Respiratory Syncytial Virus and Metapneumovirus Infection Have Different Clinical Presentation in Children

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Abstract

Respiratory syncytial virus (RSV) and Human metapneumovirus (hMPV), members of *Pneumoviridae* family are common causes of acute respiratory tract infections (ARTI) among children. Study material includes routine nasopharyngeal samples obtained during 8-year period for hMPV and one single season for RSV in children aged 0 to 15 years at the Centre Hospitalier Universitaire (CHU) Saint Pierre in Brussels. Positive samples for RSV or hMPV identified by viral culture, lateral flow chromatography test for RSV or direct fluorescent assay for hMPV were selected retrospectively. The medical charts of these patients were reviewed. Hospitalization rate was 37% (219/591) and 39% (187/476) for hMPV and RSV respectively. Children hospitalized for RSV infection were significantly younger and more dyspneic, requiring more respiratory support, longer hospital stay and transfers in Pediatric intensive Care Units (PICU) than those hospitalized for hMPV infection. Pneumonia diagnostic and antibiotics therapies were more significantly associated with hMPV infections.

In conclusion, despite their genetic similarities, RSV and hMPV present epidemiological and clinical differences in pediatric infections.

What Is Known

- RSV and hMPV are members of *Pneumoviridae* family and are common causes of ARTI
- Their epidemiology and seasonality descriptions seems concordant in the literature

What Is New

- RSV are frequently associated with more severe hospitalizations in younger children, hMPV infections is associated with more antibiotics prescription
- Despite their genetic resemblance, RSV and hMPV are leading to two pathogenic entities

Introduction

Acute respiratory tract infections (ARTI) remain the leading causes of children morbidity and mortality worldwide [1]. In industrialized countries, the most common etiology of bronchiolitis [2, 3] and of viral pneumonia [4–6] is respiratory syncytial virus (RSV). Since its description by van den Hoogen et al. in 2001, the human metapneumovirus (hMPV) has been described as a common cause of viral ARTI in children [7–10]. Both viruses belong to the *Pneumoviridae* family and share almost 50% of nucleotide identity [8].

Whereas some studies have described a very similar spectrum of clinical presentations with these 2 viruses [11–13], others have highlighted some differences including hMPV infections affecting older children and presenting more frequently with pneumonia and bacterial complications [12, 14–16]. On the other hand, the description of the prevalence and the seasonality of RSV and hMPV seems concordant in recent European studies [17–19].

The aim of this study was to compare retrospectively the clinical features of hMPV and RSV infection in children admitted to the Centre Hospitalier Universitaire (CHU) Saint-Pierre . Since hMPV is much less prevalent than RSV, our study included all children hospitalized with hMPV infection over a 8 year period (2010 to 2017) and children hospitalized with RSV infection during a single winter period (2014-2015) in order to compare similar numbers of children infected by each of the viruses.

Materials And Methods

Study setting and population

The CHU Saint-Pierre is a university affiliated general hospital located in downtown Brussels. About 40,000 children attend its pediatric emergency room and outpatient clinics every year. According to local guidelines, nasopharyngeal aspirates (NPA) and nasopharyngeal swabs (NPS) for rapid viral antigen testing and viral culture are performed in all children hospitalized for an ARTI or fever of unknown origin (FUO). Every infant younger than one month old presenting with fever is hospitalized and get a nasopharyngeal aspirate. For non-hospitalized children, these procedures are left at the physicians' discretion. We retrospectively reviewed the medical charts of all children aged < 15 years who had a positive nasopharyngeal specimen for hMPV between the 01/01/2010 and the 31/12/2017 and for RSV from 29/09/2014 to 31/04/2015. Positive samples were identified from a database issued by the hospital's microbiology laboratory with characteristics including date, type of specimen, type of test performed, and presence of any another virus. Duplicates (more than one positive respiratory specimen during the same viral episode) were excluded. Medical files were screened to identify hospitalization and record from hospitalized children signs and symptoms on admission, vital parameters, presence of any risk factor for ARTI, history of preterm birth, laboratory tests results, chest radiology findings, clinical diagnosis on admission, treatment during hospitalization, oxygen requirement, method of oxygen administration, pediatric intensive care unit (PICU) admission, need of nasogastric feeding or parenteral nutrition, and length of stay in hospital.

For the comparison of clinical characteristics in children hospitalized for RSV or hMPV infection, hospitalization for a non-respiratory infection (i.e. urinary tract infection, acute gastroenteritis) were excluded. The CHU Saint-Pierre Ethical Committee approved the study protocol.

Definitions

Upper respiratory tract infection (URTI) was defined as rhinitis, pharyngitis or acute otitis media. Children with lower respiratory tract infection (LRTI) presented with hypoxemia, clinical or radiological findings of pneumonia, bronchitis or bronchiolitis.

Fever was defined as body temperature > 38°C measured on admission or reported by parents. Hypoxemia referred to an oxygen saturation measured by pulse oximetry < 95%. Respiratory rate was compared with age-related normal values [20]. Clinical signs of respiratory distress included the use of accessory muscles, thoraco-abdominal balance and nasal flaring.

