




Impact of public health measures on the post-COVID-19 respiratory syncytial virus epidemics in France

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Abstract

Since the beginning of the COVID-19 pandemic, other respiratory illnesses decreased worldwide. This study described the consequences of public health measures on respiratory syncytial virus (RSV) severe infections in France, where an interseasonal resurgence of RSV occurred recently. All patients admitted to Necker Hospital (Paris) between August 2018 and April 2021 with a diagnosis of RSV-associated acute lung respiratory infection (ALRI) were enrolled. Characteristics of subjects with RSV-associated ALRI in 2020/2021 were compared to those infected during the two previous outbreaks. Overall, 664 inpatients were diagnosed with RSV-associated ALRI: 229, 183, and 252 during the 2018/2019, 2019/2020, and 2020/2021 outbreaks, respectively. During autumn 2020, a national lockdown began in France but schools remained open. A 3-month delayed RSV epidemic occurred at the end of this lockdown. Compared to previous outbreaks, the 2020/2021 epidemics involved more children aged 6 to 11 months (25.8% versus 13.1%, $p < 0.0001$), but less infants aged < 6 months (41.3% versus 56.6%, $p < 0.0001$) and less adults (0.0 versus 2.7%, $p < 0.0001$). Shorter length of stay at hospital, less frequent requirement of admission to intensive care unit, use of non-invasive ventilation, and/or high-flow nasal oxygen were observed in 2020/2021 than during previous epidemics ($p < 0.0001$). Delayed RSV outbreak was associated with more hospitalizations for ALRI, higher age of pediatric inpatients, but milder median clinical phenotype. Reinforced public health measures (even while keeping nurseries and schools open with mandatory face masks since six years of age) could impact, at least transiently, the burden of RSV-related hospitalizations.

Keywords Respiratory syncytial virus · COVID-19 · Children · Adults · Reservoir · Infection control

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Introduction

Respiratory syncytial virus (RSV) is the most common cause of acute lung respiratory infections (ALRIs) in infants, in subjects with comorbidities and in the elderly, who are also at increased risk from RSV infection [1–3]. Although epidemics of RSV occur yearly, the question of who is the RSV reservoir in the off-season remains unresolved [4]. In 2020, since the implementation of public health measures to control the COVID-19 pandemic, pediatric RSV infections, such as other non-COVID-19 respiratory illnesses, dramatically decreased in both hemispheres [5–13]. Recently, Foley DA et al. described a marked interseasonal resurgence of RSV detection in Australian children from late September 2020 following several months of relaxed physical distancing recommendations (from June 2020) [14]. However, no conclusion could be drawn regarding the source of this outbreak, because public health measures were concomitantly relaxed in both children (school reopening) and adults before this resurgence. Moreover, the authors did not describe the burden of RSV-related hospitalizations, or the frequency of RSV nosocomial infections in the context of increased attention to hospital infection control measures during the COVID-19 pandemic.

Facing these unresolved questions, our study aims to describe the interactions between public health measures and the epidemiology of RSV severe infections in France, where an interseasonal resurgence of RSV infections recently occurred. We studied the burden of community-acquired and nosocomial RSV-associated ALRIs in adult and pediatric inpatients between 2018 and 2021 in Necker Hospital (Paris, France), a French 600-bed tertiary hospital (including around 75% of pediatric beds), where large cohorts of subjects with chronic complex conditions (CCC) are regularly followed.

Patients and methods

Epidemiological context

Since the beginning of the outbreak of COVID-19 in France at the end of winter 2019/2020, several bundles of public health measures have been successively introduced by the French government. We summarized the main measures introduced in the Parisian area in 2020 and 2021, which can also be found in the websites of the French government (<https://www.gouvernement.fr/en/coronavirus-covid-19>) and the French Ministry of Solidarity and Health (<https://solidarites-sante.gouv.fr/>).

