pandemic. Interestingly, during the COVID period, no Influenza was found and the only 3 infants with a PCR positive for SARS-CoV-2 were also positive for RSV, suggesting that SARS-CoV-2 alone does not cause bronchiolitis.

This winter, we observed a strong decrease in the number of hospitalizations for acute bronchiolitis. This observation is consistent with data from Australia and South America (10, 11). Two recent studies confirm our findings and suggest that social distancing and other lockdown strategies are effective in slowing down the spreading of respiratory diseases and decreasing the need for hospitalization among children (12, 13). Indeed, after reaching France on January 2020, a major progression of COVID-19 led to public health prevention interventions. The first national lockdown officially started on March 17, 2020 and ended on May 10, 2020. Masks had to be worn by persons 11 years of age and older in enclosed public places as of July 20, 2020. As shown in this study, the number of hospitalizations for acute bronchiolitis has therefore drastically decreased, even while schools and nurseries have remained open during winter. A recent publication shows the extent to which transmission of common pediatric infections can be altered when close contact with other children is eliminated (14). However, in our study, infants hospitalized for acute bronchiolitis had a mean age of 3.5 months, so a majority of these infants were not yet in collective nurseries, but were at home

with their mothers (who were on maternity leave). Moreover, since September 2020, professionals in nurseries are required to wear a mask in the presence of children. It can therefore be suggested that the RSV transmission to these young children can also occur through their parents or older siblings. Intriguingly, we observed a lower proportion of infants with comorbidities hospitalized during the COVID period. This could be due to the fact that parents have protected these at-risk children much more for fear that they would develop severe infections during the pandemic period.

The outbreak of acute bronchiolitis was not only lower, but was also delayed by several weeks. Besides, RSV emerged in January, after the Christmas break. One explanation might be that families got together during this celebration break, and social distancing measures might have been followed less strictly. Interestingly, we observed that while the proportions of RSV and Rhinovirus were similar to that of previous years during the COVID-19 period, those of Parainfluenzae 3, Bocavirus, Coronavirus NL63 and Coronavirus OC43 were higher. Our results on the prevalence of the various respiratory viruses during the pre-COVID period are in agreement with the literature (15). Moreover, during the COVID period, no Influenza was found, suggestive that this virus is sensitive to the hygiene measures adopted during the pandemic. A recent epidemiological study on common communicable diseases in the general population in France during the COVID pandemic also showed that patients who presented with ALRI symptoms and underwent a PCR test were most likely infected by Influenza in 2019, but by SARS-CoV-2 or Metapneumovirus in 2020 (16). Moreover, in contradiction to assumptions made at the pandemic onset, our data suggest that SARS-CoV-2 alone does not cause bronchiolitis, as the only 3 infants SARS-CoV-2 positive were also positive for RSV. It will be important to confirm these results in the future, especially if SARS-CoV-2 remains endemic in the years to come.

The high impact of bronchiolitis in terms of cost of hospitalization is not insignificant. In Italy, a recent study showed that the main cost item is related to young infants, in particular, those below 3 months of age, and RSV continues to be the main causative agent of severe bronchiolitis. They highlight that new vaccination strategies, such as the extension of immunoprophylaxis to infants (17), is essential. Therefore, it would be useful, after the COVID-19 pandemic, for adults to continue to wear masks and wash their hands regularly to mitigate the risk of transmission of respiratory infection to young children. Acute severe RSV bronchiolitis in early childhood is associated with long-term morbidities including recurrent wheezing, asthma, and lower lung function in later life (18). Therefore, the decrease in the number of severe bronchiolitis cases due to RSV or other viruses might not only have financial consequences, but also impact the long-term respiratory outcome of children.

We are aware of some limitations of our study. The decrease in the number of hospitalizations may have been partly the consequence of a decrease in the overall number of emergency room visits since the start of the COVID-19 pandemic. However, it is likely that, despite the COVID-19 pandemic, children with the most severe respiratory distress were still seen in the emergency room. In the UK, a significant reduction of non-urgent health care demands were observed during the pandemic and were associated with an increase in severe or urgent cases (19).

In conclusion, our work provides an overview of the infants' hospitalizations for acute bronchiolitis during the COVID period in the winter of 2020-2021. This dramatic reduction in infants' hospitalizations constitutes a great opportunity to change our habits for future autumn and winter seasons by advising people, especially adults, to wear masks and increase social distancing and hygiene measures in case of upper and lower respiratory tract infections. This may drastically change the worldwide burden of bronchiolitis and hospitalizations caused by

RSV in the future, as well have important implications for patient outcomes and prevalence of asthma in children (20).

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Contributors: LB and HC conceptualized and designed the study, collected the data, drafted the initial manuscript, and reviewed and revised the manuscript. RG designed the data collection, collected data, carried out the statistical analyses, and reviewed and revised the manuscript. ASR, SR, AS, MP, ML, RC participated in the study conceptualization and data collection. They also reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Tables

Table 1. Clinical characteristics of the infants hospitalized for acute bronchiolitis in a tertiary university pediatric hospital in Paris (France) between 2017 and 2021

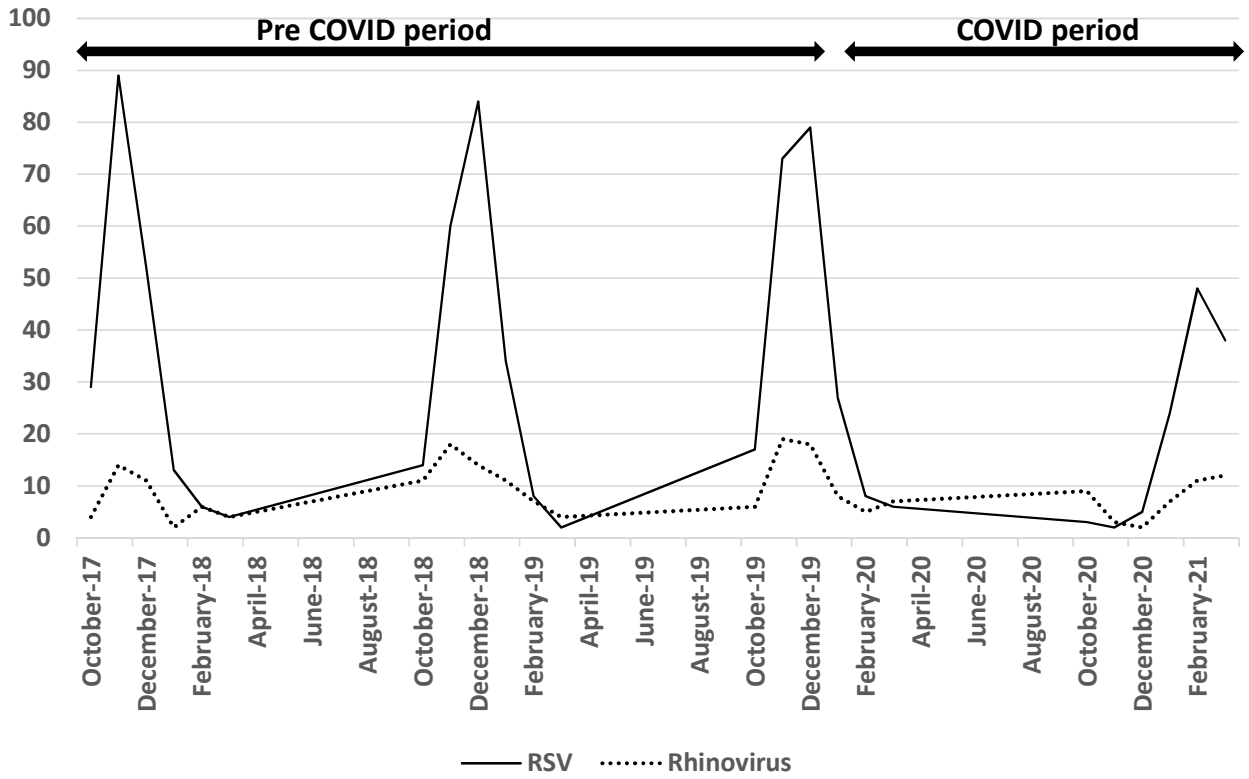
	Pre-COVID period				COVID period	
	2017-2018	**2018-2019**	**2019-2020**	**2017-2020 aggregated data**	**2020-2021**	**P-value***
Number of infants, n	**479**	**451**	**417**	**1347**	**205**	**-**
Age (months): mean ± SD	3.7 (± 3.3)	3.6 (± 3.2)	3.3 (± 2.9)	3.5	3.3 (± 2.2)	0.3
Gender: boys, n (%)	279 (58.2)	249 (55.2)	244 (58.5)	772 (57)	119 (58)	0.5
Co-morbidities, n (%)	66 (14)	66 (15)	53 (13)	185 (14)	16 (8)	**0.02**
Weight (kg): mean (± SD)	5.9 (± 3.4)	5.7 (±3.5)	5.6 (±3.1)	5.7 (3.2)	5.8 (±1.6)	0.2
Evolution						
Duration of hospitalization, days (± SD)	3.3 (± 4.7)	3.5 (± 2.4)	4.2 (± 3.7)	3.6 (±3.8)	3.4 (± 2.9)	0.8
Oxygen therapy, n (%)	259 (54)	237 (52)	257 (61)	753 (56)	93 (45)	**0.01**
ICU, n (%)	48 (13)	42 (9)	67 (16)	157 (12)	21 (11)	0.6
Non-invasive ventilation, n (%)	42 (8)	38 (8)	67 (16)	147 (11)	22 (12)	0.9
Invasive ventilation, n (%)	5 (1)	5 (1)	7 (1.6)	17 (1.2)	3 (1.7)	0.6
Extracorporeal circulation, n (%)	2 (0.4)	0 (0)	2 (0.4)	4 (0.2)	0 (0)	0.4