The risk factors for severe respiratory infections included bronchopulmonary dysplasia, asthma, heart defects, in utero Human Immunodeficiency Virus (HIV) exposure, neuromuscular diseases, severe epileptics affections, genetic diseases (like Down syndrome and sickle cell disease), immunosuppression and polymalformative genetic syndromes. Preterm birth (before 37 weeks of gestation) was analyzed separately; children born before 28 weeks of gestation were considered extremely premature.

Virological methods

The hospital's microbiology laboratory performs year-round respiratory pathogens surveillance. Routine laboratory testing for RSV and hMPV includes rapid antigen detection tests and viral culture. A lateral flow chromatography test (LFC) (BinaxNOW RSV, Alere, Waltham, MA, USA) is used to detect RSV and a direct fluorescent assay (DFA) (Argene, Biomérieux,Marcy L'Etoile, France) to detect hMPV. Cell culture is performed for each nasopharyngeal (NP) specimen on confluent Vero, MRC5 and LLC-MK2 cell cultures. Cultures are examined every two to three days for cytopathic effect for at least 14 days. Viral detection by reverse transcriptase polymerase chain reaction is available but was rarely performed during the study period; it was thus not included in this study. The Belgian government only reimburses antigen detection tests for 3 different respiratory viruses per day, from a total of 5 tests available at the laboratory performing the analyses for the CHU Saint-Pierre (influenza A+B, RSV, hMPV, adenovirus and parainfluenzae). Viral cultures are performed systematically whereas realization of the rapid antigen detection tests vary according to the season and are based on the most prevalent circulating viruses. Therefore, RSV was not detected by antigen detection tests during the whole period. The detection of hMPV by DFA is performed throughout the year as this virus grows poorly in cell cultures and could be missed if only this latter technique is used.

Statistical analysis

Statistical analysis was performed using SPSS Statistics (version 25, SPSS, Inc., Chicago, IL, USA). Categorical variables were compared using a χ^2 test or Fisher's exact test and quantitative variables were analyzed with the Mann-Whitney U nonparametric test or t-test for two samples with equal variance. In addition, logistic regression models were used to compare risk factors of hMPV and RSV severe infections. A two-sided p-value of <0.05 was considered significant.

Results

Seasonal Distribution

From October 1st 2010 to December 31st 2017, a total of 22,953 NP samples collected in children were received by the laboratory to detect respiratory pathogens. hMPV was detected in 634 (2.8%) samples. The proportion of samples in which hMPV was detected varied between 1.5% in 2012 and 2016 and 4.3% in 2014. hMPV infections followed a seasonal distribution, with 76% of all cases occurring between December and April (Figure 1), with an annual peak in the spring (March and April).

From October 29th 2014 to April 31st 2015, RSV was detected in 493 (19.9%) of 2474 respiratory samples collected in children. RSV peaked in November and December 2014 with 166 and 201 cases respectively, accounting for 74% of all RSV cases collected during the 2014-2015 winter season.

Laboratory Data

After exclusion of duplicates, we identified 600 children with hMPV infection and 485 children with RSV infection. Nine children were coinfected with RSV and hMPV. The NPA was the most commonly used sampling method for identification of hMPV and RSV (78% and 87% respectively). For hMPV, an antigen test was performed for 532 samples (89%) and was positive in 522/532 (98%), while 68 cases were identified by culture only. For RSV, an antigen test was performed in 469 samples (97%) and was positive in 399/469 (85%) while 17 cases were identified by culture only. When considering true positive samples as having a positive antigen detection test and/or viral culture, viral culture was much less sensitive for hMPV detection than for RSV detection (33% vs 96%).

Demographic characteristics of the study population of children infected by hMPV or RSV

Age and gender of the children infected with RSV and hMPV were compared. The 9 children who were co-infected with hMPV and RSV were excluded from this analysis. Children with hMPV were significantly older than children with RSV (Figure 2, median age 7.7 and 5.4 months, respectively, p-value <0.0001). Overall, the gender distribution was not different between hMPV and RSV infections, but among children who had hMPV infection, males were significantly younger (median 7.2 months) than females (8.9 months, p-value = 0.014).

Co-infections with other respiratory viruses are described in Table 1. Children with hMPV presented more often with a viral co-infection than children with RSV (13 % versus 5%, p-value <0.0001). This difference remained significant after adjustment for age, gender and hospitalization (adjusted odds ratio (aOR) = 3.3, p-value <0.0001). Globally children who were hospitalized were significantly younger than those who were not, but the rate of hospitalization was similar for both viruses: 37% (219/591) for hMPV and 39% (187/476) for RSV. Figure 3 illustrates the proportion of children hospitalized in each age category, for hMPV or RSV. Children younger than 3 months were hospitalized significantly more often with RSV than with hMPV infection (75% versus 59%, p-value = 0.007) but after 3 months, there were no difference in hospitalization rates between RSV and hMPV.

Clinical Characteristics in Hospitalized Children

A comparison of characteristics of children hospitalized for hMPV or RSV infection is presented in Table 2. As previously mentioned, children with RSV infection were significantly younger than children with hMPV infection.

