



# Preventing respiratory syncytial virus infections in hospitalized children and adults: should we do better?

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## SUMMARY

**Objective:** To compare the burden of nosocomial and community-acquired respiratory syncytial virus (RSV)-associated acute lower respiratory tract infections (ALRIs) in adult and pediatric patients concomitantly admitted to a French tertiary hospital, and to evaluate the effectiveness of existing infection control measures.

**Patients and methods:** We prospectively included all adult and pediatric patients admitted to Necker hospital (Paris) between October 2018 and February 2019 with a diagnosis of RSV-associated ALRI. We compared characteristics of ALRIs between patients with community-acquired versus nosocomial infections and, in each group, between children and adults.

**Results:** Community-acquired and nosocomial RSV-associated ALRIs were diagnosed in 229 and 11 inpatients, respectively. The burden of community-acquired infections was higher in children than in adults: 2.1% versus 0.2% of the total number of pediatric and adult inpatients, respectively ( $p < 0.0001$ ); 4.2% versus 0.2% of the total number of hospitalization days in pediatric and adult units, respectively ( $p < 0.0001$ ). Compared to inpatients with community-acquired ALRIs, those with nosocomial infections were more frequently adults (45.5% versus 2.6%,  $p = 0.0005$ ) and subjects with at least one chronic complex condition (100.0% versus 41.0%,  $p < 0.0001$ ). The total number of hospitalization days due to nosocomial ALRIs was higher in adults than in children (0.32% versus 0.11%,  $p < 0.0001$ ).

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**Conclusions:** Nosocomial RSV-associated ALRIs rarely occurred, suggesting a good effectiveness of our infection control strategy. However, the burden of nosocomial infection was higher in adults than in children, suggesting that education and training of healthcare personnel, patients and visitors about the risk of nosocomial RSV infections should be reinforced in adult wards.

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## Introduction

Respiratory syncytial virus (RSV) is associated with 19–81% of viral acute respiratory infections causing hospitalization in infants and children [1]. RSV also has a burden on healthcare services and winter mortality in older adults [2–4]. Published data on the epidemiology of nosocomial RSV infections are still limited. In infants, a severe course of nosocomial disease has been described, especially in subjects with comorbidities [5], even more severe than community-acquired RSV infections [6]. In adults, RSV acquisition seems to be frequently nosocomial or healthcare-related, with a higher mortality than with influenza virus infection [7]. However, to the best of our knowledge, no previous study compared the burden of community-acquired versus nosocomial RSV-associated acute lower respiratory tract infections (ALRIs) in both adult and pediatric patients concomitantly admitted at the same hospital.

Necker hospital (Paris) is a French 600 bed tertiary hospital, where large cohorts of adult and pediatric patients with chronic complex conditions (CCC) are regularly followed. A bundle of measures has been implemented to prevent nosocomial RSV-associated ALRIs, including implementation of droplet and contact precautions for symptomatic patients, annual education and training of all healthcare personnel, providing instructional materials for patients and visitors on recommended hand hygiene, respiratory hygiene/cough practices and limitation of pediatric visitors during seasonal outbreaks of viral ALRIs. Infants predisposed to developing severe RSV disease receive passive antiviral immunization with palivizumab in accordance to French guidelines [8]. Finally, our hospital has recently been partly rebuilt and includes now a high rate of single-patient rooms (91%), which may help to prevent healthcare-associated infections.

This study aims to compare the burden of nosocomial and community-acquired RSV-associated ALRIs in both adult and pediatric inpatients and to evaluate the effectiveness of our infection control measures.

## Patients and methods

### Ethics

Participants provided informed consent for the anonymous use of their clinical and biological data for biomedical research (for paediatric 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).

### Patients and definitions

We performed a prospective observational study in adult and pediatric patients admitted to Necker hospital between October 1, 2018 and February 28, 2019, with a minimum hospital stay of 2 days and a diagnosis of RSV-associated ALRI. RSV-infected patients were identified from the data provided by the virology laboratory. 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.