*P-value for the comparison between pre-COVID aggregated data and COVID

Table 2. Results of the PCR performed in nasopharyngeal swabs for virus identification in the infants hospitalized in pediatric general wards for acute bronchiolitis between 2017 and 2021

	Pre-COVID				Post-COVID	
	2017-2018	**2018-2019**	**2019-2020**	**2017-2020 aggregated data**	**2020-2021**	**P-value***
Number of infants, n	**479**	**451**	**417**	**1347**	**205**	
Nasal PCR, n (%)	**245 (51.1)**	**274 (60.7)**	**281 (67.4)**	**800 (59.4)**	**167 (74.2)**	**< 0.01**
RSV	193 (78)	202 (73)	211 (75)	606 (75)	120 (71)	0.3
Rhinovirus	41 (17)	65 (24)	63 (22)	169 (12)	44 (21)	0.1
Adenovirus	17 (7)	10 (4)	14 (5)	16 (11)	12 (7)	0.3
Metapneumovirus	17 (7)	10 (4)	10 (4)	37 (2.7)	19 (11)	**0.001**
Influenzae A	0 (0)	2 (0.4)	1 (0.2)	3 (0.2)	0 (0)	0.4
Influenzae B	0 (0)	2 (0.7)	1 (0.3)	3 (0.2)	0 (0)	0.4
Parainfluenzae 3	9 (4)	6 (2)	10 (4)	27 (2)	16 (10)	**< 0.01**
Bocavirus	6 (2)	11 (4)	7 (2)	24 (1.7)	14 (8)	**0.001**
SARS CoV-2	0 (0)	0 (0)	0 (0)	0 (0)	3 (2)	**0.02**
Coronavirus NL63	2 (0.8)	5 (2)	3 (1)	10 (0.7)	9 (5)	**< 0.01**
Coronavirus OC43	0 (0)	1 (0.3)	2 (0.7)	3 (0.2)	7 (4)	**< 0.01**
No PCR, n (%)	**234 (48.8)**	**177 (39)**	**136 (32)**	**547 (40)**	**38 (18)**	**< 0.01**

*P-value for the comparison between pre-COVID aggregated data and COVID


Pre COVID period
COVID period
100
90
80
70
60
50
40
30
20
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October-17
December-17
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RSV
Rhinovirus

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Abstract

Objectives. Acute bronchiolitis is a major public health issue with high number of infants hospitalised worldwide each year. In France, hospitalisations mostly occur between October and March, and peak in December. A reduction of emergency visits for bronchiolitis has been observed at onset of the COVID outbreak. We aimed to assess the pandemic effects on the hospitalisations for bronchiolitis during the 2020-2021 winter (COVID-period) compared to 3 previous winters (pre-COVID).

Design. Retrospective, observational and cross-sectional study.

Setting. Tertiary university paediatric hospital in Paris (France).

Participants. All infants aged under 12-months who were hospitalised for acute bronchiolitis during the autumn/winter seasons (October 1-March 31) from 2017 to 2021 were included. Clinical and laboratory data were collected using standardized forms.

Results. During the COVID-period was observed a 54.3% reduction in hospitalisations for bronchiolitis associated with a delayed peak (February instead of November-December). Clinical characteristics and hospitalisation courses were substantially similar. The differences during the COVID period were: smaller proportion of infants with comorbidities (14% *vs* 8% p = 0.02), lower need for oxygen (45% *vs* 55%, p = 0.01), higher proportions of Metapneumovirus, Parainfluenzae 3, Bocavirus, Coronavirus NL63 and OC43 (all $p \leq 0.01$), and no Influenza. The three infants positive for SARS-CoV-2 were also positive for RSV, suggesting that SARS-CoV-2 alone does not cause bronchiolitis, despite previous assumptions.

Conclusion. The dramatic reduction in infants' hospitalisations for acute bronchiolitis is an opportunity to change our future habits such as advising the population to wear masks and apply additional hygiene measures in case of respiratory tract infections. This may change the worldwide bronchiolitis burden and improve children respiratory outcomes.

Data availability statement: Data are available upon reasonable request.

Strengths and limitations of this study

- The vast majority of infants admitted to our paediatric hospital between 2017 and 2021 for acute bronchiolitis in their first year after birth will have been identified.
- The clinical and viral characteristics of these infants hospitalised during the COVID-epidemic season 2020-2021 were compared to those of 3 previous winters.
- Three physicians independently reviewed the medical records to collect clinical data and laboratory tests results using a standardized specific form.

Introduction

In autumn and winter in the northern hemisphere, community medicine (paediatricians and general practitioners), as well as emergency and general paediatric departments, are usually overwhelmed by children, especially infants, with acute bronchiolitis (1, 2). Hospital paediatric inpatient departments have to reorganize every winter to handle the high number of infants with this acute lower respiratory infection (ALRI), mostly due to the respiratory syncytial virus (RSV) (1-5). Neonates and young infants often require hospitalisation in general wards, and some even require intensive care unit (ICU) care (2, 6). Moreover, RSV is the third leading cause of death in children aged below 5 years (from ALRI, after pneumonia), secondary to *Streptococcus pneumonia* and *Haemophilus influenzae* type b (2). Acute bronchiolitis is thus a yearly worldwide public health issue. In France, similar epidemic patterns are seen each year with a large majority of hospitalisations between October and March, with a peak in December (7). Management is largely supportive, focusing on maintaining oxygenation and hydration.

The emergence of the coronavirus disease 2019 (COVID-19) pandemic and the global public health responses related to this pandemic have influenced the viruses' epidemiology. A striking reduction of admission for ALRIs in paediatric ICUs was observed during the winter 2020 in the southern hemisphere (8). In France, collective measures to contain the pandemic have been implemented since mid-March 2020, namely lockdowns, curfews, social distancing, requirement of masks, strict hand hygiene, and restriction of commerce activities. We observed a reduction in the visits to the paediatric emergency department of our hospital for bronchiolitis in the autumn 2020 (9). Here, we aimed to assess the effects of the COVID-19 pandemic on the clinical and viral characteristics of infants hospitalised for bronchiolitis during the epidemic season 2020-2021 (COVID period) compared to previous winters (pre-COVID period).

Methods

Study design and patients

This retrospective, observational and cross-sectional study was conducted in the Paediatric University Hospital Armand Trousseau, Assistance Publique Hôpitaux de Paris (APHP), in Paris (France). All infants aged less than 12 months, hospitalised for a first episode of acute bronchiolitis during the autumn/winter seasons (October 1 to March 31) from 2017 to 2021 (*i.e.,* 2017-2018; 2018-2019; 2019-2020; and 2020-2021) were included. Exclusion criteria were age over 12 months, a second episode (or more) of bronchiolitis, and/or an asthma attack. The study was approved by the Institutional Review Board of the French Society for Respiratory Medicine (*Société de Pneumologie de Langue Française,* #CEPRO_2020-080). In accordance with French laws for observational studies, the requirement for written informed consent was waived (study BronChioVID N°20201119185601).

Patient's selection was performed using the ICD10 code diagnoses of bronchiolitis (J21.0, J21.1, J21.8, and J21.9). Three physicians reviewed the medical records to collect demographic and clinical data as well as laboratory tests results using a standardized specific form. The demographic data collected comprised date of birth, gender and underlying conditions such as prematurity, bronchopulmonary dysplasia, intrauterine growth retardation, congenital heart disease, sickle cell disease, and genetic disease. The clinical data collected at the time of the bronchiolitis episode included date, age, weight, results of the PCR in nasopharyngeal swabs or aspirates for virus identification (Allplex™ Respiratory Panel Assays [Seegene], and/or Simplexa™ Flu A/B & RSV Direct Gen II Kit [Diasorin Molecular]), and medical evolution with duration of the hospitalisation, hopitalisation in ICU, respiratory support (oxygen therapy, high-flow nasal cannula oxygen therapy, non-invasive ventilation, invasive ventilation, and extracorporeal membrane oxygenation [ECMO]), and nutritional support.

Statistical analysis

The normality of the distribution for continuous variables was tested using the Shapiro-wilk test and was rejected for each variable. Patients' characteristics were described as medians with interquartile range for continuous variables and percentages for categorical variables. We compared the patients' characteristics between the pre-COVID periods, defined as October 1 to March 31 2017-2018, 2018-2019, and 2019-2020, with those of the COVID period, defined as October 1, 2020 to March 31, 2021, by using a chi-square test for categorical variables and a Mann-Whitney test for continuous variables. The analyses were performed using STATA 14.2.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Number of hospitalisations

Over the pre-COVID period, 1,347 infants were hospitalised for bronchiolitis in our hospital, with a mean of 449 infants per winter, compared to 205 infants during the COVID period; which corresponds to a 54.3% reduction in the number of hospitalisations (**Table 1**). As shown in **Figure 1**, the bronchiolitis outbreak was delayed during the COVID period, with a peak in the hospitalisations in February, compared to the usual peaks in November-December during the pre-COVID periods.

Characteristics of the patients

The clinical characteristics of the infants hospitalised for bronchiolitis are shown in **Table 1**. The age distribution and the sex ratio were not significantly different between the pre-COVID and the COVID periods ($p = 0.7$ and 0.5 respectively). During the pre-COVID periods, 14% of the infants presented with comorbidities (with 11% of preterm), whereas only 8% had comorbidities during the COVID period, ($p = 0.02$).

The number of infants who received oxygen therapy was significantly lower during the COVID period than during the pre-COVID period (45% vs 55% respectively, $p = 0.01$). There were no significant differences between the pre-COVID and the COVID periods regarding the length of hospitalisation ($p = 0.3$), the number of patients transferred to a paediatric ICU ($p = 0.6$), and the need for non-invasive ($p = 0.9$) or invasive ventilation ($p = 0.6$).