The length of stay was significantly longer for children with RSV. History of prematurity was significantly more frequent in children hospitalized for RSV, except for extreme prematurity which was slightly more observed in children hospitalized (6/219 and 3/187 for hMPV and RSV respectively, NS). Children hospitalized with hMPV presented more other risk factors or comorbidities. Regarding symptoms on admission, children with hMPV infection presented more often with fever, cough, rhinitis or gastro-intestinal symptoms (such as vomiting or diarrhea), while children with RSV presented more often with LRTI symptoms and respiratory distress. However, there was no significant difference in the rate of hypoxemia or tachypnea between the two groups. The majority of children with RSV (71%) had a diagnosis of bronchiolitis/bronchitis on admission, compared to 37% in children with hMPV for whom diagnosis on admission were more diversified: 33% FUO, 25% pneumonia and 4% febrile seizure. Chest X-ray and blood tests were more often performed in children with hMPV infection. Among the children who had a chest radiography, a pulmonary infiltrate was significantly more observed in hMPV than in RSV infected children (58% versus 40%, p-value =0.004). Interestingly, females presented significantly more often a pulmonary infiltrate than males (64% versus 41%, aOR = 2.49, 95% CI [1.41 – 4.37], p-value = 0.002) and this difference was found in the hMPV and RSV subgroups (Data not shown).

Therapeutical interventions administered during hospitalization are presented in Figure 4. Children with hMPV received more bronchodilators and antibiotics. When intravenous antibiotics were administered, the duration was longer for hMPV (median in days interquartile (IQR) = 3 [2 - 4]) than for RSV (2 [2 - 3], p-value = 0.043). By contrast, children with RSV required more oxygen administration, respiratory support including high flow oxygen therapy, continuous positive airway pressure (CPAP) and bilevel positive airway pressure and nasogastric or intravenous feeding. Intensive care admission was required in only 2/214 (1%) children with hMPV (5 children had an unknown status as they were transferred to another hospital), compared to 18/184 (10%) children with RSV (3 children with unknown status).

Discussion

RSV and hMPV are frequent causes of hospitalization among young children [2–6, 17–19, 21–28]. RSV was the most common etiology of hospitalization for ARTI among children in our hospital during the winter 2014-2015 whereas hMPV was found in a much smaller proportion of children as reported in the literature [15, 27, 29]. Our study refers to one of the longest period of observation published for hMPV infection. Both viruses show a preferential but distinct seasonality with a predictable peak for the RSV in November and December in Belgium and epidemics of hMPV occurring in late winter or early spring as previously reported [18, 19]. Nonetheless, the recent impact of COVID-19 pandemic and lockdowns may affect the predictability of upcoming outbreaks of RSV as recently seen in Australia [30].

Molecular diagnostic tests remain the gold standard for the detection of respiratory viruses, but they are more costly and only reimbursed by the Belgian social security for children in intensive care units or in oncologic wards. Using molecular rather than non-molecular diagnostic tests could impact therapeutical strategies, the prescription of antibiotic drugs or the duration of hospitalization [31, 32]. However, PCR methods can detect resolved infections and interfere with the objectivity of the results including cured, asymptomatic or even ill patients enduring another viral infection or a bacterial superinfection. If molecular

diagnosis is not available or not deemed necessary, the use of antigen detection tests and viral culture are other options [25]. When an antigen detection test or a cell culture is positive for a specific virus, the probability of its implication in the actual infection is thus higher, making this kind of tests a good choice when studying disease symptoms. We could confirm the lower sensitivity of viral culture for hMPV than for RSV detection [6]. In contrasts with other publications, we observed more co-infections with hMPV than with RSV in children hospitalized, [18, 33]. This could be explained by the longer period of observation in the hMPV group which may result in a longer exposition to other germs.

The age distribution of children infected with RSV infection is similar to another Belgian study, RSV showing a peak in children younger than 3 months, while for hMPV, the peak is around 6-12 months [19]. The younger age of children hospitalized for RSV infection than for hMPV infection is concordant with the literature [12, 15, 16, 34]. In contrasts with other studies, we observed a significantly higher proportion of children born prematurely, but not extreme premature, in the RSV group than in hMPV group [14, 23, 35]. Preterm birth is a well-known risk factor for severe RSV infection [36]. Belgium follows the international consensus on the Palivizumab policy and reimburses this prophylaxis during the RSV season in all infants born before 28 weeks gestational age [37]. This is probably the reason why extreme prematurity was not increased in the group of RSV infected children. Other comorbidities such as chronic respiratory disease were more associated with hMPV in concordance with other publications [16, 17, 23, 35], but did not remain significant after adjusting for age and gender. Nevertheless, much remains to be discovered in hMPV infections in order to propose a vaccine strategy for children with risk factors for severe disease [9, 10].