Because the RSV incubation period may range from 2 to 8 days [9], the origin of ALRIs was designated as “possibly nosocomial” and “definitely nosocomial” when the patient had been hospitalized continuously 2–7 days and  $\geq 8$  days before the onset of respiratory symptoms, respectively. ALRIs were considered community-acquired in patients whose symptoms occurred before hospitalization or  $< 2$  days after hospital admission.

### Clinical and microbiological data

The clinical data collected included age, gender, term of birth (for infants), underlying complex chronic conditions (CCC; as previously defined [10]), laboratory-confirmed bacterial and viral co-/supra-infections, level of care required (admission to the intensive care unit [ICU], ventilation requirement, prescription of antibiotics), length of hospital stay (in the case of nosocomial infection, the length of hospital stay after the onset of symptoms was recorded) and death.

The number of hospital admissions and total hospitalization days of patients with ALRIs were compared to those of all patients admitted to our hospital during the study period, in order to estimate the burden of RSV infection.

Finally, we evaluated the proportion of RSV-infected subjects who adequately received palivizumab-based prophylaxis before the onset of their ALRIs according to the 1999 marketing authorization of palivizumab by the European Medicines Agency (EMA) [11], the 2007 guidelines of the French Health Authority (HAS), [8] and the 2014 guidance for palivizumab use of the American Academy of Pediatrics (AAP) [12].

## 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 with community-acquired versus nosocomial ALRIs.  $P < 0.05$  was considered statistically significant.

## Results

### Community-acquired RSV-associated ALRIs requiring hospitalization: characteristics and burden

Between October 2018 and February 2019, 229 patients admitted to our hospital were diagnosed with community-acquired RSV-associated ALRIs. Their characteristics are summarized in Table 1. The majority were less than 6 months old (60.3%) and, among them, few were born pre-term (18.8%). At least one CCC was present in 40.1% of subjects, most frequently a respiratory CCC. Viral and bacterial co-/supra-infections were documented in 17.5% and 5.7% of cases, respectively, but around one in two patients received antibiotics. The proportion of patients requiring ICU admission was high (40.1%) but only 3 patients (1.3%) died. All of them were children with severe cardiovascular  $\pm$  respiratory CCC and died from acute respiratory distress syndrome.

When compared to all other patients admitted to our hospital during the same period of time, patients with community-acquired RSV infections accounted for 1.6% of inpatients and 3.1% of the total number of hospitalization days. The burden of community-acquired RSV infections was disproportionately higher in pediatric than in adult patients: 2.1% versus 0.2% of the total number of pediatric and adult inpatients, respectively ( $p < 0.0001$ ); 4.2% versus 0.2% of the total number of hospitalization days in pediatric and adult units, respectively ( $p < 0.0001$ ).

Among children with community-acquired RSV infections, palivizumab-based prophylaxis was given to 6/18 (33.3%), 6/6 (100%) and 4/4 (100%) of those for whom antiviral prophylaxis was recommended by the 1999 EMA, the 2007 French and the 2014 American guidelines, respectively.

### Nosocomial RSV-associated ALRIs: characteristics and burden

Eleven patients were diagnosed with a possibly ( $n = 6$ ) or definitely ( $n = 5$ ) nosocomial RSV-associated ALRI (Table 1). Almost half of them (45.1%) were 60 years old or older. All subjects with nosocomial RSV infection had at least one CCC but none of them died from RSV.

Compared to inpatients with community-acquired RSV-associated ALRIs, those with nosocomial infections were more frequently adults ( $p = 0.0005$ ) and subjects with at least one CCC ( $p < 0.0001$ ). The rates of viral and bacterial co-/supra-infections, oxygen/ventilation requirement, ICU admissions, antibiotic treatments and deaths did not differ between inpatients diagnosed with community-acquired versus nosocomial

infections. However, the length of stay was statistically longer in the latter than in the former ( $p < 0.0001$ ).