Viral epidemiology

PCR in nasopharyngeal swabs for virus identification were performed increasingly across the years ($p < 0.01$) (**Table 2**). RSV remains the most common virus found (74%), followed by Rhinovirus and Adenovirus (**Table 2**). The RSV outbreak was significantly

delayed during the COVID period compared to the previous winters, with a plateau between January and March 2021, compared to peaks in November-December during the pre-COVID periods (**Figure 1**).

The proportion of the following viruses was significantly higher during the COVID period than during the pre-COVID period: Metapneumovirus ($p = 0.001$), Parainfluenzae 3 ($p < 0.01$), Bocavirus ($p = 0.001$), Coronavirus OC43 ($p < 0.01$) and NL63 ($p < 0.01$) (**Table 2**). No Influenza (A and B) was found during the COVID period. Only 3 infants with bronchiolitis had a PCR positive for SARS-CoV-2 in nasopharyngeal swabs during the COVID period, but all 3 were also positive for RSV.

Discussion

This study highlights the dramatic reduction in the number of infants who required a hospitalisation for acute bronchiolitis during the COVID-19 outbreak compared to the three previous years. The outbreak of acute bronchiolitis was not only smaller, but also delayed by several weeks. The clinical characteristics of the infants hospitalised for acute bronchiolitis as well as the hospitalisation courses were substantially similar during pre-COVID and COVID periods. While the proportions of RSV and Rhinovirus were similar between both periods, those of Metapneumovirus, Parainfluenzae 3, Bocavirus, Coronavirus NL63 and Coronavirus OC43 increased during the COVID pandemic. Interestingly, during the COVID period, no Influenza was found and the only 3 infants with a PCR positive for SARS-CoV-2 were also positive for RSV, suggesting that SARS-CoV-2 alone does not cause bronchiolitis.

This winter, we observed a strong decrease in the number of hospitalisations for acute bronchiolitis. This observation is consistent with data first from the southern hemisphere, Australia and South America (10, 11), and, more recently, from Europe and North-America (9, 12-15). Several studies reported reductions in the rate of admission to paediatric emergency departments for acute bronchiolitis during the COVID-19 outbreak (9, 13). Results similar to ours were reported in Belgium with a dramatic decrease in bronchiolitis hospitalisations and very limited RSV positive as compared to the last three years (15). Two recent studies also suggest that social distancing and other lockdown strategies are effective in slowing down the spreading of respiratory diseases and decreasing the need for hospitalisation among children (12, 14). Indeed, after reaching France on January 2020, a major progression of COVID-19 led to public health prevention interventions. The first national lockdown officially started on March 17, 2020 and ended on May 10, 2020. Masks had to be worn by persons 11 years of age and older in enclosed public places as of July 20, 2020. As shown in this study, the number of hospitalisations for acute bronchiolitis has therefore drastically decreased, even while schools

and nurseries have remained open during winter. A recent publication shows the extent to which transmission of common paediatric infections can be altered when close contact with other children is eliminated (16). However, in our study, infants hospitalised for acute bronchiolitis had a mean age of 3.5 months, so a majority of these infants were not yet in collective nurseries, but were at home with their mothers (who were on maternity leave). Moreover, since September 2020, professionals in nurseries are required to wear a mask in the presence of children. It can therefore be suggested that the RSV transmission to these young children can also occur through their parents or older siblings. Intriguingly, we observed a lower proportion of infants with comorbidities hospitalised during the COVID period. This could be due to the fact that parents have protected these at-risk children much more for fear that they would develop severe infections during the pandemic period.

The outbreak of acute bronchiolitis was not only lower, but was also delayed by several weeks. Besides, RSV emerged in January, after the Christmas break. One explanation might be that families got together during this celebration break, and social distancing measures might have been followed less strictly. Interestingly, we observed that while the proportions of RSV and Rhinovirus were similar to that of previous years during the COVID-19 period, those of Parainfluenzae 3, Bocavirus, Coronavirus NL63 and Coronavirus OC43 were higher. Our results on the prevalence of the various respiratory viruses during the pre-COVID period are in agreement with the literature (17). Moreover, during the COVID period, no Influenza was found, suggestive that this virus is sensitive to the hygiene measures adopted during the pandemic. A recent epidemiological study on common communicable diseases in the general population in France during the COVID pandemic also showed that patients who presented with ALRI symptoms and underwent a PCR test were most likely infected by Influenza in 2019, but by SARS-CoV-2 or Metapneumovirus in 2020 (18). Moreover, in contradiction to assumptions made at the pandemic onset, our data suggest that SARS-CoV-2 alone does not

cause bronchiolitis, as the only 3 infants SARS-CoV-2 positive were also positive for RSV. It will be important to confirm these results in the future, especially if SARS-CoV-2 remains endemic in the years to come.

The high impact of bronchiolitis in terms of cost of hospitalisation is not insignificant. In Italy, a recent study showed that the main cost item is related to young infants, in particular, those below 3 months of age, and RSV continues to be the main causative agent of severe bronchiolitis (19). The authors highlight that new vaccination strategies, such as the extension of immunoprophylaxis to infants is essential. Therefore, it would be useful, after the COVID-19 pandemic, for adults to continue to wear masks and wash their hands regularly to mitigate the risk of transmission of respiratory infection to young children. Acute severe RSV bronchiolitis in early childhood is associated with long-term morbidities including recurrent wheezing, asthma, and lower lung function in later life (20). Therefore, the decrease in the number of severe bronchiolitis cases due to RSV or other viruses might not only have financial consequences, but also impact the long-term respiratory outcome of children.

We are aware of some limitations of our study. The decrease in the number of hospitalisations may have been partly the consequence of a decrease in the overall number of emergency room visits since the start of the COVID-19 pandemic. However, it is likely that, despite the COVID-19 pandemic, children with the most severe respiratory distress were still seen in the emergency room. In the UK, a significant reduction of non-urgent health care demands were observed during the pandemic and were associated with an increase in severe or urgent cases (21).

In conclusion, our work provides an overview of the infants' hospitalisations for acute bronchiolitis during the COVID period in the winter of 2020-2021. This dramatic reduction in infants' hospitalizations constitutes a great opportunity to change our habits for future autumn and winter seasons by advising people, especially adults, to wear masks and increase social

distancing and hygiene measures in case of upper and lower respiratory tract infections. This may drastically change the worldwide burden of bronchiolitis and hospitalisations caused by RSV in the future, as well have important implications for patient outcomes and prevalence of asthma in children (22). The scientific community should nevertheless keep close surveillance of RSV epidemics since, as underlined by Di Mattia et al., the increase of an immunologically naïve population with infants born from mothers who have not reinforced their immunity to RSV, could lead to greater epidemics in the next winters (23).

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Figure's caption

Figure 1. Evolution of the number of RSV and Rhinovirus cases during the pre-COVID period (between 2017 and 2020) and the COVID period (2020-2021)

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Tables

Table 1. Clinical characteristics of the infants hospitalised for acute bronchiolitis in a tertiary university paediatric hospital in Paris (France) between 2017 and 2021

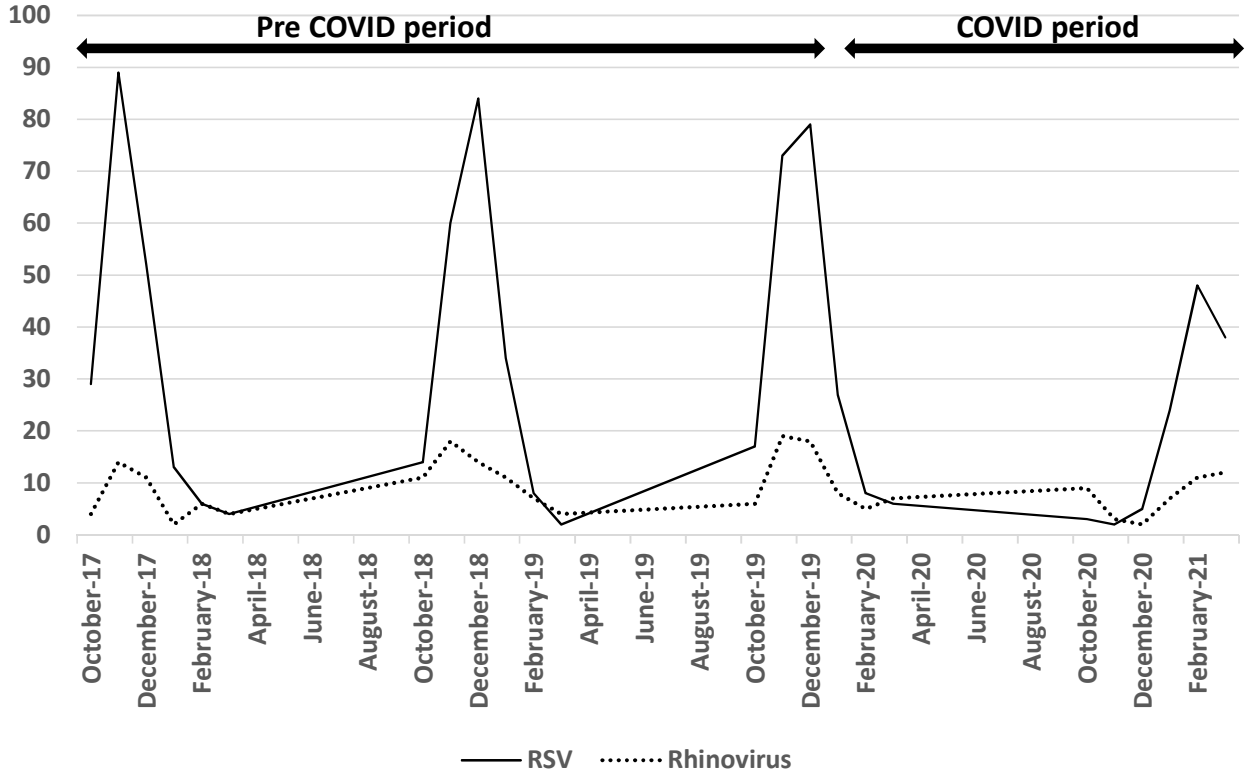
	Pre-COVID period				COVID period	
	2017-2018	**2018-2019**	**2019-2020**	**2017-2020 aggregated data**	**2020-2021**	**P-value***
Number of infants, n	**479**	**451**	**417**	**1347**	**205**	**-**
Age (months): median (IQR)	2.8 (1.5-4.9)	2.6 (1.4-4.8)	2.4 (1.3-4.4)	2.5 (1.4-4.7)	2.7 (1.5-4.7)	0.7
Gender: boys, n (%)	279 (58.2)	249 (55.2)	244 (58.5)	772 (57)	119 (58)	0.5
Comorbidities, n (%)	66 (14)	66 (15)	53 (13)	185 (14)	16 (8)	**0.02**
Weight (kg): median (IQR)	5.6 (4.4-6.9)	5.5 (4.6-7.0)	5.4 (4.3-7.0)	5.5 (4.4-7.0)	5.7 (4.5-6.9)	0.6
Evolution						
Duration of hospitalisation (days), median (IQR)	2.4 (1.2-4.0)	3.0 (2.0-4.0)	3.9 (2.0-5.0)	3.0 (2.0-4.9)	3.0 (1.5-4.2)	0.3
Oxygen therapy, n (%)	259 (54)	237 (52)	257 (61)	753 (56)	93 (45)	**0.01**
Intensive Care Unit, n (%)	48 (13)	42 (9)	67 (16)	157 (12)	21 (11)	0.6
Non-invasive ventilation, n (%)	42 (8)	38 (8)	67 (16)	147 (11)	22 (12)	0.9
Invasive ventilation, n (%)	5 (1)	5 (1)	7 (1.6)	17 (1.2)	3 (1.7)	0.6
Extracorporeal circulation, n (%)	2 (0.4)	0 (0)	2 (0.4)	4 (0.2)	0 (0)	0.4