In our observation, children hospitalized with RSV infection suffered from more severe respiratory involvement requiring frequently supportive treatments, whereas children with hMPV were more often febrile, diagnosed with pneumonia and treated with antibiotics. Literature comparing RSV and hMPV infections is controversial. If some studies did not report any difference between RSV and hMPV infection in children [13], others reported that non-specific symptoms such as fever or gastrointestinal complains were more related to hMPV [14, 15, 23] while respiratory symptoms or feeding difficulties were more associated with RSV [16, 34]. It is also recognized that RSV and hMPV can differ in X-ray patterns [38]. Although inconsistently, hMPV has been associated with more pneumonia than RSV [14, 15, 39]. Furthermore, our study shows more frequent pulmonary infiltrates in females. In a Canadian prospective study, Papenbourg et al reported that females with hMPV infection experienced more severe disease [40]. Our data did not show any increased morbidity in female. However the demonstration of pulmonary superinfections by chest x-ray has limtations, the emergent use of lung ultrasound to diagnose pneumonia seems more sensitive [41].We found no difference in the rate of hospitalization between these 2 viruses but we observed longer hospitalization for RSV than for hMPV infection which is not in line with other studies [11, 13, 16, 42].

Our study presents some limitations. Related to the retrospective design, data collection was based on non-standardized medical charts completed by different physicians. As a result, missing data are numerous. The indication for a NPA or a NPS was not standardized which may result in an overestimation of hospitalization rates related to each virus. While our number of hMPV infected children is one of the biggest in European publications, we compared 8 years hMPV circulation with only one RSV season. As the pathogenicity of RSV vary from one year to another, one year might not be representative of the

pathogenicity of RSV. Finally, identification of the viruses were not based on molecular methods antigen detection tests and viral culture are less sensitive than molecular methods for the detection of RSV and hMPV, but the sensitivity of rapid antigen methods are closer to the one of molecular tests for patients with recent symptoms [42, 43].

To conclude, despite their genetic resemblance, RSV and hMPV are leading to two distinct clinical entities. hMPV is is an important source of pneumonia, requiring hospitalization with more antibiotics administration and is more often present with co-infection.

RSV is 10 times more prevalent, the epidemic starts earlier and causes more severe symptoms in youngest children with more respiratory distress requiring oxygen administration or respiratory support, and a higher rate of transfer in a PICU compared to hMPV. Recent trials for a RSV maternal vaccine using transplacental transfer of maternal antibodies strategy are promising perspective [44].

Abbreviations

aOR : adjusted odds ration - ARTI : acute respiratory tract infection - BiPap : bilevel positive airway pressure –

CHU : Centre Hospitalier Universitaire - CI : confidence interval - CPAP : continuous positive airway pressure –

DFA : direct fluorescent assay - FUO : fever of unknown origin - hMPV : human metapneumovirus –

LFC : lateral flow chromatography - LRTI : low respiratory tract infection - NP : nasopharyngeal - NPA : nasopharyngeal aspirates NPS : nasopharyngeal swabs - NS : non-significant - PICU : pediatric intensive care units - RSV : respiratory syncytial virus -

URTI : upper respiratory tract infection

Declarations

Authors contribution

Jonathan Illan Montero and Alice Berger collected the data, drafted the manuscript. Alice Berger and Tessa Goetghebuer performed statistical analysis. Jack Levy, Laurent Busson, Marc Hainaut and Tessa Goetghebuer performed a critical revision of the manuscript. All authors read and approved the final manuscript.

Compliance with ethical statements

Conflict of interest : the authors declare that they have no conflict of interest.

Ethical approval

All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Tables

Table 1 Co-Infection with other respiratory viruses

Respiratory virus	hMPV N = 78/591 (13) N (%)	RSV N = 22/458 (5) N(%)
Adenovirus	20 (25)	5 (23)
Cytomegalovirus	15 (19)	2 (9)
Rhinovirus	15 (19)	3 (14)
Enterovirus	12 (15)	6 (27)
Parainfluenzae	10 (13)	1 (5)
Influenza	6 (7)	5 (23)
Sensitivity of non-molecular laboratory procedures		
	hMPV (N = 591) [A] N (%)	RSV (N= 476) [A] N (%)
Positive viral culture	195 (33)	454 (96)
Positive antigen test (if performed)	513/522 (98)	399/469 (85)

[A] Ruled out RSV and hMPV co-infections

Table 2. Comparison of demographic, medical history and clinical characteristics in children hospitalized with hMPV or RSV infection

[B] Odds Ratio adjusted for age, gender, presence of a risk factor and history of prematurity
[C] *NA* : Non applicable
[D] PICU : pediatric intensive care unit
[E] Odds ratio adjusted for age, gender and presence of a risk factor
[F] Comorbidities exposing to a higher rate of complications of viral respiratory infections include chronic respiratory diseases such as bronchopulmonary dysplasia, asthma or cystic fibrosis, heart defects, intra-uterine HIV exposure, neuromuscular diseases, severe epileptics affections, genetic diseases (down syndrome and sickle cell disease), immunosuppression and polymalformative syndromes
[G] Odds ratio adjusted for age, gender and history of prematurity
[H] Elevated CRP was defined as follow : CRP >20mg/L for children < 6 months and CRP > 50mg/L for children ≥ 6 months