When compared to all patients admitted to our hospital during the same period of time and free from community-acquired RSV-associated ALRIs, patients with nosocomial RSV ALRIs accounted for 0.08% of all inpatients and 0.17% of the total number of hospitalization days. The proportion of inpatients with nosocomial infections did not differ between children and adults (0.06% versus 0.15%,  $p = 0.14$ ). However, the total number of hospitalization days due to nosocomial RSV-infected patients was higher in adults than in children (0.32% versus 0.11%,  $p < 0.0001$ ).

No children with nosocomial RSV received palivizumab-based prophylaxis prior to the onset of their infection. Retrospectively, such prophylaxis was not recommended for any of these children by the EMA, the French or the American guidelines.

## Discussion

To the best of our knowledge, we report one of the first studies evaluating the efficacy of the same bundle of infection control measures to prevent RSV ALRIs in both adult and pediatric patients admitted to the same tertiary hospital.

Some results regarding community-acquired RSV infections requiring hospitalization are in line with previous reports: most of the subjects hospitalized with RSV were aged  $\leq 12$  months, and especially  $\leq 6$  months [13–21]. The median length of hospital stay was in the range of that reported in previous pediatric studies (between 2 and 11 days). However, the prevalence of admission to ICU and the mortality rate were higher than previously described in high-income countries (41.0% versus 2–12%, and 1.3% versus  $< 0.5\%$ , respectively) [1]. This could be explained by the high prevalence of CCC in the population of children followed in our tertiary hospital, and, consequently, in those admitted for community-acquired RSV infections. This proportion was higher than in previous studies, where typically  $> 70\%$  of children hospitalized with RSV-related ALRI/bronchiolitis had no underlying medical conditions [16–18,22–24]. Thus, the epidemiological characteristics of patients admitted at our hospital with community-acquired RSV infections cannot be extrapolated to other French pediatric centers.

In our study, the burden of RSV among community-acquired ALRIs requiring hospitalization was strongly lower in adults compared to infants and children, despite the high prevalence of CCC (especially immunodeficiency) among adults followed in our center (data not shown). Our findings suggest that, although RSV has the potential to cause severe community-acquired ALRIs in high-risk adults (such as immunocompromised patients) [25], RSV infections seem to rarely require hospitalization in this population.

Few of our patients (2.6%) admitted with community-acquired infections received palivizumab-based antiviral prophylaxis prior to the onset of the infection. However, the retrospective evaluation of the medical files of all RSV-infected inpatients revealed that no other patient required palivizumab according to the 2007 French and the 2014 American guidelines [8,12]. Our results suggest that guidelines of antiviral prophylaxis are appropriately applied in our center but that most of

**Table 1**

Comparison of characteristics and follow-up of patients admitted at Necker Hospital (Paris, France) between October 2018 and February 2019 and presenting with community-acquired versus nosocomial RSV-associated ALRI