Patients and definitions

The current analysis, focused on subjects admitted to the Necker Hospital between August 1, 2018, and April 30, 2021, was part of a larger prospective observational study to assess RSV-associated ALRI in adult and pediatric patients admitted to our center, with at least one overnight hospital stay. RSV-infected patients were identified from the data provided by the virology laboratory: the medical record of each inpatient with a positive RSV testing was examined in order to evaluate if inclusion criteria were fulfilled and, if so, to collect clinical and microbiological data (see below). RSV-associated ALRI was defined as diagnosis of pneumonia, bronchiolitis, bronchitis, or bronchial hyper-reactivity with concomitant detection of RSV in upper respiratory (nose/throat swabs) or lower respiratory (bronchial aspirate or bronchoalveolar lavage fluid) samples using PCR (RSV/hMPV r-gene®-Argene®, bioMérieux, Marcy l’Etoile, France). Patients with isolated upper respiratory tract infection and those without respiratory symptoms were excluded from this analysis, even if RSV was detected from their clinical samples.

The periods of time between August 2018 and July 2019, August 2019 and July 2020, and August 2020 and April 2021 were designated as 2018/2019, 2019/2020, and 2020/2021 RSV outbreaks, respectively.

Because the RSV incubation period may range from 2 to 8 days [15], the origin of ALRIs was designated as “possibly nosocomial” and “definitely nosocomial” when the patient had been hospitalized continuously 2–7 days and ≥ 8 days before the onset of respiratory symptoms, respectively. ALRIs were considered community-acquired in patients whose first symptoms occurred before hospitalization or < 2 days after hospital admission.

Clinical and microbiological data

The clinical data collected included age, gender, gestational age (for infants), underlying complex chronic conditions (CCC; as previously defined [16]), laboratory-confirmed bacterial and viral co-/super-infections, level of care required (admission to the intensive care unit [ICU], ventilation requirement, prescription of antibiotics), length of hospital stay (in case of nosocomial infection, the length of hospital stay after the onset of symptoms was recorded), and death.

Statistical analysis

Categorical variables appear with their frequency distribution. Non-normally distributed continuous variables are expressed as the median and interquartile range. Chi-squared tests or Fisher’s exact tests were used to compare discrete variables, and the Wilcoxon rank test was used to compare continuous

variables between patients presenting with a RSV-associated ALRI during the 2020/2021 outbreak and those of inpatients admitted during the 2 previous seasonal outbreaks.

Results

Epidemiological context due to the COVID-19 pandemic (2020/2021)

In March 2020, a first national lockdown with school closures began in France on Week 12 and was maintained until week 19 (Fig. 1a). Thereafter, apart from normal school

holidays, schools remained open, including during the curfew and the second lockdown (see below). In October 2020, because of a rise of SARS-CoV-2 infections in France, a curfew with reinforced public health was instituted on week 43 (Fig. 1b). Two weeks later, a second national lockdown began (weeks 45–50). However, contrary to the first lockdown, it was decided to keep nurseries and all schools, from kindergartens to high school, open, with reinforcement of social distancing and mandatory face masks since 6 years of age [17]. At the end of this second lockdown, a night curfew has been maintained between 7 PM and 6 AM and non-essential shops, bars, restaurants, cinemas, theaters, museums, and gyms remained close.