*P-value for the comparison between pre-COVID aggregated data and COVID data using chi-square test for categorical variables and Mann-Whitney test for continuous variables.

Table 2. Results of the PCR performed in nasopharyngeal swabs for virus identification in the infants hospitalised in paediatric general wards for acute bronchiolitis between 2017 and 2021

	Pre-COVID				Post-COVID	
	2017-2018	2018-2019	2019-2020	2017-2020 aggregated data	2020-2021	P-value*
Number of infants, n	**479**	**451**	**417**	**1347**	**205**	
Nasal PCR$, n (%)	**245 (51.1)**	**274 (60.7)**	**281 (67.4)**	**800 (59.4)**	**167 (74.2)**	**< 0.01**
Respiratory syncytial virus	193 (78)	202 (73)	211 (75)	606 (75)	120 (71)	0.3
Rhinovirus	41 (17)	65 (24)	63 (22)	169 (12)	44 (21)	0.1
Adenovirus	17 (7)	10 (4)	14 (5)	16 (11)	12 (7)	0.3
Metapneumovirus	17 (7)	10 (4)	10 (4)	37 (2.7)	19 (11)	**0.001**
Influenzae A	0 (0)	2 (0.4)	1 (0.2)	3 (0.2)	0 (0)	0.4
Influenzae B	0 (0)	2 (0.7)	1 (0.3)	3 (0.2)	0 (0)	0.4
Parainfluenzae 3	9 (4)	6 (2)	10 (4)	27 (2)	16 (10)	**< 0.01**
Bocavirus	6 (2)	11 (4)	7 (2)	24 (1.7)	14 (8)	**0.001**
SARS CoV-2	0 (0)	0 (0)	0 (0)	0 (0)	3 (2)	**0.02**
Coronavirus NL63	2 (0.8)	5 (2)	3 (1)	10 (0.7)	9 (5)	**< 0.01**
Coronavirus OC43	0 (0)	1 (0.3)	2 (0.7)	3 (0.2)	7 (4)	**< 0.01**
No PCR, n (%)	**234 (48.8)**	**177 (39)**	**136 (32)**	**547 (40)**	**38 (18)**	**< 0.01**

*P-value for the comparison between pre-COVID aggregated data and COVID data using chi-square test. $Virus identifications by PCR in nasopharyngeal swabs or aspirates were performed by means of Allplex Respiratory Panel Assays (Seegene) and/or Simplexa™ Flu A/B & RSV Direct Gen II Kit (Diasorin Molecular).


Pre COVID period
COVID period
100
90
80
70
60
50
40
30
20
10
0
October-17
December-17
February-18
April-18
June-18
August-18
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RSV
Rhinovirus

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Retrospective observational study of the influence of the COVID outbreak on infants' hospitalisation for acute bronchiolitis

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Retrospective observational study of the influence of the COVID outbreak on infants' hospitalisation for acute bronchiolitis

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Abstract

Objectives. Acute bronchiolitis is a major public health issue with high number of infants hospitalised worldwide each year. In France, hospitalisations mostly occur between October and March, and peak in December. A reduction of emergency visits for bronchiolitis has been observed at onset of the COVID outbreak. We aimed to assess the pandemic effects on the hospitalisations for bronchiolitis during the 2020-2021 winter (COVID-period) compared to 3 previous winters (pre-COVID).

Design. Retrospective, observational and cross-sectional study.

Setting. Tertiary university paediatric hospital in Paris (France).

Participants. All infants aged under 12-months who were hospitalised for acute bronchiolitis during the autumn/winter seasons (October 1-March 31) from 2017 to 2021 were included. Clinical and laboratory data were collected using standardized forms.

Results. During the COVID-period was observed a 54.3% reduction in hospitalisations for bronchiolitis associated with a delayed peak (February instead of November-December). Clinical characteristics and hospitalisation courses were substantially similar. The differences during the COVID period were: smaller proportion of infants with comorbidities (14% *vs* 8% p = 0.02), lower need for oxygen (45% *vs* 55%, p = 0.01), higher proportions of Metapneumovirus, Parainfluenzae 3, Bocavirus, Coronavirus NL63 and OC43 (all $p \leq 0.01$), and no Influenza. The three infants positive for SARS-CoV-2 were also positive for RSV, suggesting that SARS-CoV-2 alone does not cause bronchiolitis, despite previous assumptions.

Conclusion. The dramatic reduction in infants' hospitalisations for acute bronchiolitis is an opportunity to change our future habits such as advising the population to wear masks and apply additional hygiene measures in case of respiratory tract infections. This may change the worldwide bronchiolitis burden and improve children respiratory outcomes.

Data availability statement: Data are available upon reasonable request.

Strengths and limitations of this study

- The vast majority of infants admitted to our paediatric hospital between 2017 and 2021 for acute bronchiolitis in their first year after birth will have been identified.
- The clinical and viral characteristics of these infants hospitalised during the COVID-epidemic season 2020-2021 were compared to those of 3 previous winters.
- Three physicians independently reviewed the medical records to collect clinical data and laboratory tests results using a standardized specific form.

Introduction

In autumn and winter in the northern hemisphere, community medicine (paediatricians and general practitioners), as well as emergency and general paediatric departments, are usually overwhelmed by children, especially infants, with acute bronchiolitis (1, 2). Hospital paediatric inpatient departments have to reorganize every winter to handle the high number of infants with this acute lower respiratory infection (ALRI), mostly due to the respiratory syncytial virus (RSV) (1-5). Neonates and young infants often require hospitalisation in general wards, and some even require intensive care unit (ICU) care (2, 6). Moreover, RSV is the third leading cause of death in children aged below 5 years (from ALRI, after pneumonia), secondary to *Streptococcus pneumonia* and *Haemophilus influenzae* type b (2). Acute bronchiolitis is thus a yearly worldwide public health issue. In France, similar epidemic patterns are seen each year with a large majority of hospitalisations between October and March, with a peak in December (7). Management is largely supportive, focusing on maintaining oxygenation and hydration.

The emergence of the coronavirus disease 2019 (COVID-19) pandemic and the global public health responses related to this pandemic have influenced the viruses' epidemiology. A striking reduction of admission for ALRIs in paediatric ICUs was observed during the winter 2020 in the southern hemisphere (8). In France, collective measures to contain the pandemic have been implemented since mid-March 2020, namely lockdowns, curfews, social distancing, requirement of masks, strict hand hygiene, and restriction of commerce activities. We observed a reduction in the visits to the paediatric emergency department of our hospital for bronchiolitis in the autumn 2020 (9). Here, we aimed to assess the effects of the COVID-19 pandemic on the clinical and viral characteristics of infants hospitalised for bronchiolitis during the epidemic season 2020-2021 (COVID period) compared to previous winters (pre-COVID period).

Methods

Study design and patients

This retrospective, observational and cross-sectional study was conducted in the Paediatric University Hospital Armand Trousseau, Assistance Publique Hôpitaux de Paris (APHP), in Paris (France). All infants aged less than 12 months, hospitalised for a first episode of acute bronchiolitis during the autumn/winter seasons (October 1 to March 31) from 2017 to 2021 (*i.e.,* 2017-2018; 2018-2019; 2019-2020; and 2020-2021) were included. Exclusion criteria were age over 12 months, a second episode (or more) of bronchiolitis, and/or an asthma attack. These exclusion criteria were chosen based on the French National Guidelines for bronchiolitis (10). The study was approved by the Institutional Review Board of the French Society for Respiratory Medicine (*Société de Pneumologie de Langue Française,* #CEPRO_2020-080). In accordance with French laws for observational studies, the requirement for written informed consent was waived (study BronChioVID N°20201119185601).