	Total (n = 240)	Patients with community acquired RSV-associated ALRI (n = 229)	Patients with nosocomial RSV-associated ALRI (n = 11)	p
Male sex (n, %)	113 (47.1)	107 (46.7)	6 (54.5)	0.61
<b>Age (n, %)</b>				0.0005
0–5 months	141 (58.8)	138 (60.3)	3 (27.3)	
including children born between 32 and 36 WOG	23	23	0	
including children born < 32 WOG	3	3	0	
6–11 months	28 (11.7)	27 (11.8)	1 (9.1)	
12–23 months	23 (9.6)	23 (10.0)	0 (0.0)	
2–17 years	37 (15.4)	35 (15.3)	2 (18.2)	
18–59 years	4 (1.7)	4 (1.7)	0 (0.0)	
≥ 60 years	7 (2.9)	2 (0.9)	5 (45.5)	
<b>Underlying medical conditions (n, %)</b>				
At least one CCC	105 (43.8)	94 (41.0)	11 (100.0)	<0.0001
Neuromuscular CCC	15 (6.3)	13 (5.7)	2 (18.2)	
Cardiovascular CCC	24 (10.0)	21 (9.2)	3 (27.3)	
Respiratory CCC	52 (21.7)	48 (21.0)	4 (36.4)	
Renal CCC	11 (4.6)	7 (3.1)	4 (36.4)	
Gastrointestinal CCC	7 (2.9)	6 (2.6)	1 (9.1)	
Hematological CCC and/or immune deficiency	24 (10.0)	18 (7.9)	6 (54.5)	
Metabolic CCC	2 (0.8)	2 (0.9)	0 (0.0)	
Other congenital or genetic defect	22 (9.2)	21 (9.2)	1 (9.1)	
<b>Antiviral prophylaxis (n, %)</b>				
palivizumab	6 (2.5)	6 (2.6)	0 (0.0)	1.0
i.v. or s.c. polyvalent immunoglobulin	3 (1.3)	3 (1.3)	0 (0.0)	1.0
<b>Viral co-/super-infection (n, %)</b>				
At least one virus	42 (17.5)	40 (17.5)	2 (18.2)	1.0
influenza virus	4	3	1	
parainfluenza virus	3	3	0	
rhinovirus	24	23	1	
adenovirus	4	4	0	
human metapneumovirus	1	1	0	
coronavirus	11	10	1	
<b>Bacterial lower respiratory tract co-/super-infection</b>				
Microbiologically proven infection	14 (5.8)	13 (5.7)	1 (9.1)	0.49
Suspected infection	67 (27.9)	64 (27.9)	3 (27.3)	1.0
<b>Clinical follow-up</b>				
LOS (days) (median, IQR)	7 [5–10]	7 [5–9]	17 [11–26] <sup>a</sup>	< 0.0001
ICU admission (n, %)	97 (40.4)	94 (41.0)	3 (27.3)	0.53
Oxygen requirement (n, %)	189 (78.8)	182 (79.5)	7 (63.6)	0.25
Mechanical ventilation requirement (n, %)	9 (3.8)	8 (3.5)	1 (9.1)	0.35
Non-invasive ventilation and/or high-flow nasal oxygen requirement (n, %)	73 (30.4)	72 (31.4)	1 (9.1)	0.18
Antibiotic treatment (n, %)	142 (59.2)	137 (59.8)	5 (45.5)	0.36
Death (n, %)	3 (1.3)	3 (1.3)	0 (0.0)	1.0

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.

<sup>a</sup> For healthcare-associated infections, the length of stay after the diagnosis of RSV ALRI was described.

the patients admitted for RSV infections (and most of those admitted to pediatric ICU), did not fall into the recognized indications for RSV prophylaxis, as recently reported by Ghazaly et al. [26]. In light with the ongoing research into the development of new and more cost-effective strategies against RSV infections than palivizumab (including long acting monoclonal antibodies and vaccines), further larger studies defining the characteristics of patients hospitalized with severe RSV infections, may help to rethink the guidelines of RSV prophylactic strategies.

RSV is known to be a major nosocomial hazard on paediatric wards, especially in cases of age less than 5 months, prematurity and chronic lung disease of prematurity [6]. Previous studies described rates of nosocomial RSV infections between 0.4 and 9.6% [6,27–29], with poorer clinical outcomes than community-acquired RSV infections [6]. Contrasting with these results, we observed in our pediatric wards a low rate of nosocomial RSV-related ALRIs (0.06% of inpatients) and no death related to nosocomial RSV infection. This low rate of nosocomial infections could be related to our multifaceted infection control strategy including a high proportion of single-patient rooms (for both infected and uninfected patients), staff training repeated before each season of viral epidemics, screening of symptomatic patients, isolation/cohorting, hand washing, gloves and masks, gowns (for staff attending infants with respiratory symptoms) and restriction of visitors.