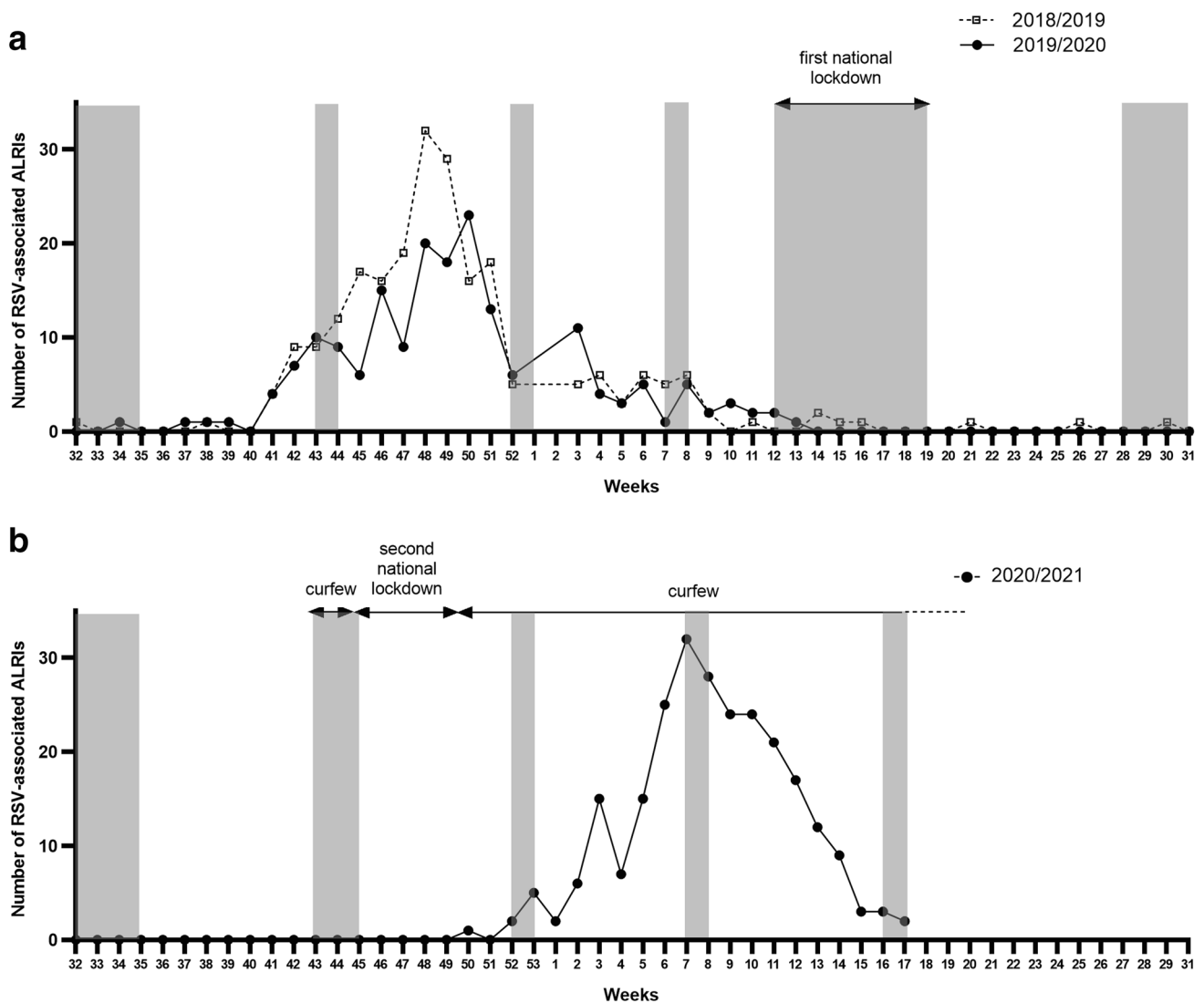


Fig. 1 Community-acquired acute lung respiratory infections (ALRIs) due to respiratory syncytial virus (RSV) diagnosed in adult and pediatric subjects admitted at Necker Hospital (Paris, France) between August 2018 and July 2019 (2018/2019 outbreak), between August 2019 and July 2020 (2019/2020 outbreak; see **a**) and between

August 2020 and April 2021 (2020/2021 outbreak; see **b**). Periods when schools were closed (because of holidays or public health measures due to the COVID-19 pandemic) in 2019/2020 (**a**) and 2020/2021 (**b**) are represented by gray rectangles

RSV outbreaks from 2018 to 2021

During the 2018/2019, 2019/2020, and 2020/2021 periods, RSV PCR was performed in our virology laboratory in 5402, 5396, and 4804 respiratory samples, respectively.

Overall, 664 inpatients were diagnosed with community-acquired RSV-associated ALRIs: 229, 183, and 252 during each successive outbreak, respectively. During the 2018/2019 and 2019/2020 outbreaks, more than 90% of RSV infections occurred between October and January (week 41–week 6) and the epidemic peaked between end of November and mid-December (weeks 48–50) (Fig. 1a). No patient was admitted with community-acquired RSV-associated ALRI after the beginning of the first national lockdown in March 2020, but RSV cases had already declined sharply before the lockdown.

No case of RSV-associated infection requiring hospitalization was observed between April and November 2020. An interseasonal RSV epidemic began after the end of the second national lockdown (at the very end of December 2020), and peaked between mid-February and mid-March 2021 (weeks 7–10).