Patient's selection was performed using the ICD10 code diagnoses of bronchiolitis (J21.0, J21.1, J21.8, and J21.9). Three physicians reviewed the medical records to collect demographic and clinical data as well as laboratory tests results using a standardized specific form. The demographic data collected comprised date of birth, gender and underlying conditions such as prematurity, bronchopulmonary dysplasia, intrauterine growth retardation, congenital heart disease, sickle cell disease, and genetic disease. The clinical data collected at the time of the bronchiolitis episode included date, age, weight, results of the PCR in nasopharyngeal swabs or aspirates for virus identification (Allplex™ Respiratory Panel Assays [Seegene], and/or Simplexa™ Flu A/B & RSV Direct Gen II Kit [Diasorin Molecular]), and medical evolution with duration of the hospitalisation, hopitalisation in ICU, respiratory support

(oxygen therapy, high-flow nasal cannula oxygen therapy, non-invasive ventilation, invasive ventilation, and extracorporeal membrane oxygenation [ECMO]), and nutritional support.

Statistical analysis

The normality of the distribution for continuous variables was tested using the Shapiro-wilk test and was rejected for each variable. Patients' characteristics were described as medians with interquartile range for continuous variables and percentages for categorical variables. We compared the patients' characteristics between the pre-COVID periods, defined as October 1 to March 31 2017-2018, 2018-2019, and 2019-2020, with those of the COVID period, defined as October 1, 2020 to March 31, 2021, by using a chi-square test for categorical variables and a Mann-Whitney test for continuous variables. The analyses were performed using STATA 14.2.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Number of hospitalisations

Over the pre-COVID period, 1,347 infants were hospitalised for bronchiolitis in our hospital, with a mean of 449 infants per winter, compared to 205 infants during the COVID period; which corresponds to a 54.3% reduction in the number of hospitalisations (**Table 1**). As shown in **Figure 1**, the bronchiolitis outbreak was delayed during the COVID period, with a peak in the hospitalisations in February, compared to the usual peaks in November-December during the pre-COVID periods.

Characteristics of the patients

The clinical characteristics of the infants hospitalised for bronchiolitis are shown in **Table 1**. The age distribution and the sex ratio were not significantly different between the pre-COVID and the COVID periods ($p = 0.7$ and 0.5 respectively). During the pre-COVID periods, 14% of the infants presented with comorbidities (with 11% of preterm), whereas only 8% had comorbidities during the COVID period, ($p = 0.02$).

The number of infants who received oxygen therapy was significantly lower during the COVID period than during the pre-COVID period (45% vs 55% respectively, $p = 0.01$). There were no significant differences between the pre-COVID and the COVID periods regarding the length of hospitalisation ($p = 0.3$), the number of patients transferred to a paediatric ICU ($p = 0.6$), and the need for non-invasive ($p = 0.9$) or invasive ventilation ($p = 0.6$).

Viral epidemiology

PCR in nasopharyngeal swabs for virus identification were performed increasingly across the years ($p < 0.01$) (**Table 2**). RSV remains the most common virus found (74%), followed by Rhinovirus and Adenovirus (**Table 2**). The RSV outbreak was significantly

delayed during the COVID period compared to the previous winters, with a plateau between January and March 2021, compared to peaks in November-December during the pre-COVID periods (**Figure 1**).

The proportion of the following viruses was significantly higher during the COVID period than during the pre-COVID period: Metapneumovirus ($p = 0.001$), Parainfluenzae 3 ($p < 0.01$), Bocavirus ($p = 0.001$), Coronavirus OC43 ($p < 0.01$) and NL63 ($p < 0.01$) (**Table 2**). No Influenza (A and B) was found during the COVID period. Only 3 infants with bronchiolitis had a PCR positive for SARS-CoV-2 in nasopharyngeal swabs during the COVID period, but all 3 were also positive for RSV.

Discussion

This study highlights the dramatic reduction in the number of infants who required a hospitalisation for acute bronchiolitis during the COVID-19 outbreak compared to the three previous years. The outbreak of acute bronchiolitis was not only smaller, but also delayed by several weeks. The clinical characteristics of the infants hospitalised for acute bronchiolitis as well as the hospitalisation courses were substantially similar during pre-COVID and COVID periods. While the proportions of RSV and Rhinovirus were similar between both periods, those of Metapneumovirus, Parainfluenzae 3, Bocavirus, Coronavirus NL63 and Coronavirus OC43 increased during the COVID pandemic. Interestingly, during the COVID period, no Influenza was found and the only 3 infants with a PCR positive for SARS-CoV-2 were also positive for RSV, suggesting that SARS-CoV-2 alone does not cause bronchiolitis.

This winter, we observed a strong decrease in the number of hospitalisations for acute bronchiolitis. This observation is consistent with data first from the southern hemisphere, Australia and South America (11, 12), and, more recently, from Europe and North-America (9, 13-16). Several studies reported reductions in the rate of admission to paediatric emergency departments for acute bronchiolitis during the COVID-19 outbreak (9, 14). Results similar to ours were reported in Belgium with a dramatic decrease in bronchiolitis hospitalisations and very limited RSV positive as compared to the last three years (16). Two recent studies also suggest that social distancing and other lockdown strategies are effective in slowing down the spreading of respiratory diseases and decreasing the need for hospitalisation among children (13, 15). Indeed, after reaching France on January 2020, a major progression of COVID-19 led to public health prevention interventions. The first national lockdown officially started on March 17, 2020 and ended on May 10, 2020. Masks had to be worn by persons 11 years of age and older in enclosed public places as of July 20, 2020. As shown in this study, the number of hospitalisations for acute bronchiolitis has therefore drastically decreased, even while schools

and nurseries have remained open during winter. A recent publication shows the extent to which transmission of common paediatric infections can be altered when close contact with other children is eliminated (17). However, in our study, infants hospitalised for acute bronchiolitis had a mean age of 3.5 months, so a majority of these infants were not yet in collective nurseries, but were at home with their mothers (who were on maternity leave). Moreover, since September 2020, professionals in nurseries are required to wear a mask in the presence of children. It can therefore be suggested that the RSV transmission to these young children can also occur through their parents or older siblings. Intriguingly, we observed a lower proportion of infants with comorbidities hospitalised during the COVID period. This could be due to the fact that parents have protected these at-risk children much more for fear that they would develop severe infections during the pandemic period.

The outbreak of acute bronchiolitis was not only lower, but was also delayed by several weeks. Besides, RSV emerged in January, after the Christmas break. One explanation might be that families got together during this celebration break, and social distancing measures might have been followed less strictly. Interestingly, we observed that while the proportions of RSV and Rhinovirus were similar to that of previous years during the COVID-19 period, those of Parainfluenzae 3, Bocavirus, Coronavirus NL63 and Coronavirus OC43 were higher. Our results on the prevalence of the various respiratory viruses during the pre-COVID period are in agreement with the literature (18). Moreover, during the COVID period, no Influenza was found, suggestive that this virus is sensitive to the hygiene measures adopted during the pandemic. A recent epidemiological study on common communicable diseases in the general population in France during the COVID pandemic also showed that patients who presented with ALRI symptoms and underwent a PCR test were most likely infected by Influenza in 2019, but by SARS-CoV-2 or Metapneumovirus in 2020 (19). Moreover, in contradiction to assumptions made at the pandemic onset, our data suggest that SARS-CoV-2 alone does not

cause bronchiolitis, as the only 3 infants SARS-CoV-2 positive were also positive for RSV. It will be important to confirm these results in the future, especially if SARS-CoV-2 remains endemic in the years to come.

The high impact of bronchiolitis in terms of cost of hospitalisation is not insignificant. In Italy, a recent study showed that the main cost item is related to young infants, in particular, those below 3 months of age, and RSV continues to be the main causative agent of severe bronchiolitis (20). The authors highlight that new vaccination strategies, such as the extension of immunoprophylaxis to infants is essential. Therefore, it would be useful, after the COVID-19 pandemic, for adults to continue to wear masks and wash their hands regularly to mitigate the risk of transmission of respiratory infection to young children. Acute severe RSV bronchiolitis in early childhood is associated with long-term morbidities including recurrent wheezing, asthma, and lower lung function in later life (21). Therefore, the decrease in the number of severe bronchiolitis cases due to RSV or other viruses might not only have financial consequences, but also impact the long-term respiratory outcome of children.

We are aware of some limitations of our study. The decrease in the number of hospitalisations may have been partly the consequence of a decrease in the overall number of emergency room visits since the start of the COVID-19 pandemic. However, it is likely that, despite the COVID-19 pandemic, children with the most severe respiratory distress were still seen in the emergency room. In the UK, a significant reduction of non-urgent health care demands were observed during the pandemic and were associated with an increase in severe or urgent cases (22).

In conclusion, our work provides an overview of the infants' hospitalisations for acute bronchiolitis during the COVID period in the winter of 2020-2021. This dramatic reduction in infants' hospitalizations constitutes a great opportunity to change our habits for future autumn and winter seasons by advising people, especially adults, to wear masks and increase social

distancing and hygiene measures in case of upper and lower respiratory tract infections. This may drastically change the worldwide burden of bronchiolitis and hospitalisations caused by RSV in the future, as well have important implications for patient outcomes and prevalence of asthma in children (23). The scientific community should nevertheless keep close surveillance of RSV epidemics since, as underlined by Di Mattia et al., the increase of an immunologically naïve population with infants born from mothers who have not reinforced their immunity to RSV, could lead to greater epidemics in the next winters (24).