Figures

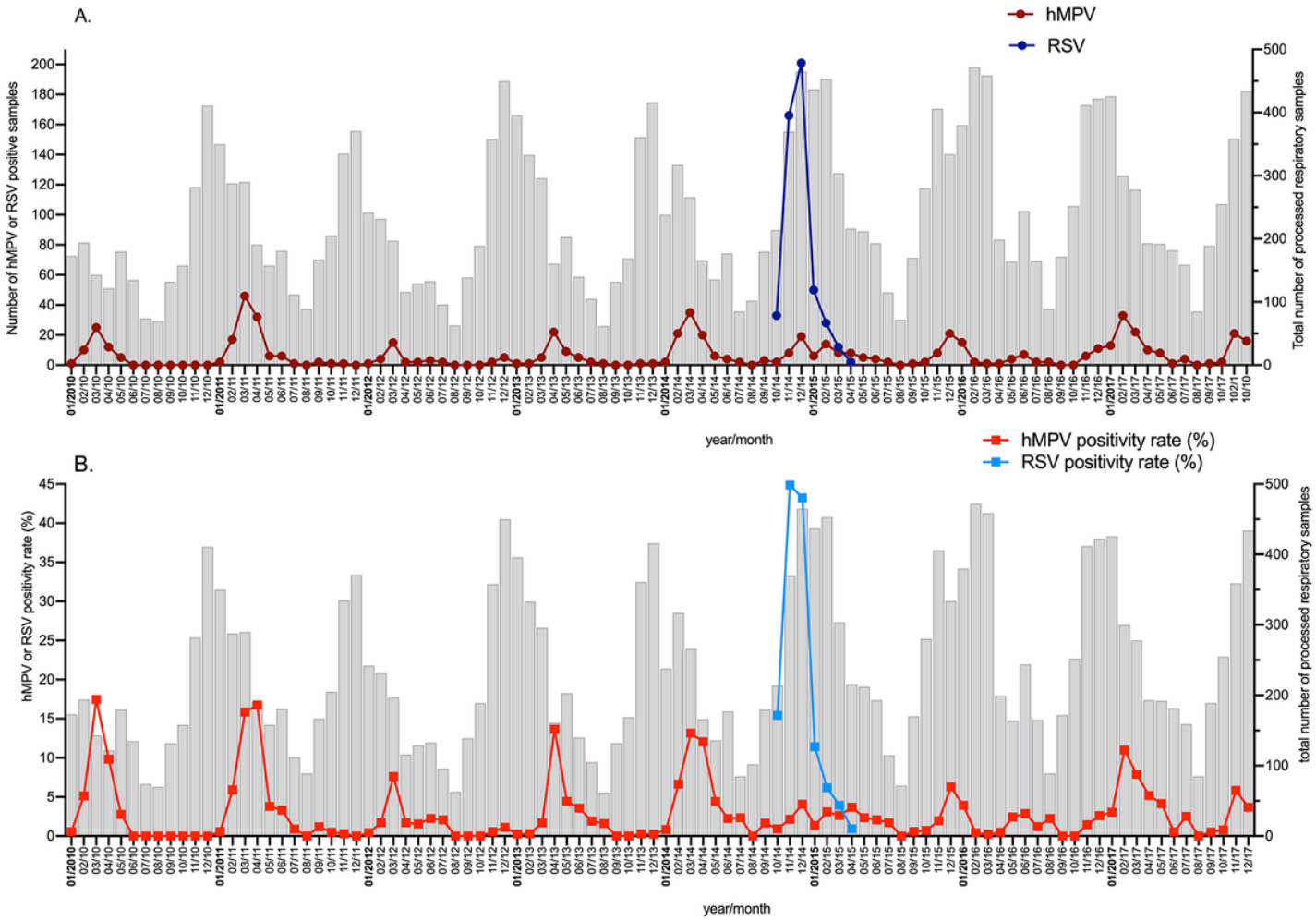

Figure 1

Characteristic	hMPV (N = 219) N (%)	RSV (N= 187) N (%)	P value	Crude Odds Ratio (95% CI)	P value	Adjusted Odds Ratio[B] (95% CI)	P value
Demographic characteristics							
Age							
Mean in months	**12.28**	**6.99**	**<0.0001**	*NA*[C]			
Median in months [IQR]	**5.66 [2.50 – 12.83]**	**2.93 [1.38 – 9.11]**	**<0.0001**	*NA*			
Age categories			**0.003**	*NA*			
0 – 3 months	78 (36)	100 (53)					
3 – 6 months	34 (16)	24 (13)					
6 – 12 months	48 (22)	27 (14)					
12 – 24 months	27 (12)	25 (13)					
24 months – 5 years	28 (13)	10 (5)					
> 5 years	4 (2)	1 (0.5)					
Gender (male)	129 (59)	108 (58)	NS				
Medical history							
Transfers in a PICU[D]	**2/219 (1)**	**18/184 (10)**	**<0.0001**	**0.09 (0.02 – 0.38)**	**0.001**	**0.08 (0.02 – 0.38)**	**0.001**
History of prematurity	**24/216 (11)**	**36/182 (20)**	**0.012**	**0.51 (0.29 – 0.89)**	**0.017**	**0.45 (0.25 – 0.81)**[E]	**0.008**
Presence of a risk factor[F]	**30/215 (14)**	**13/184 (7)**	**0.019**	**2.13 (1.08 – 4.22)**	**0.03**	1.82 (0.86 – 3.84)[G]	NS
Signs and Symptoms							
Fever	**207/218 (95)**	**151/187 (81)**	**<0.0001**	**4.49 (2.21 – 9.10)**	**<0.0001**	**3.27 (1.57 – 6.796)**	**0.002**