Compared to subjects admitted with community-acquired RSV-associated ALRIs during the 2018/2019 and 2019/2020 outbreaks, those admitted during the 2020/2021 interseasonal epidemic were more frequently aged 6 to 11 months (65/252 (25.8%) versus 54/412 (13.1%), $p < 0.0001$) and less frequently infants aged less than 6 months (104/252 (41.3%) versus 233/412 (56.6%), $p < 0.0001$) or adults (0.0 versus 11/412 (2.7%), $p < 0.0001$), respectively (Table 1). Viral co-infections were more frequently diagnosed in 2020/2021 than during previous years (24.2% versus 16.0%, $p = 0.01$). They involved mostly rhinovirus and/or human coronavirus 229E, HKU1, NL63, and OC43 (isolated in 8.6% and 6.3% of cases during the whole study period) but rarely severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2; 2 cases (0.8%) in 2020/2021, both in children). Compared to those presenting with RSV-associated ALRI during 2 previous outbreaks, subjects admitted during the 2020/2021 outbreak had shorter median length of stay at hospital (6 days [4–8] versus 7 [5–9], $p < 0.0001$) and less frequent requirement of ICU admission (27.0% versus 42.2%, $p < 0.0001$), use of non-invasive ventilation and/or high-flow nasal oxygen (17.1% versus 31.8%, $p < 0.0001$) or antibiotic treatment (46.0 versus 56.3%, $p = 0.01$).

Healthcare-associated RSV-associated ALRIs were diagnosed during the 2018/2019, 2019/2020, and 2020/2021 outbreaks in 11, 10, and 9 subjects, respectively (including 5, 7, and 7 “definitely nosocomial” RSV infections). The characteristics of patients with nosocomial RSV infections are summarized in Supplementary Table 1.

Discussion

To the best of our knowledge, this is the first study describing the characteristics of subjects hospitalized with RSV-associated ALRIs during the first post-COVID-19 epidemic. Unlike previous years where French RSV outbreaks began in October, no patient was admitted with RSV-associated ALRIs during autumn 2020. Similar observations were done worldwide: hospitalizations due to non-COVID-19 respiratory illnesses dramatically decreased in 2020 [7–10]. However, because countries have implemented concomitantly numerous health measures in order to control the COVID-19 pandemic, it was not possible to evaluate the specific role of each of these measures on the suppression of the RSV epidemic. Similarly, because health measures were concomitantly relaxed in children (school reopening) and adults before the interseasonal rise of RSV cases in Australia, no conclusion could be drawn regarding the trigger of this resurgence [14]. Of note, the observed resurgence reported by Foley et al. occurred following months of relaxed social distancing measures (not immediately following relaxation of measures), suggesting either an introduction of virus from elsewhere or a low level residual transmission leading to an epidemic once the RSV-naïve population reached a threshold to allow transmission. In France, health measures implemented for the adult and the pediatric populations differed in October 2020, as nurseries and schools remained open during the second national lockdown. The RSV yearly epidemic did not start during autumn 2020, and the rise of RSV-associated ALRIs was concomitant to the relaxation of health measures in adults. These findings suggest that, in the context of reinforced public health measures in adults (strong limitation of non-essential travels, night curfew, shut of non-essential business, encouragement for working from home), maintaining children’s communities open (with reinforcement of social distancing and mandatory face masks since 6 years old) had low impact on RSV infections. This study may also suggest that the off-season RSV reservoirs may be the adult population, or at least than adults play a major role in chains of RSV transmission in the population. Further studies are needed to assess this hypothesis.

Compared to previous RSV outbreaks, the higher number and the older age of children admitted with RSV-associated ALRIs during the 2020/2021 epidemic may be due to the expanded cohort of RSV-naïve patients, as previously suggested during the RSV interseasonal resurgence in Western Australian children [14]. The older median age of children with RSV-associated ALRI in 2020/2021 may also explain the smaller proportion of severe infections, as suggested by the shorter length of stay in hospital and the lower need of admission to ICU in 2020/2021 compared to what observed during previous outbreaks. Neither the

Table 1 Comparison between characteristics and follow-up of patients admitted at Necker Hospital (Paris, France) with community-acquired RSV-associated ALRI between August 2018 and July 2020 (2018/2019 and 2019/2020 RSV outbreaks) and those of subjects admitted between August 2020 and April 2021 (2020/2021 RSV outbreak)