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Figure's caption

Figure 1. Evolution of the number of RSV and Rhinovirus cases during the pre-COVID period (between 2017 and 2020) and the COVID period (2020-2021)

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Tables

Table 1. Clinical characteristics of the infants hospitalised for acute bronchiolitis in a tertiary university paediatric hospital in Paris (France) between 2017 and 2021

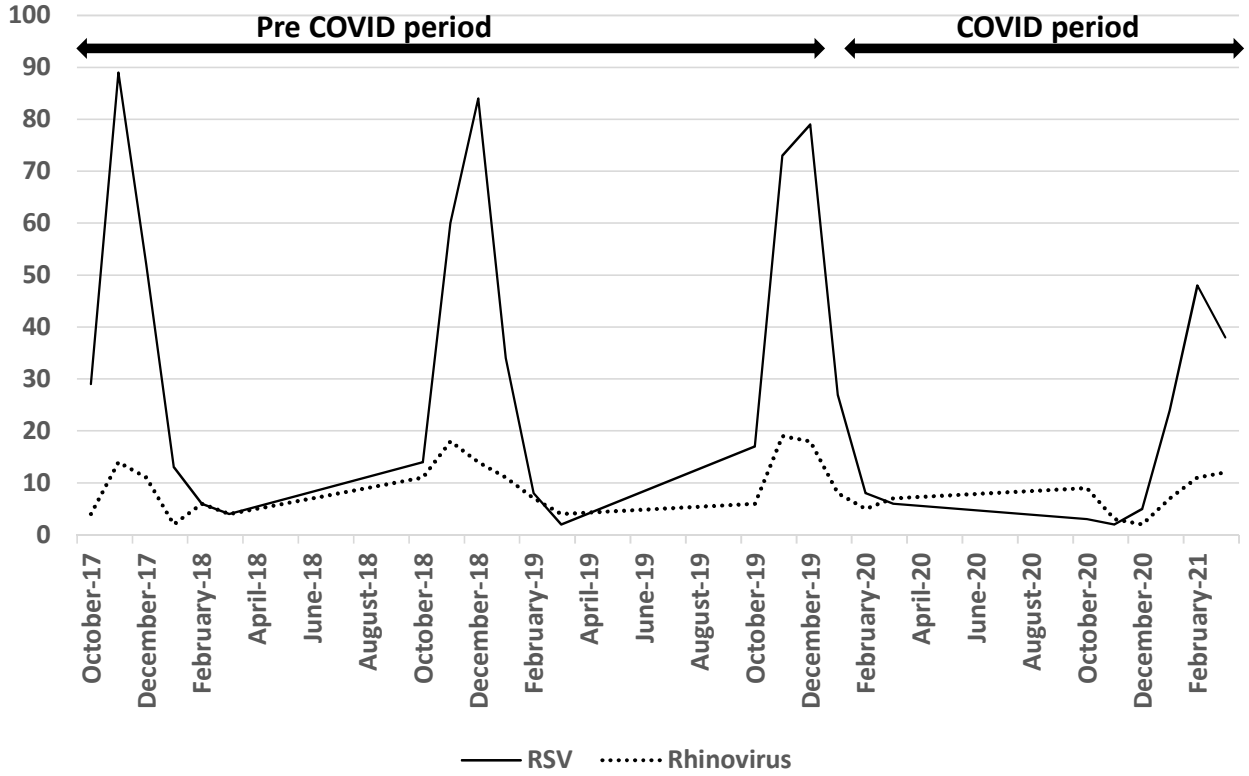
	Pre-COVID period				COVID period	
	2017-2018	**2018-2019**	**2019-2020**	**2017-2020 aggregated data**	**2020-2021**	**P-value***
Number of infants, n	**479**	**451**	**417**	**1347**	**205**	**-**
Age (months): median (IQR)	2.8 (1.5-4.9)	2.6 (1.4-4.8)	2.4 (1.3-4.4)	2.5 (1.4-4.7)	2.7 (1.5-4.7)	0.7
Gender: boys, n (%)	279 (58.2)	249 (55.2)	244 (58.5)	772 (57)	119 (58)	0.5
Comorbidities, n (%)	66 (14)	66 (15)	53 (13)	185 (14)	16 (8)	**0.02**
Weight (kg): median (IQR)	5.6 (4.4-6.9)	5.5 (4.6-7.0)	5.4 (4.3-7.0)	5.5 (4.4-7.0)	5.7 (4.5-6.9)	0.6
Evolution						
Duration of hospitalisation (days), median (IQR)	2.4 (1.2-4.0)	3.0 (2.0-4.0)	3.9 (2.0-5.0)	3.0 (2.0-4.9)	3.0 (1.5-4.2)	0.3
Oxygen therapy, n (%)	259 (54)	237 (52)	257 (61)	753 (56)	93 (45)	**0.01**
Intensive Care Unit, n (%)	48 (13)	42 (9)	67 (16)	157 (12)	21 (11)	0.6
Non-invasive ventilation, n (%)	42 (8)	38 (8)	67 (16)	147 (11)	22 (12)	0.9
Invasive ventilation, n (%)	5 (1)	5 (1)	7 (1.6)	17 (1.2)	3 (1.7)	0.6
Extracorporeal circulation, n (%)	2 (0.4)	0 (0)	2 (0.4)	4 (0.2)	0 (0)	0.4

*P-value for the comparison between pre-COVID aggregated data and COVID data using chi-square test for categorical variables and Mann-Whitney test for continuous variables.

Table 2. Results of the PCR performed in nasopharyngeal swabs for virus identification in the infants hospitalised in paediatric general wards for acute bronchiolitis between 2017 and 2021

	Pre-COVID				Post-COVID	
	2017-2018	2018-2019	2019-2020	2017-2020 aggregated data	2020-2021	P-value*
Number of infants, n	**479**	**451**	**417**	**1347**	**205**	
Nasal PCR$, n (%)	**245 (51.1)**	**274 (60.7)**	**281 (67.4)**	**800 (59.4)**	**167 (74.2)**	**< 0.01**
Respiratory syncytial virus	193 (78)	202 (73)	211 (75)	606 (75)	120 (71)	0.3
Rhinovirus	41 (17)	65 (24)	63 (22)	169 (12)	44 (21)	0.1
Adenovirus	17 (7)	10 (4)	14 (5)	16 (11)	12 (7)	0.3
Metapneumovirus	17 (7)	10 (4)	10 (4)	37 (2.7)	19 (11)	**0.001**
Influenzae A	0 (0)	2 (0.4)	1 (0.2)	3 (0.2)	0 (0)	0.4
Influenzae B	0 (0)	2 (0.7)	1 (0.3)	3 (0.2)	0 (0)	0.4
Parainfluenzae 3	9 (4)	6 (2)	10 (4)	27 (2)	16 (10)	**< 0.01**
Bocavirus	6 (2)	11 (4)	7 (2)	24 (1.7)	14 (8)	**0.001**
SARS CoV-2	0 (0)	0 (0)	0 (0)	0 (0)	3 (2)	**0.02**
Coronavirus NL63	2 (0.8)	5 (2)	3 (1)	10 (0.7)	9 (5)	**< 0.01**
Coronavirus OC43	0 (0)	1 (0.3)	2 (0.7)	3 (0.2)	7 (4)	**< 0.01**
No PCR, n (%)	**234 (48.8)**	**177 (39)**	**136 (32)**	**547 (40)**	**38 (18)**	**< 0.01**

*P-value for the comparison between pre-COVID aggregated data and COVID data using chi-square test. $Virus identifications by PCR in nasopharyngeal swabs or aspirates were performed by means of Allplex Respiratory Panel Assays (Seegene) and/or Simplexa™ Flu A/B & RSV Direct Gen II Kit (Diasorin Molecular).


Pre COVID period
COVID period
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RSV
Rhinovirus

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Retrospective observational study of the influence of the COVID outbreak on infants' hospitalisation for acute bronchiolitis

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Abstract

Objectives. Acute bronchiolitis is a major public health issue with high number of infants hospitalised worldwide each year. In France, hospitalisations mostly occur between October and March, and peak in December. A reduction of emergency visits for bronchiolitis has been observed at onset of the COVID outbreak. We aimed to assess the pandemic effects on the hospitalisations for bronchiolitis during the 2020-2021 winter (COVID-period) compared to 3 previous winters (pre-COVID).

Design. Retrospective, observational and cross-sectional study.

Setting. Tertiary university paediatric hospital in Paris (France).

Participants. All infants aged under 12-months who were hospitalised for acute bronchiolitis during the autumn/winter seasons (October 1-March 31) from 2017 to 2021 were included. Clinical and laboratory data were collected using standardized forms.

Results. During the COVID-period was observed a 54.3% reduction in hospitalisations for bronchiolitis associated with a delayed peak (February instead of November-December). Clinical characteristics and hospitalisation courses were substantially similar. The differences during the COVID period were: smaller proportion of infants with comorbidities (14% *vs* 8% p = 0.02), lower need for oxygen (45% *vs* 55%, p = 0.01), higher proportions of Metapneumovirus, Parainfluenzae 3, Bocavirus, Coronavirus NL63 and OC43 (all $p \leq 0.01$), and no Influenza. The three infants positive for SARS-CoV-2 were also positive for RSV, suggesting that SARS-CoV-2 alone does not cause bronchiolitis, despite previous assumptions.

Conclusion. The dramatic reduction in infants' hospitalisations for acute bronchiolitis is an opportunity to change our future habits such as advising the population to wear masks and apply additional hygiene measures in case of respiratory tract infections. This may change the worldwide bronchiolitis burden and improve children respiratory outcomes.

Data availability statement: Data are available upon reasonable request.

Strengths and limitations of this study

- The vast majority of infants admitted to our paediatric hospital between 2017 and 2021 for acute bronchiolitis in their first year after birth will have been identified.
- The clinical and viral characteristics of these infants hospitalised during the COVID-epidemic season 2020-2021 were compared to those of 3 previous winters.
- Three physicians independently reviewed the medical records to collect clinical data and laboratory tests results using a standardized specific form.