Cough	**195/217 (90)**	**138/187 (74)**	**<0.0001**	**3.15 (1.82 – 5.45)**	**<0.0001**	**3.04 (1.706 – 5.40)**	**<0.0001**
Rhinitis	**183/217 (84)**	**119/187 (64)**	**<0.0001**	**3.08 (1.92 – 4.93)**	**<0.0001**	**3.495 (2.10 – 5.81)**	**<0.0001**
Dyspnea	**99/218 (45)**	**133/187 (71)**	**<0.0001**	**0.34 (0.22 – 0.51)**	**<0.0001**	**0.30 (0.19 – 0.47)**	**<0.0001**
Hypoxemia	76/217 (35)	55/186 (30)	NS				
Tachypnea	70/201 (35)	61/178 (34)	NS				
Respiratory Distress	**119/215 (55)**	**129/187 (69)**	**0.003**	**0.557 (0.37 – 0.84)**	**0.005**	**0.55 (0.36 – 0.84)**	**0.006**
Vomiting or Diarrhea	**78/218 (36)**	**28/187 (15)**	**<0.0001**	**3.16 (1.94 – 5.15)**	**<0.0001**	**3.20 (1.91 – 5.35)**	**<0.0001**
Feeding difficulties/loss of appetite	124/218 (57)	106/187 (57)	NS				
Neurological impairment	10/219 (5)	5/187 (3)	NS				
Complementary investigations							
Chest radiography performed	**154/218 (71)**	**101/187 (54)**	**<0.0001**	**2.05 (1.36 – 3.09)**	**0.001**	**1.87 (1.20 – 2.90)**	**0.006**
Pulmonary infiltrate	**89/154 (58)**	**40/101 (40)**	**0.004**	**2.09 (1.25 – 3.48)**	**0.005**	**1.96 (1.12 – 3.44)**	**0.019**
Blood test	**205/218 (94)**	**153/187 (82)**	**<0.0001**	**3.50 (1.79 – 6.87)**	**<0.0001**	**3.26 (1.64 – 6.50)**	**0.001**
Elevated CRP[H]	**59/202 (29)**	**28/153 (18)**	**0.012**	**1.84 (1.11 – 3.07)**	**0.019**	1.61 (0.95 – 2.74)	NS
WBC>15000/mcl	62/204	36/129	NS				

	(30)	(28)					
Diagnosis at admission							
Fever of unknown origin	**72/218 (33)**	**16/187 (9)**	**<0.0001**	**5.27 (2.94 – 9.46)**	**<0.0001**	**7.62 (4.07 – 14.27)**	**<0.0001**
Bronchiolitis/Bronchitis	**80/218 (37)**	**133/187 (71)**	**<0.0001**	**0.24 (0.16 – 0.36)**	**<0.0001**	**0.24 (0.15 – 0.37)**	**<0.0001**
Pneumonia	**54/218 (25)**	**23/187 (12)**	**0.001**	**2.35 (1.38 – 4.00)**	**0.002**	**1.87 (1.05 – 3.32)**	**0.035**
Febrile seizure	9/219 (4)	3/187 (2)	NS				

monthly distribution of hMPV and RSV cases Ordered right line on both graphs : total number of processed respiratory samples reported to months and years by light grey bars. (A) Total number of respiratory samples positive for hMPV (dark red line graph) or RSV (dark blue line graph). (B) Positivity rate of hMPV cases (light red line graph) or RSV cases (light blue line graph).