	2018/2019 and 2019/2020 outbreaks						2020/2021 outbreak		<i>p</i>
	August 2018– July 2019 (<i>n</i> = 229)		August 2019– July 2020 (<i>n</i> = 183)		Total (<i>n</i> = 412)		<i>n</i> = 252		
Male sex (<i>n</i> , %)	107	(46.7)	94	(51.4)	201	(48.8)	129	(51.1)	0.58
Age (<i>n</i> , %)									
0–5 months	138	(60.3)	95	(51.9)	233	(56.6)	104	(41.3)	<0.0001
Including children born between 32 and 36 WOG	23		10		33		8		
Including children born <32 WOG	3		1		4		0		
6–11 months	27	(11.8)	27	(14.8)	54	(13.1)	65	(25.8)	<0.0001
12–23 months	23	(10.0)	29	(15.8)	52	(12.6)	43	(17.1)	0.14
2–17 years	35	(15.3)	27	(14.8)	62	(15.0)	40	(15.9)	0.82
≥ 18 years	6	(2.6)	5	(2.7)	11	(2.7)	0	(0.0)	0.009
Underlying medical conditions (<i>n</i> , %)									
At least one	94	(41.0)	66	(36.1)	160	(38.8)	86	(34.1)	0.25
Neuromuscular CCC	13	(5.7)	12	(6.6)	25	(6.1)	13	(5.2)	
Cardiovascular CCC	21	(9.2)	19	(10.4)	40	(9.7)	7	(2.8)	
Respiratory CCC	48	(21.0)	47	(25.7)	95	(23.1)	54	(21.4)	
Renal CCC	7	(3.1)	8	(4.4)	15	(3.6)	1	(0.4)	
Gastrointestinal CCC	6	(2.6)	6	(3.3)	12	(2.9)	5	(2.0)	
Hematological CCC and/or immune deficiency	18	(7.9)	11	(6.0)	29	(7.0)	16	(6.3)	
Metabolic CCC	2	(0.9)	10	(5.5)	12	(2.9)	5	(2.0)	
Other congenital or genetic defect	21	(9.2)	15	(8.2)	36	(8.7)	16	(6.3)	
Antiviral prophylaxis (<i>n</i> , %)									
Palivizumab	6	(2.6)	0	(0.0)	6	(1.5)	0	(0.0)	0.09
<i>i.v.</i> or <i>s.c.</i> polyvalent immunoglobulin	3	(1.3)	0	(0.0)	3	(0.7)	1	(0.4)	
Viral co-/super-infection (<i>n</i> , %)									
At least one virus	40	(17.5)	26	(14.2)	66	(16.0)	61	(24.2)	0.01
Influenza virus	3		0		3		1		
Parainfluenza virus	3		2		5		6		
Rhinovirus	23		11		34		23		
Adenovirus	4		4		8		6		
Human metapneumovirus	1		1		2		6		
Severe acute respiratory syndrome coronavirus type 2	0		0		0		2		
Human coronavirus 229E, HKU1, NL63, and OC43	10		8		18		24		
Bacterial lower respiratory tract co-/super-infection									
Microbiologically proven infection	13	(5.7)	5	(2.7)	18	(4.4)	9	(3.6)	0.69
Suspected infection	64	(27.9)	78	(42.6)	142	(34.5)	83	(32.9)	0.74
Clinical follow-up									
LOS (days) (median, IQR)	7	[5–9]	7	[5–10]	7	[5–9]	6	[4–8]	<0.0001
ICU admission (<i>n</i> , %)	94	(41.0)	80	(43.7)	174	(42.2)	68	(27.0)	<0.0001
Oxygen requirement (<i>n</i> , %)	182	(79.5)	151	(82.5)	333	(80.8)	197	(78.2)	0.43
Mechanical ventilation requirement (<i>n</i> , %)	8	(3.5)	9	(4.9)	17	(4.1)	8	(3.2)	0.68
Non-invasive ventilation and/or high-flow nasal oxygen requirement (<i>n</i> , %)	72	(31.4)	59	(32.2)	131	(31.8)	43	(17.1)	<0.0001
Antibiotic treatment (<i>n</i> , %)	137	(59.8)	95	(51.9)	232	(56.3)	116	(46.0)	0.01
Death (<i>n</i> , %)	3	(1.3)	1	(0.5)	4	(1.0)	0	(0.0)	0.30

RSV, respiratory syncytial virus; ALRI, acute lower respiratory tract infection; WOG, weeks of gestation; CCC, chronic complex conditions; *i.v.*, intravenous; *s.c.*, subcutaneous; LOS, length of stay; ICU, intensive care unit

frequency of underlying medical conditions nor bacterial co-/supra-infections may explain this milder clinical phenotype in 2020/2021, as these factors were as frequently observed than during previous time periods. Of note, the prevalence of admission to ICU during the recent outbreak remains higher in our center than previously described in high-income countries (27% versus 2–12%) [18]; this could be explained by the high prevalence of CCC in subjects followed in our tertiary hospital.