Introduction

In autumn and winter in the northern hemisphere, community medicine (paediatricians and general practitioners), as well as emergency and general paediatric departments, are usually overwhelmed by children, especially infants, with acute bronchiolitis (1, 2). Hospital paediatric inpatient departments have to reorganize every winter to handle the high number of infants with this acute lower respiratory infection (ALRI), mostly due to the respiratory syncytial virus (RSV) (1-5). Neonates and young infants often require hospitalisation in general wards, and some even require intensive care unit (ICU) care (2, 6). Moreover, RSV is the third leading cause of death in children aged below 5 years (from ALRI, after pneumonia), secondary to *Streptococcus pneumonia* and *Haemophilus influenzae* type b (2). Acute bronchiolitis is thus a yearly worldwide public health issue. In France, similar epidemic patterns are seen each year with a large majority of hospitalisations between October and March, with a peak in December (7). Management is largely supportive, focusing on maintaining oxygenation and hydration.

The emergence of the coronavirus disease 2019 (COVID-19) pandemic and the global public health responses related to this pandemic have influenced the viruses' epidemiology. A striking reduction of admission for ALRIs in paediatric ICUs was observed during the winter 2020 in the southern hemisphere (8). In France, collective measures to contain the pandemic have been implemented since mid-March 2020, namely lockdowns, curfews, social distancing, requirement of masks, strict hand hygiene, and restriction of commerce activities. We observed a reduction in the visits to the paediatric emergency department of our hospital for bronchiolitis in the autumn 2020 (9). Here, we aimed to assess the effects of the COVID-19 pandemic on the clinical and viral characteristics of infants hospitalised for bronchiolitis during the epidemic season 2020-2021 (COVID period) compared to previous winters (pre-COVID period).

Methods

Study design and patients

This retrospective, observational and cross-sectional study was conducted in the Paediatric University Hospital Armand Trousseau, Assistance Publique Hôpitaux de Paris (APHP), in Paris (France). All infants aged less than 12 months, hospitalised for a first episode of acute bronchiolitis during the autumn/winter seasons (October 1 to March 31) from 2017 to 2021 (*i.e.,* 2017-2018; 2018-2019; 2019-2020; and 2020-2021) were included. Exclusion criteria were age over 12 months, a second episode (or more) of bronchiolitis, and/or an asthma attack. These exclusion criteria were chosen based on the French National Guidelines for bronchiolitis (10). The study was approved by the Institutional Review Board of the French Society for Respiratory Medicine (*Société de Pneumologie de Langue Française,* #CEPRO_2020-080). In accordance with French laws for observational studies, the requirement for written informed consent was waived (study BronChioVID N°20201119185601).

Patient's selection was performed using the ICD10 code diagnoses of bronchiolitis (J21.0, J21.1, J21.8, and J21.9). Three physicians reviewed the medical records to collect demographic and clinical data as well as laboratory tests results using a standardized specific form. The demographic data collected comprised date of birth, gender and underlying conditions such as prematurity, bronchopulmonary dysplasia, intrauterine growth retardation, congenital heart disease, sickle cell disease, and genetic disease. The clinical data collected at the time of the bronchiolitis episode included date, age, weight, results of the PCR in nasopharyngeal swabs or aspirates for virus identification (Allplex™ Respiratory Panel Assays [Seegene], and/or Simplexa™ Flu A/B & RSV Direct Gen II Kit [Diasorin Molecular]), and medical evolution with duration of the hospitalisation, hopitalisation in ICU, respiratory support

(oxygen therapy, high-flow nasal cannula oxygen therapy, non-invasive ventilation, invasive ventilation, and extracorporeal membrane oxygenation [ECMO]), and nutritional support.

Statistical analysis

The normality of the distribution for continuous variables was tested using the Shapiro-wilk test and was rejected for each variable. Patients' characteristics were described as medians with interquartile range for continuous variables and percentages for categorical variables. We compared the patients' characteristics between the pre-COVID periods, defined as October 1 to March 31 2017-2018, 2018-2019, and 2019-2020, with those of the COVID period, defined as October 1, 2020 to March 31, 2021, by using a chi-square test for categorical variables and a Mann-Whitney test for continuous variables. The analyses were performed using STATA 14.2.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Number of hospitalisations

Over the pre-COVID period, 1,347 infants were hospitalised for bronchiolitis in our hospital, with a mean of 449 infants per winter, compared to 205 infants during the COVID period; which corresponds to a 54.3% reduction in the number of hospitalisations (**Table 1**). As shown in **Figure 1**, the bronchiolitis outbreak was delayed during the COVID period, with a peak in the hospitalisations in February, compared to the usual peaks in November-December during the pre-COVID periods.

Characteristics of the patients

The clinical characteristics of the infants hospitalised for bronchiolitis are shown in **Table 1**. The age distribution and the sex ratio were not significantly different between the pre-COVID and the COVID periods ($p = 0.7$ and 0.5 respectively). During the pre-COVID periods, 14% of the infants presented with comorbidities (with 11% of preterm), whereas only 8% had comorbidities during the COVID period, ($p = 0.02$).

The number of infants who received oxygen therapy was significantly lower during the COVID period than during the pre-COVID period (45% vs 55% respectively, $p = 0.01$). There were no significant differences between the pre-COVID and the COVID periods regarding the length of hospitalisation ($p = 0.3$), the number of patients transferred to a paediatric ICU ($p = 0.6$), and the need for non-invasive ($p = 0.9$) or invasive ventilation ($p = 0.6$).

Viral epidemiology

PCR in nasopharyngeal swabs for virus identification were performed increasingly across the years ($p < 0.01$) (**Table 2**). RSV remains the most common virus found (74%), followed by Rhinovirus and Adenovirus (**Table 2**). The RSV outbreak was significantly

delayed during the COVID period compared to the previous winters, with a plateau between January and March 2021, compared to peaks in November-December during the pre-COVID periods (**Figure 1**).

The proportion of the following viruses was significantly higher during the COVID period than during the pre-COVID period: Metapneumovirus ($p = 0.001$), Parainfluenzae 3 ($p < 0.01$), Bocavirus ($p = 0.001$), Coronavirus OC43 ($p < 0.01$) and NL63 ($p < 0.01$) (**Table 2**). No Influenza (A and B) was found during the COVID period. Only 3 infants with bronchiolitis had a PCR positive for SARS-CoV-2 in nasopharyngeal swabs during the COVID period, but all 3 were also positive for RSV.

Discussion

This study highlights the dramatic reduction in the number of infants who required a hospitalisation for acute bronchiolitis during the COVID-19 outbreak compared to the three previous years. The outbreak of acute bronchiolitis was not only smaller, but also delayed by several weeks. The clinical characteristics of the infants hospitalised for acute bronchiolitis as well as the hospitalisation courses were substantially similar during pre-COVID and COVID periods. While the proportions of RSV and Rhinovirus were similar between both periods, those of Metapneumovirus, Parainfluenzae 3, Bocavirus, Coronavirus NL63 and Coronavirus OC43 increased during the COVID pandemic. Interestingly, during the COVID period, no Influenza was found and the only 3 infants with a PCR positive for SARS-CoV-2 were also positive for RSV, suggesting that SARS-CoV-2 alone does not cause bronchiolitis.

This winter, we observed a strong decrease in the number of hospitalisations for acute bronchiolitis. This observation is consistent with data first from the southern hemisphere, Australia and South America (11, 12), and, more recently, from Europe and North-America (9, 13-16). Several studies reported reductions in the rate of admission to paediatric emergency departments for acute bronchiolitis during the COVID-19 outbreak (9, 14). Results similar to ours were reported in Belgium with a dramatic decrease in bronchiolitis hospitalisations and very limited RSV positive as compared to the last three years (16). Two recent studies also suggest that social distancing and other lockdown strategies are effective in slowing down the spreading of respiratory diseases and decreasing the need for hospitalisation among children (13, 15). Indeed, after reaching France on January 2020, a major progression of COVID-19 led to public health prevention interventions. The first national lockdown officially started on March 17, 2020 and ended on May 10, 2020. Masks had to be worn by persons 11 years of age and older in enclosed public places as of July 20, 2020. As shown in this study, the number of hospitalisations for acute bronchiolitis has therefore drastically decreased, even while schools

and nurseries have remained open during winter. A recent publication shows the extent to which transmission of common paediatric infections can be altered when close contact with other children is eliminated (17). However, in our study, infants hospitalised for acute bronchiolitis had a mean age of 3.5 months, so a majority of these infants were not yet in collective nurseries, but were at home with their mothers (who were on maternity leave). Moreover, since September 2020, professionals in nurseries are required to wear a mask in the presence of children. It can therefore be suggested that the RSV transmission to these young children can also occur through their parents or older siblings. Intriguingly, we observed a lower proportion of infants with comorbidities hospitalised during the COVID period. This could be due to the fact that parents have protected these at-risk children much more for fear that they would develop severe infections during the pandemic period.

The outbreak of acute bronchiolitis was not only lower, but was also delayed by several weeks. Besides, RSV emerged in January, after the Christmas break. One explanation might be that families got together during this celebration break, and social distancing measures might have been followed less strictly. Interestingly, we observed that while the proportions of RSV and Rhinovirus were similar to that of previous years during the COVID-19 period, those of Parainfluenzae 3, Bocavirus, Coronavirus NL63 and Coronavirus OC43 were higher. Our results on the prevalence of the various respiratory viruses during the pre-COVID period are in agreement with the literature (18). Moreover, during the COVID period, no Influenza was found, suggestive that this virus is sensitive to the hygiene measures adopted during the pandemic. A recent epidemiological study on common communicable diseases in the general population in France during the COVID pandemic also showed that patients who presented with ALRI symptoms and underwent a PCR test were most likely infected by Influenza in 2019, but by SARS-CoV-2 or Metapneumovirus in 2020 (19). Moreover, in contradiction to assumptions made at the pandemic onset, our data suggest that SARS-CoV-2 alone does not

cause bronchiolitis, as the only 3 infants SARS-CoV-2 positive were also positive for RSV. It will be important to confirm these results in the future, especially if SARS-CoV-2 remains endemic in the years to come.