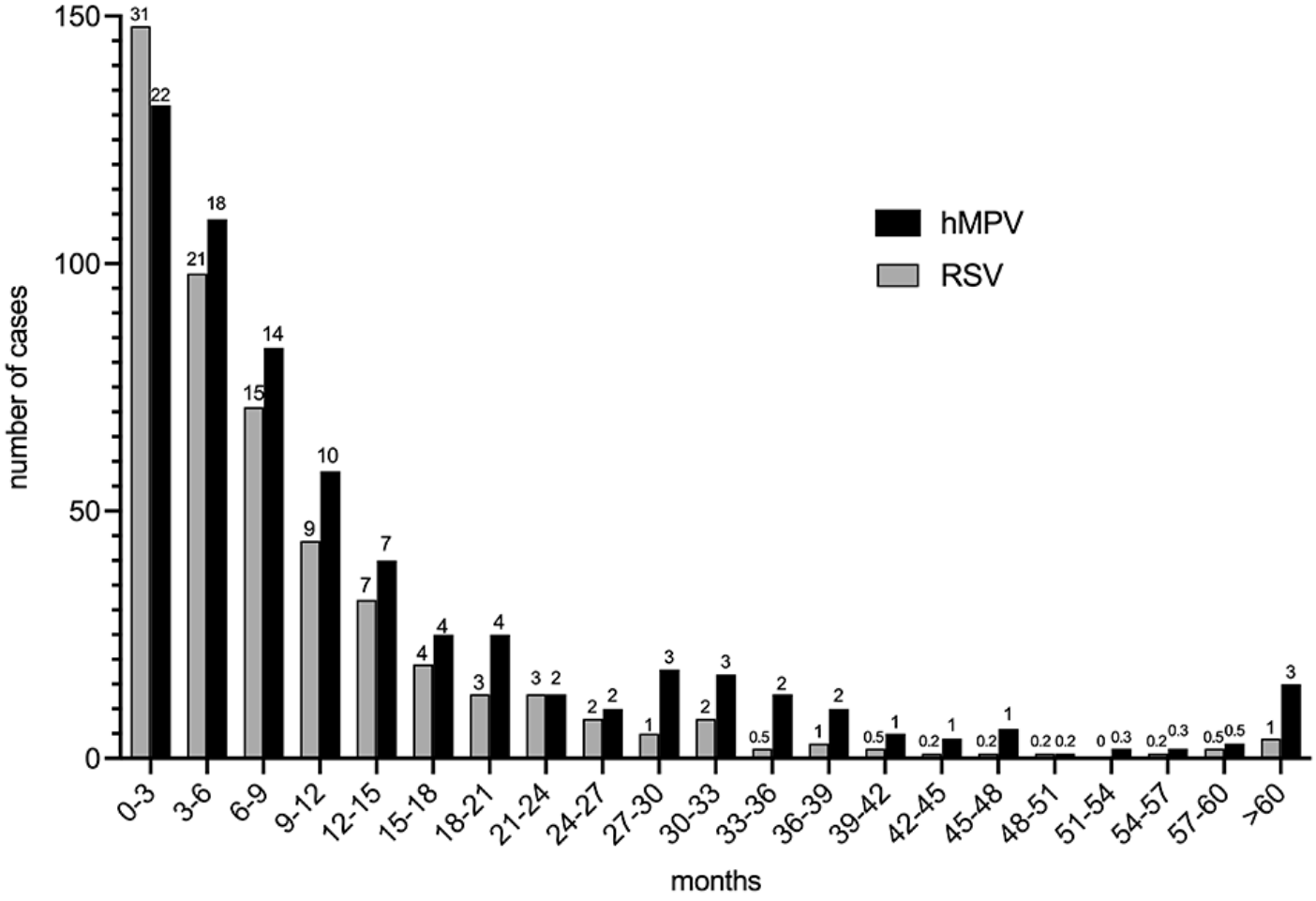

Figure 2

age distribution of RSV and hMPV infections. Number of cases by age categories (in months). Black bars represent hMPV cases and grey bars RSV cases. Numbers above bars represent proportion (%) of cases compared to the total amount of hMPV or RSV cases.