Interestingly, our study suggests that the efficacy of this infection control strategy may be less effective in adult than in pediatric wards. Indeed, nosocomial infections were proportionately more frequently diagnosed in adults than community-acquired ALRIs ( $p < 0.0001$ ) and the total number of hospitalization days due to nosocomial RSV infection was higher in adults than in children (0.32% versus 0.11%,  $p < 0.0001$ ). Similarly, Kestler M et al. recently described that RSV acquisition was frequently nosocomial or healthcare-related in adults during flu season [7]. Although we did not observe the high RSV-related mortality described in adults by Kestler (14.7%), we described longer length of hospital stay in case of nosocomial versus community-acquired infections in adults. Our results suggest that, despite a low rate of nosocomial infections observed in adults (0.15% of inpatients), our multifaceted infection control strategy may be reinforced in adults wards in order to obtain similar results seen in pediatric units. Because of the low number of nosocomial infections during the 2018/2019 RSV epidemic, it could be interesting to repeat this study during several successive seasonal epidemics in order to evaluate the effectiveness of our bundle of measures in a larger population.

This study has five main limitations. First, RSV-related ALRIs were defined from the data provided by the virology laboratory. Because RSV may not have been screened in a significant proportion of 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 mild symptoms (especially those with isolated upper respiratory tract infection), where RSV may have been less frequently screened than in case of severe infection. However this potential limitation does not hamper evaluation of the efficacy of our infection control strategy, which mainly aims to prevent severe infections. Second, although the ALRIs were primarily attributed to RSV

by clinicians in all patients described in this study, we cannot exclude that viral and bacterial co-infections may have influenced their clinical outcome. This confounding factor cannot be excluded in our non interventional study because all other respiratory pathogens may not have been screened for. In order to evaluate the impact of this potential bias, further prospective studies are needed with systematic screening of all potential viral and bacterial co-infections. Third, this observational study does not allow the effectiveness of individual components of our multi-component control measures to be assessed. Similar observation was done by French CE *et al.* in the recent review of published and unpublished literature about the effectiveness of control measures to prevent nosocomial RSV transmission events [30]. However, because similar preventive strategies were applied in all units of our center, this limitation does not hamper the comparison of their efficacy on pediatric versus adult wards. Further studies are needed in order to evaluate to what extent the compliance with each measure of our infection control bundle differs between adult and paediatric populations. Because nosocomial infections may be transmitted by healthcare personnel, visitors and patients, it would be interesting to differentiate the compliance to measures targeting each of these populations in such further studies. Fourth, as previously discussed, the high prevalence of CCC among patients followed in our tertiary hospital hampers extrapolation of our results to other French hospitals. The higher prevalence of CCC among patients with nosocomial versus community-acquired RSV infections (100.0% versus 41.0%) may at least partly explain the longer length of stay in the former than in the latter. Fifth, we used a very large definition of a nosocomial case, by pooling “possibly” and “definitely” nosocomial infections. In previous studies investigating the risk of RSV transmission to patients and providing a clear definition of a nosocomial case, various cut-off were used to define it (mostly 5 days or more after hospital admission) [30]. Here, we chose a wider definition of a nosocomial case (i.e. infection occurring in a patient hospitalized continuously  $\geq 2$  days before the onset of respiratory symptoms), because (i) the RSV incubation period may be as short as 2 days [9], and (ii) we did not want to minimize the real burden of RSV nosocomial ALRIs. Interestingly, although we used such a wide cut-off, the burden was not high in our center. This limitation does not hamper comparison of the burden of nosocomial infections between pediatric and adult wards at our center.

## Conclusions

In summary, the burden of community-acquired infections requiring hospitalization is disproportionately higher in infants/children than in adults admitted to our center. Nosocomial RSV-associated ALRIs rarely occurred, suggesting good efficacy of our multi-component preventive strategy. However, the burden of nosocomial infection was higher in adults than in children, suggesting that education and training of healthcare workers, patients and visitors about the risk of nosocomial respiratory viral disease should be reinforced on adult wards. The fact that  $> 97\%$  of patients hospitalized with community-acquired or nosocomial RSV-associated ALRI were not

considered at “high-risk” (i.e. requiring immunoprophylaxis with palivizumab) according to the French and American guidelines, highlights the urgent need to develop new and more cost-effective antiviral preventive strategies, in order to decrease the burden of RSV infections requiring hospitalizations.

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## Declaration of interest

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