Several factors could be discussed as possible contributors to this RSV late resurgence, such as viral introductions (or lack thereof), changes in travel between countries, RSV dynamics in other countries, and climatic factors [4, 14]. Indeed, during the pre-COVID-19 era, studies suggested that RSV virulence may follow enhanced transmission when the weather turns cold and relative indoor humidity is decreased, favoring stability and transmission of RSV [19]. During winter 2020/2021, the weather conditions (temperature, air humidity, wind conditions) measured in the Parisian area by the French national meteorological service did not differ to those observed during previous winters (<https://donneespubliques.meteofrance.fr>). Our study suggests that strong public health measures can, at least transiently, counterbalance the meteorological effect on the timing of RSV outbreak. Moreover, our data underline the greater fragility of RSV control in the population compared to that of influenza virus: a slight relaxation of public health measures (with maintain of night curfew, social distancing, and respiratory hygiene practices) was concomitant to the resurgence of RSV in France; in contrast, no post-COVID-19 outbreak of influenza virus infection occurred to date, neither in France nor in other countries worldwide [5, 7, 8, 11–13].

Before the COVID-19 pandemic, more than 2.5% of community-acquired RSV-associated ALRIs were diagnosed in adult inpatients, especially among the large cohorts of adults with severe immune deficiencies followed in our center. Interestingly, none severe RSV infection was diagnosed in adults during the 2020/2021 outbreak, probably illustrating the high adherence of fragile adults to barrier measures taken during the COVID-19 pandemic.

This study has three main limitations. First, because RSV may not have been screened in all patients with ALRI, this study may underestimate the real burden of RSV infection in our center. This underestimation may be more pronounced in patients with milder symptoms, where RSV may have been less frequently screened than in case of severe infection. Second, although the ALRIs were primarily attributed to RSV by clinicians in all patients described in this study, we cannot exclude that bacterial co-infections may have influenced their clinical outcome. Microbiologically proven and suspected bacterial infections were not significantly different between RSV seasons. However, this confounding factor cannot be excluded in our non-interventional study because all other respiratory

pathogens may not have been screened in several RSV-infected patients. In order to evaluate the impact of this potential bias, further prospective studies are needed with systematic screening of all potential co-infections. Finally, the high prevalence of CCC among patients followed in our tertiary hospital hampers extrapolation of our results to other French hospitals.

Conclusions

Our study suggests that reinforced public health measures (while keeping nurseries and schools open with social distancing and mandatory face masks since 6 years of age) could have, at least transiently, a major impact on the control of RSV-associated ALRIs. The expanded cohort of RSV-naïve patients may explain the characteristics of children admitted with RSV-associated ALRIs during the recent French RSV interseasonal resurgence compared to previous RSV outbreaks (larger numbers in an older age group in children, less severe diseases). The burden of RSV infections on the health system underlines the need for ongoing monitoring in other jurisdictions and the identification of public health measures targeted to the RSV reservoirs in the population.

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Author contribution JF and PF conceived the study and drafted the manuscript; JT, HC, CD, FM, PP, AS, HA, and MLV provided contribution to the analysis of the data and the revision of the manuscript. All authors approved the final version to be published and agreed to be accountable for all aspects of the work.

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Data availability Data will be made available on reasonable request.

Declarations

Ethics approval, consent to participate, and consent for publication Participants provided informed consent for the anonymous use of their clinical and biological data for biomedical research and publication (for pediatric patients, informed consent was provided by parents/guardians). This study was reviewed and approved by the Necker Hospital Institutional Review Board (registration number in the registry of the Assistance Publique—Hôpitaux de Paris: 20190729122906). All data processing and storage comply with the General Data Protection Regulation (GDPR) and ethical standards of the National Research Committee.

Conflict of interest P.F. has received honoraria and travel grants from ViiV Healthcare, Janssen Cilag, Gilead Sciences, and MSD France for participation in advisory boards, educational programs, and conferences, outside the submitted work. M. L.-V. has received non-financial and other support from BioMérieux and non-financial support from Abbott and Ferring SAS, outside the submitted work. The other authors declare no competing interests.

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