The high impact of bronchiolitis in terms of cost of hospitalisation is not insignificant. In Italy, a recent study showed that the main cost item is related to young infants, in particular, those below 3 months of age, and RSV continues to be the main causative agent of severe bronchiolitis (20). The authors highlight that new vaccination strategies, such as the extension of immunoprophylaxis to infants is essential. Therefore, it would be useful, after the COVID-19 pandemic, for adults to continue to wear masks and wash their hands regularly to mitigate the risk of transmission of respiratory infection to young children. Acute severe RSV bronchiolitis in early childhood is associated with long-term morbidities including recurrent wheezing, asthma, and lower lung function in later life (21). Therefore, the decrease in the number of severe bronchiolitis cases due to RSV or other viruses might not only have financial consequences, but also impact the long-term respiratory outcome of children.

We are aware of some limitations of our study. The decrease in the number of hospitalisations may have been partly the consequence of a decrease in the overall number of emergency room visits since the start of the COVID-19 pandemic. However, it is likely that, despite the COVID-19 pandemic, children with the most severe respiratory distress were still seen in the emergency room. In the UK, a significant reduction of non-urgent health care demands were observed during the pandemic and were associated with an increase in severe or urgent cases (22).

In conclusion, our work provides an overview of the infants' hospitalisations for acute bronchiolitis during the COVID period in the winter of 2020-2021. This dramatic reduction in infants' hospitalizations constitutes a great opportunity to change our habits for future autumn and winter seasons by advising people, especially adults, to wear masks and increase social

distancing and hygiene measures in case of upper and lower respiratory tract infections. This may drastically change the worldwide burden of bronchiolitis and hospitalisations caused by RSV in the future, as well have important implications for patient outcomes and prevalence of asthma in children (23). The scientific community should nevertheless keep close surveillance of RSV epidemics since, as underlined by Di Mattia et al., the increase of an immunologically naïve population with infants born from mothers who have not reinforced their immunity to RSV, could lead to greater epidemics in the next winters (24).

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Figure's caption

Figure 1. Evolution of the number of RSV and Rhinovirus cases during the pre-COVID period (between 2017 and 2020) and the COVID period (2020-2021)

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Tables

Table 1. Clinical characteristics of the infants hospitalised for acute bronchiolitis in a tertiary university paediatric hospital in Paris (France) between 2017 and 2021

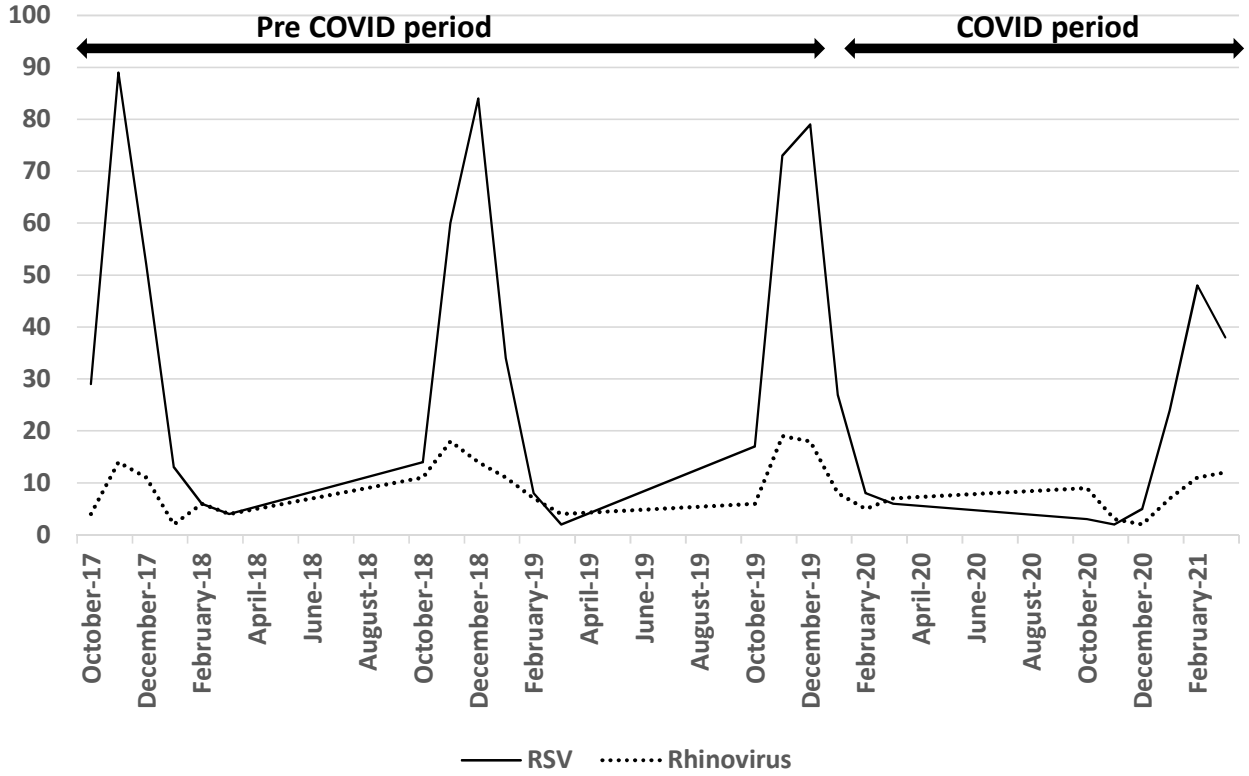
	Pre-COVID period				COVID period	
	2017-2018	**2018-2019**	**2019-2020**	**2017-2020 aggregated data**	**2020-2021**	**P-value***
Number of infants, n	**479**	**451**	**417**	**1347**	**205**	**-**
Age (months): median (IQR)	2.8 (1.5-4.9)	2.6 (1.4-4.8)	2.4 (1.3-4.4)	2.5 (1.4-4.7)	2.7 (1.5-4.7)	0.7
Gender: boys, n (%)	279 (58.2)	249 (55.2)	244 (58.5)	772 (57)	119 (58)	0.5
Comorbidities, n (%)	66 (14)	66 (15)	53 (13)	185 (14)	16 (8)	**0.02**
Weight (kg): median (IQR)	5.6 (4.4-6.9)	5.5 (4.6-7.0)	5.4 (4.3-7.0)	5.5 (4.4-7.0)	5.7 (4.5-6.9)	0.6
Evolution						
Duration of hospitalisation (days), median (IQR)	2.4 (1.2-4.0)	3.0 (2.0-4.0)	3.9 (2.0-5.0)	3.0 (2.0-4.9)	3.0 (1.5-4.2)	0.3
Oxygen therapy, n (%)	259 (54)	237 (52)	257 (61)	753 (56)	93 (45)	**0.01**
Intensive Care Unit, n (%)	48 (13)	42 (9)	67 (16)	157 (12)	21 (11)	0.6
Non-invasive ventilation, n (%)	42 (8)	38 (8)	67 (16)	147 (11)	22 (12)	0.9
Invasive ventilation, n (%)	5 (1)	5 (1)	7 (1.6)	17 (1.2)	3 (1.7)	0.6
Extracorporeal circulation, n (%)	2 (0.4)	0 (0)	2 (0.4)	4 (0.2)	0 (0)	0.4

*P-value for the comparison between pre-COVID aggregated data and COVID data using chi-square test for categorical variables and Mann-Whitney test for continuous variables.

Table 2. Results of the PCR performed in nasopharyngeal swabs for virus identification in the infants hospitalised in paediatric general wards for acute bronchiolitis between 2017 and 2021

	Pre-COVID				Post-COVID	
	2017-2018	2018-2019	2019-2020	2017-2020 aggregated data	2020-2021	P-value*
Number of infants, n	**479**	**451**	**417**	**1347**	**205**	
Nasal PCR$, n (%)	**245 (51.1)**	**274 (60.7)**	**281 (67.4)**	**800 (59.4)**	**167 (74.2)**	**< 0.01**
Respiratory syncytial virus	193 (78)	202 (73)	211 (75)	606 (75)	120 (71)	0.3
Rhinovirus	41 (17)	65 (24)	63 (22)	169 (12)	44 (21)	0.1
Adenovirus	17 (7)	10 (4)	14 (5)	16 (11)	12 (7)	0.3
Metapneumovirus	17 (7)	10 (4)	10 (4)	37 (2.7)	19 (11)	**0.001**
Influenzae A	0 (0)	2 (0.4)	1 (0.2)	3 (0.2)	0 (0)	0.4
Influenzae B	0 (0)	2 (0.7)	1 (0.3)	3 (0.2)	0 (0)	0.4
Parainfluenzae 3	9 (4)	6 (2)	10 (4)	27 (2)	16 (10)	**< 0.01**
Bocavirus	6 (2)	11 (4)	7 (2)	24 (1.7)	14 (8)	**0.001**
SARS CoV-2	0 (0)	0 (0)	0 (0)	0 (0)	3 (2)	**0.02**
Coronavirus NL63	2 (0.8)	5 (2)	3 (1)	10 (0.7)	9 (5)	**< 0.01**
Coronavirus OC43	0 (0)	1 (0.3)	2 (0.7)	3 (0.2)	7 (4)	**< 0.01**
No PCR, n (%)	**234 (48.8)**	**177 (39)**	**136 (32)**	**547 (40)**	**38 (18)**	**< 0.01**

*P-value for the comparison between pre-COVID aggregated data and COVID data using chi-square test. $Virus identifications by PCR in nasopharyngeal swabs or aspirates were performed by means of Allplex Respiratory Panel Assays (Seegene) and/or Simplexa™ Flu A/B & RSV Direct Gen II Kit (Diasorin Molecular).


Pre COVID period
COVID period
100
90
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70
60
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20
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June-18
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RSV
Rhinovirus