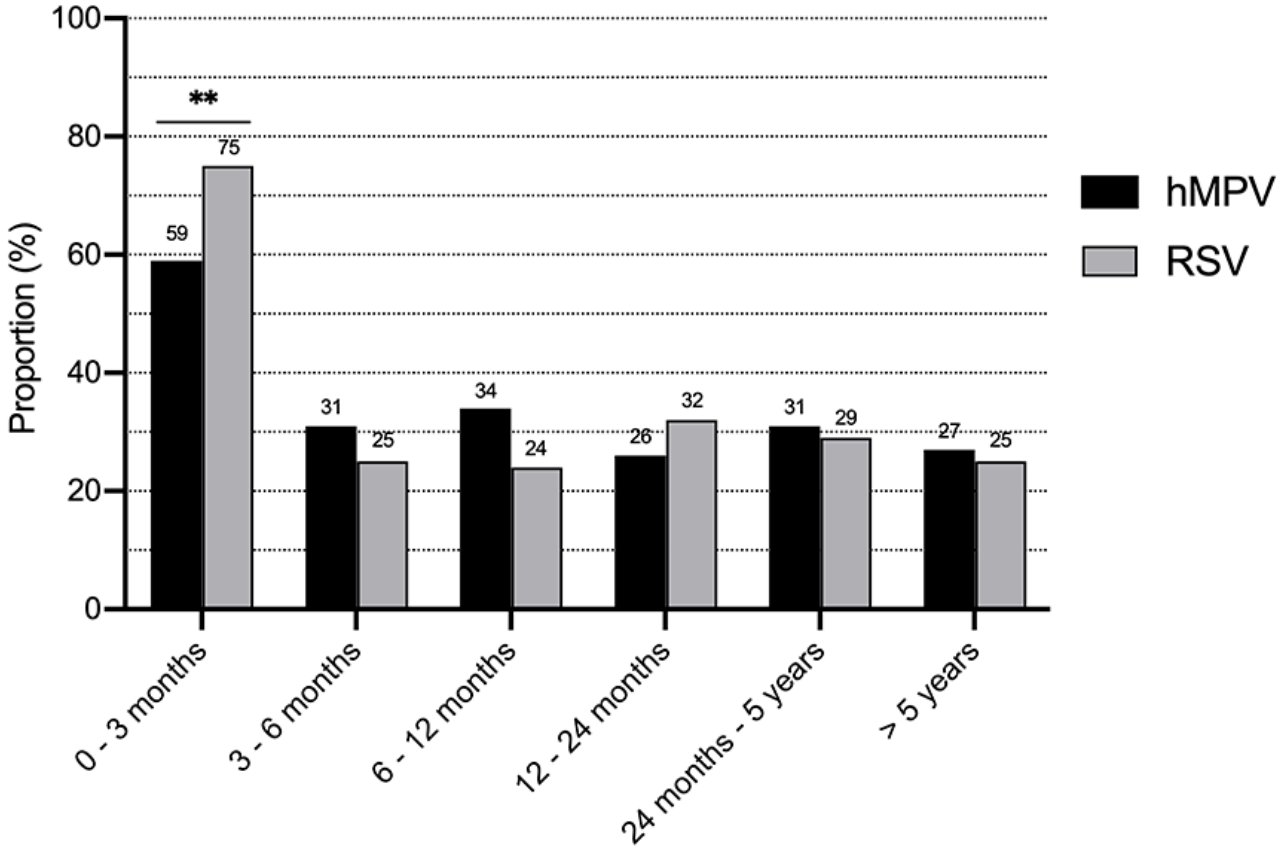

Figure 3

proportion of children hospitalized with hMPV and RSV. The percentages represent the number of children hospitalized with hMPV or RSV in different age categories, divided by the total amount of children with hMPV or RSV in that age category. Black bars represent hMPV cases and grey bars RSV cases.

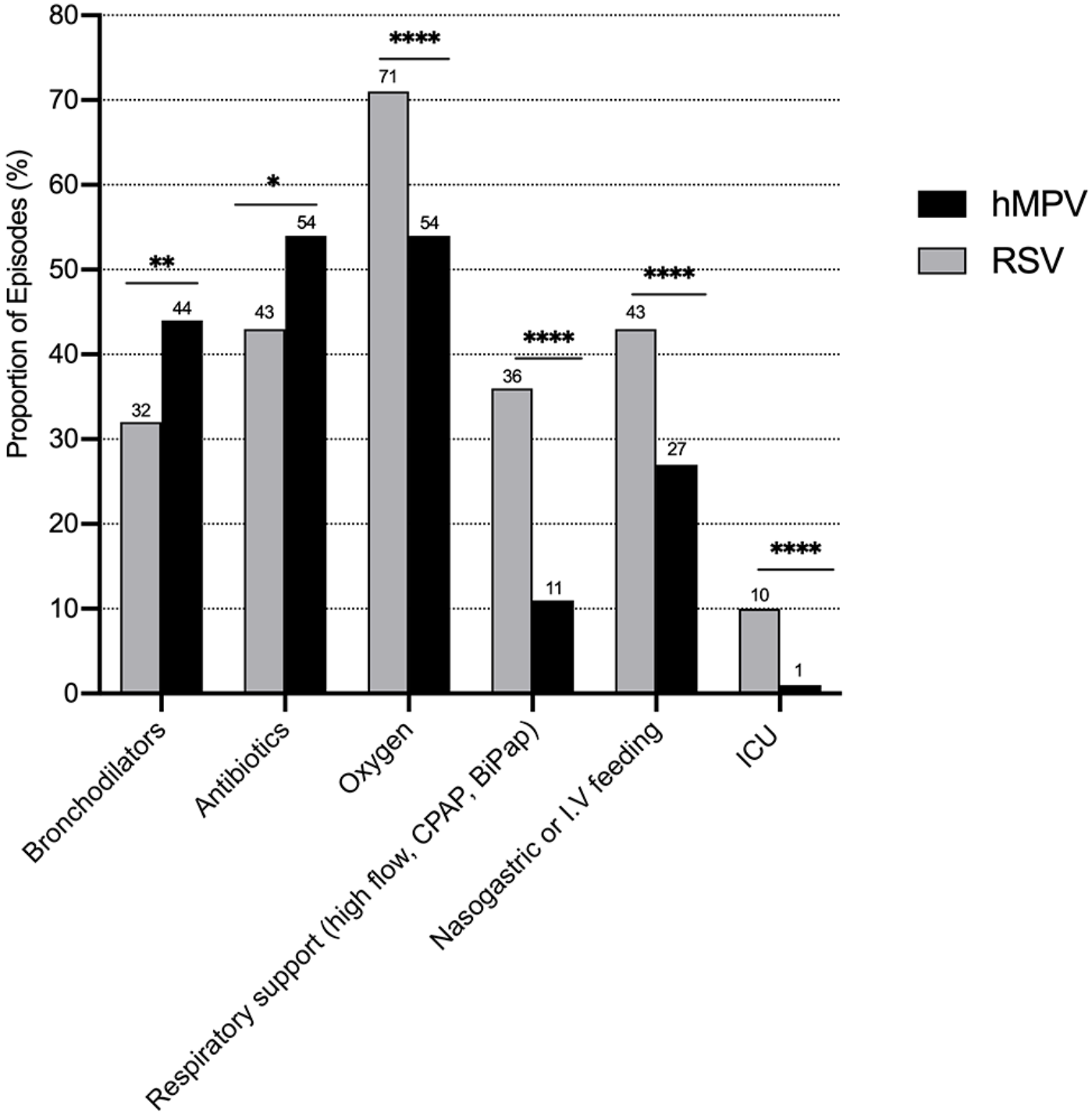

Figure 4

comparison of therapeutical Interventions during hospitalization in RSV and hMPV infected children The percentages represent the therapeutical interventions realized in hospitalized children with hMPV or RSV. Black bars represents hMPV cases and grey bars RSV cases.